MEDICAL SCIENCE MONITOR

CLINICAL RESEARCH

e-ISSN 1643-3750
© Med Sci Monit, 2018; 24: 7256-7263
DOI: 10.12659/MSM.910614

Received: 2018.04.15
Accepted: 2018.06.05
Published: 2018.10.11

Iron Deficiency in Patients with Paroxysmal Nocturnal Hemoglobinuria: A Cross-Sectional Survey from a Single Institution in China

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Source of support: National Public Health Benefit Research Foundation of China (Grant No. 201202017), Important National Science and Technology-Specific Projects of China (Grant No. 2011ZX09302-007-04), and the Natural Science Foundation of Tianjin (Grant No. 11JCYBJC10500)

Background: Paroxysmal nocturnal hemoglobinuria (PNH) is an acquired clonal hematopoietic disorder that often manifests with chronic intravascular hemolysis. Iron deficiency in patients with PNH is most often due to urinary losses of iron secondary to chronic intravascular hemolysis.

Material/Methods: This cross-sectional survey assessed the prevalence of iron deficiency in a Chinese population of PNH patients who were enrolled between May 2012 and October 2014.

Results: A total of 742 PNH cases were selected by FLARE and classified as classical PNH (15.36%), PNH in the setting of another specified bone marrow disorder (12.26%), and subclinical PNH (72.38%). The median age of all the patients was 32 years (range 5–77 years). The overall prevalence of iron deficiency was 17.9% among all the PNH patients enrolled in the survey, 76.3% (87/144) among those with classical PNH, 33.0% (30/91) among those with PNH in the setting of another specified bone marrow disorder, and 3.0% (16/537) among the subclinical PNH patients. The incidence of iron deficiency among classical PNH patients was higher than that in the other 2 subcategories (*P*-value=0.000). Multivariate analyses showed that age and disease duration were independent risk factors for iron deficiency in classical patients.

Conclusions: This survey shows that PNH patients were prone to iron deficiency, especially patients with classical PNH.

MeSH Keywords: Anemia, Iron-Deficiency • Hemoglobinuria, Paroxysmal • Hemolysis

Full-text PDF: https://www.medscimonit.com/abstract/index/idArt/910614

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Background

Paroxysmal nocturnal hemoglobinuria (PNH) is an acquired clonal hematopoietic stem cell disorder that manifests as hemolytic anemia, bone marrow failure, and thrombosis [1,2]. The mutations of the PIG-A gene in the stem cells and their progeny, which lead to a reduction or absence of glycophosphatidylinositol (GPI)-anchored proteins, such as complement regulatory protein CD55 and CD59, are fundamental to the pathophysiology of PNH. The loss of complement-regulatory proteins renders PNH erythrocytes susceptible to both intravascular hemolysis and other related manifestations [3–5]. Long-term, persistent, and paroxysmal acute intravascular hemolysis often leads to iron loss accompanied by elimination of hemoglobin and hemosiderin in the urine [6], ultimately resulting in iron deficiency. Nevertheless, there has been no comprehensive study on the prevalence and characteristics of iron deficiency in PNH. Is iron deficiency more common in PNH than we suspected? Can iron deficiency exacerbate anemia in PNH patients? We performed this cross-sectional survey to assess the prevalence and distribution of iron deficiency in PNH patients, as well as to identify the associated risk factors. This study included 742 PNH patients who were referred to our hospital between May 2012 and October 2014.

Material and Methods

Study design and population

This was a single-center, cross-sectional study of outpatients and inpatients with peripheral blood PNH clones who were recruited between May 2012 and October 2014 at the Institute of Hematology and Blood Diseases Hospital, Peking Union Medical College and Chinese Academy of Medical Sciences (PUMC and CAMS). Because this institute is the largest specialized blood disease hospital in China, patients come from all parts of the country. This hospital has 650 inpatient beds and receives more than 145 000 outpatient visits per year. The aim of this cross-sectional study was to evaluate the prevalence and associated factors of PNH with iron deficiency. All 742 patients diagnosed with PNH, whether they were previously or newly diagnosed, underwent a simultaneous examination of their peripheral blood cell GPI-APs and serum ferritin between May 2012 and October 2014.

Diagnosis and classification of PNH

Patients with Coombs-negative hemolytic anemia, aplastic anemia, myelodysplastic syndrome, refractory anemia, and unexplained thrombosis in conjunction with cytopenia or hemolysis were screened for PNH. The diagnosis of PNH was confirmed by flow cytometry to detect the absence of GPI-APs on the peripheral blood cells. The presence of PNH clones were defined as greater than 1% of neutrophils, monocytes, or red cells carrying the PNH phenotype [5,7]. The size of the PNH clone was determined in erythrocytes by anti-CD59 flow cytometry analysis and in neutrophils and/or monocytes by FLARE. Classification criteria, proposed by the International PNH Interest Group, were adopted and included 3 main categories of PNH [1]: (a) classical PNH, which includes patients who have clinical evidence of intravascular hemolysis, reticulocytosis, abnormally high concentration of serum lactate dehydrogenase (LDH) and indirect bilirubin, and abnormally low concentration of serum haptoglobin but who have no evidence of another defined bone marrow abnormality; (b) PNH in the setting of another specified bone marrow disorder, in which patients have clinical and laboratory evidence of hemolysis but also have concomitantly, or have had a history of, a defined underlying marrow abnormality (e.g., aplastic anemia or myelodysplastic syndrome); and (c) subclinical PNH, in which patients have small PNH clones but no clinical or laboratory evidence of hemolysis or thrombosis. We defined the former 2 subcategories together as hemolytic PNH. We detected the presence of PNH clones on red blood cells, granulocytes, and monocytes using a FACSCalibur flow cytometer (Becton Dickinson, Franklin Lakes, NJ, USA) with CellQuest software. PNH clones were defined as FLAER/CD24 double-negative granulocytes, FLAER/CD14 double-negative monocytes, and $CD235a^{+}$ $CD59^{-}$ red blood cells [8]. Other PNH laboratory tests included the Hams test, urine Rous (hemosiderin) test, and assessments of serum-free hemoglobin (F-HB), haptoglobin (HP), and lactate dehydrogenase (LDH) levels.

Serum ferritin method and iron deficiency definition

Iron deficiency was defined as hemoglobin (HGB) <120 g/L and serum ferritin <30 ng/mL. Iron metabolic indices included serum ferritin level, serum iron concentration, unsaturated iron-binding capacity (UIBC), total iron-binding capacity (TIBC), and transferrin saturation (TSAT). Serum ferritin was detected by drawing whole blood from patients at diagnosis, and serum was separated by centrifugation at 3000 rpm for 10 min in serum separation tubes (BD Biosciences). Serum ferritin was measured using an Access Ferritin Kit and UniCel DXI 800 Immunoassay System (Chemiluminescence, Beckman Coulter Systems) according to the manufacturer's instructions.

Statistical analyses

The distributions of the clinical and laboratory characteristics were compared between the 3 subcategories and between classic PNH and PNH in the setting of another specified bone marrow disorder groups using the χ^2 test for qualitative characteristics and the Kruskal-Wallis (3 subcategories) or Mann-Whitney (2 groups) test for continuous characteristics. Logistic

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regression was used to assess independent risk factors for PNH with iron deficiency in multivariate analyses with stepwise selection of important covariates. Univariate and multivariate analyses were conducted for classical PNH. $P<0.05$ was considered statistically significant. Statistical analyses were performed using SPSS version 22.0 (SPSS Inc., Chicago, IL, USA).

Results

Patient characteristics

A total of 742 (399 male and 343 female) patients were included in this study, including 114 classical PNH patients, 91 patients with PNH in the setting of another specified bone marrow disorder, and 537 patients with subclinical PNH. The median age at diagnosis was 32 (range 5–77) years. Among the patients with PNH concomitant with another specified bone marrow disorder, 84 (84/91, 92.3%) had aplastic anemia, 6 (6/91, 6.6%) had myelodysplastic syndrome, and 1 (1/91, 1.1%) was diagnosed with thrombocytosis. Of the subclinical PNH patients, 480 (480/537, 89.4%) had aplastic anemia, 44 (44/537, 8.2%) had myelodysplastic syndrome, and 13 (13/537, 2.4%) had other blood diseases. The clinical and hematological characteristics of the 3 PNH subgroups are summarized in Table 1.

The PNH clone sizes detected in red cells and granulocytes were significantly different between the 3 clinical subcategories at diagnosis ($P=0.000$). The median PNH clone sizes in red cells and granulocytes were 64.83% (range 17.58–99.56%) and 95.06% (range 3.10–99.94%) in classical PNH patients, 50.14% (range 7.38–95.49%) and 87.57% (range 1.05–99.77%) in PNH/specified bone marrow disorder patients, and 1.42% (range 0–67.27%) and 3.90% (range 0–99.95%) in subclinical PNH patients, respectively. The PNH clone sizes in both neutrophils and erythrocytes were much higher in hemolytic PNH (classical PNH and PNH/specified bone marrow disorder) than in subclinical PNH ($P=0.000$) (Figure 1, Table 1).

The prevalence and distribution of iron deficiency in the 3 PNH subgroups

The overall prevalence of iron deficiency among PNH patients was 17.9% (133/742). Specifically, the prevalence of iron deficiency was 76.3% (87/144) among classical PNH patients, 33.0% (30/91) among patients with PNH in the setting of another specified bone marrow disorder, and 3.0% (16/537) among subclinical PNH patients (Figure 2). The incidence of iron deficiency among classical PNH patients was higher than that in either of the other 2 subgroups ($p=0.000$). In our study, the overall prevalence of iron deficiency among female patients with PNH was 20.4% (70/273). In the various subgroups of female patients with PNH, the prevalence of iron deficiency was 79.6% (39/49), 45.0% (18/22), and 5.0% (13/241) among classical PNH, among patients with PNH in the setting of another specified bone marrow disorder, and among subclinical PNH patients, respectively. In comparison, the prevalence of iron deficiency was 73.8% (48/65), 23.5% (12/51), and 1.1% (3/283), respectively, in the various subgroups of male patients with PNH. The prevalence of iron deficiency in the 2 gender groups is shown in Table 2.

Iron deficiency in classical PNH

Our results showed that the prevalence of iron deficiency in classical PNH was much higher than that in the other 2 subgroups. Therefore, we analyzed the characteristics of classical PNH patients. Eighty-seven of 114 (76.3%) classical PNH patients presented with iron deficiency. The clinical and hematological characteristics of classical PNH patients with or without iron deficiency are shown in Table 3.

Clinical characteristics

The median age of patients with classical PNH with iron deficiency (34 years, range 13–68 years) was much younger than that of patients without iron deficiency (49 years, range 16–75 years) ($p=0.0007$). The median duration of disease in classical PNH patients with iron deficiency was longer than that in non-iron-deficient classical PNH patients (80 (range 6–54) months compared with 31 (range 4–204) months, respectively; $p=0.015$).

Hematological characteristics

Statistically significant differences in hemoglobin levels ($p=0.008$), ARC ($p=0.029$), FHB ($p=0.030$), MCV ($p=0.000$), and MCHC ($p=0.000$) were found between patients with and without iron deficiency. These 5 indicators were lower in iron-deficient patients with classical PNH than in those without iron deficiency. However, the median erythrocyte PNH clone sizes were higher in iron-deficient patients (67.54%, range 18.19–98.96%) compared with non-iron-deficient patients (55.51%, range 17.58–99.56%), but this difference was not statistically significant. The median neutrophil PNH clone sizes were similar in the 2 groups (95.15% [range 3.10–99.94%] compared with 93.35% [range 20.17–99.85%] in iron-deficient and non-iron-deficient patients, respectively). There were no differences in WBC ($p=0.759$) and PLT ($p=0.109$) values between the 2 groups.

Risk factors for classical PNH with iron deficiency

Univariate analysis was performed to assess the possible correlation of iron deficiency in classical PNH with age, sex, disease duration, ARC, LDH, FHB, TBIL, hemoglobinuria, and PNH clone size in red cells and granulocytes (Table 2). According to the univariate analysis, age, disease duration, and ARC and FHB

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Table 1. Characteristics of PNH subcategories.

PNH category	Total (n=742)	a-Classical PNH (n=114)	b-PNH/specified bone marrow disorder (n=91)	c-Subclinical PNH (n=537)	*P*-value (a×b×c)	*P*-value (a×b)	*P*-value (a×c)	*P*-value (b×c)
Characteristics								
Gender, M/F	399/343	65/49	51/40	283/254	0.631			
Median age, years	32 (5–77)	39 (13–75)	34 (7–69)	31 (5–77)	0.016	0.935	0.02	0.039
Peripheral blood cell counts								
Hemoglobin, g/L	78 (23–167)	82 (32–156)	77 (23–142)	78 (29–167)	0.2			
ARC, $\times 10^9$/L	59.5 (0.7–461.0)	171.8 (62.0–461.0)	117.9 (32.9–324.6)	43.2 (0.7–218.2)	0.000	0.000	0.000	0.000
Platelet count, $\times 10^9$/L	42 (1–1317)	179 (83–452)	61 (9–1317)	29 (1–356)	0.000	0.000	0.000	0.000
ANC, $\times 10^9$/L	1.35 (0.01–9.89)	2.56 (0.43–8.95)	1.46 (0.03–8.8)	1.15 (0.01–9.89)	0.000	0.000	0.000	0.004
MCV, fL	98.8 (69.3–129.5)	97.5 (74.5–123.8)	105.7 (75.7–129.5)	98.0 (69.3–128.3)	0.000	0.000	0.579	0.000
MCHC, g/L	336 (250–417)	297 (250–355)	316 (265–360)	342 (286–417)	0.000	0.000	0.000	0.000
Parameters of iron metabolism								
Serum ferritin, ng/mL	380.91 (2.65–4028)	14.55 (2.7–702.20)	98.4 (2.65–2543.73)	547.67 (5.38–4028.0)	0.000	0.000	0.000	0.000
Serum iron, µmol/L	28.22 (1.43–90.59)	7.77 (2.01–44.02)	21.72 (1.43–90.59)	34.01 (1.88–80.84)	0.000	0.000	0.000	0.000
TIBC, µmol/L	58.19 (13.71–107.71)	69.53 (35.34–105.40)	62.1 (27.35–107.71)	55.77 (13.71–101.32)	0.000	0.002	0.000	0.000
TSAT	0.47 (0.01–1.0)	0.12 (0.02–0.98)	0.36 (0.01–0.95)	0.63 (0.02–1.00)	0.000	0.000	0.000	0.000
Parameters of hemolysis								
FHB, mg/L	18.4 (2.0–1044.5)	209.1 (12.8–995.9)	165.5 (16.7–1044.5)	13.5 (1.0–244.2)	0.000	0.019	0.000	0.000
LDH, U/L	242 (41–4732)	1569 (647–4732)	1169 (512–3116)	210 (41–1601)	0.000	0.000	0.000	0.000
Bilirubin, µmol/L	14.9 (4.2–172.3)	25.9 (9.4–84.9)	22.1 (9.5–164.1)	12.4 (4.2–172.3)	0.000	0.082	0.000	0.000
Flow cytometry								
Neutrophil clone size	8.43 (0–99.95)	95.06 (3.10–99.94)	87.57 (1.05–99.77)	3.9 (0–99.95)	0.000	0.003	0.000	0.000
Erythrocyte clone size	3.60 (0–99.56)	64.83 (17.58–99.56)	50.14 (7.38–95.49)	1.42 (0–67.27)	0.000	0.000	0.000	0.000
Iron deficiency								
Yes/No (%)	133/609 (17.9%)	87/27 (76.3%)	30/61 (33%)	16/521 (3.0%)	0.000	0.000	0.000	0.000

a – classical PNH; b – PNH in the setting of another specified bone marrow disorder (PNH/specified bone marrow disorder); c – subclinical PNH. ANC – absolute neutrophil count; ARC – absolute reticulocyte count; MCV – mean corpuscular volume; MCHC – mean corpuscular hemoglobin concentration.

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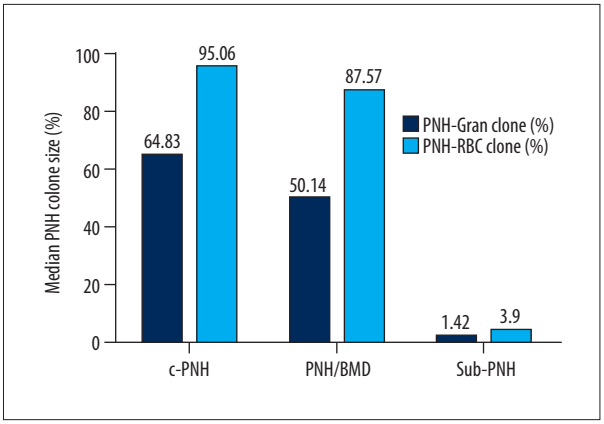

Figure 1. Median percentages of paroxysmal nocturnal hemoglobinuria.

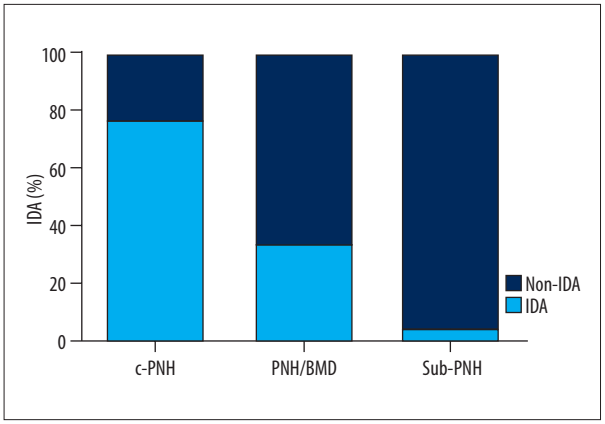

Figure 2. Incidence rate of IDA in PNH.

Table 2. Prevalence of iron deficiency according to gender.

	Classical PNH	PNH/specified bone marrow disorder	Subclinical PNH
Male	48/65 (73.8%)	12/51 (23.5%)	3/283 (1.1%)
Female	39/49 (79.6%)	18/40 (45.0%)	13/254 (5.1%)
P-value	0.477	0.032	0.006

Table 3. Clinical characteristics of classical PNH patients with and without iron deficiency.

	Iron deficiency (n=87)	Non-iron deficiency (n=27)	*P*-value
Characteristics			
Gender, M/F	48/39	17/10	0.477
Median age, years	34 (13–68)	49 (16–75)	0.007
Disease duration, months	80 (6–504)	31 (4–204)	0.015
Hemoglobinuria (Yes/No)	30/38	12/9	0.299
Peripheral blood cell counts			
Hemoglobin, g/L	81 (32–140)	90 (51–156)	0.008
ARC, $\times 10^9$/L	167.5 (62.0–461.0)	196.9 (105.2–459.5)	0.029
WBC, $\times 10^9$/L	4.56 (1.5–11.48)	4.9 (2.16–8.15)	0.759
PLT, $\times 10^9$/L	183 (89–452)	171 (83–280)	0.109
MCV, fL	96.4 (74.5–121.2)	103.0 (92.3–123.8)	0.000
MCHC, g/L	292 (250–452)	314 (280–355)	0.000
Flow cytometry			
Neutrophil clone size, (%)	95.15 (3.10–99.94)	93.35 (20.17–99.85)	0.899
Erythrocyte clone size, (%)	67.54 (18.19–98.96)	55.51 (17.58–99.56)	0.067
Parameters of hemolysis			
FHB, mg/L	204.2 (12.8–995.9)	290.7 (35.5–834.2)	0.030
LDH, U/L	1558 (647–3484)	1653 (827–4732)	0.096
Bilirubin, μmol/L	25.3 (9.4–84.9)	29.9 (11.3–80.6)	0.117

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Table 4. Multivariate analyses of the risk factors for classical PNH with iron deficiency.

	B	S.E.	Wald	*P*-value	95% C.I. for Exp (B)	
					Lower	Upper
Median age, years	0.048	0.022	4.725	0.030	1.005	1.096
Median interval to diagnosis, years	–0.013	0.006	4.452	0.035	0.976	0.999

levels influenced the incidence of iron deficiency. Multivariate logistic regression analyses showed that age and disease duration were independent risk factors for classical PNH with iron deficiency (Table 4).

Discussion

We investigated the prevalence of and factors associated with iron deficiency in PNH patients from a single blood disease hospital in China. We found that the overall prevalence of iron deficiency in PNH was 17.9%, with prevalences of 49.8% (117/235) and 3.0% in hemolytic PNH and subclinical PNH, respectively. The highest prevalence was found in female patients with classic PNH (79.6%; 39/49). Among the classic PNH patients, iron-deficient patients exhibited larger PNH clone sizes than non-iron-deficient patients. Young patients with a long disease history were more prone to have iron deficiency. Additionally, iron deficiency can aggravate the anemia caused by PNH. Although iron deficiency is a distinguishing feature of PNH, it has received relatively little attention. To the best of our knowledge, this report is the only epidemiologic study of iron deficiency in PNH patients. The information gathered by this study may contribute to improving our understanding of iron deficiency epidemiology, inform our screening of iron storage, and promote the investigation of appropriate prevention and treatment policies regarding iron deficiency in PNH patients.

In adults, the body contains 3–5 g of iron, and 20–25 mg is needed daily for the production of red blood cells and cellular metabolism. Approximately 18–19 mg of iron is recycled from damaged or old red blood cells; 1–2 mg is newly absorbed through the gastrointestinal system, mainly the duodenal enterocytes [9]; and approximately 1–2 mg of iron is lost daily as a result of menstrual bleeding, sweating, skin desquamation, and urinary excretion. Iron deficiency is the single most common nutritional deficiency; it can develop from decreased dietary intake, increased requirements for iron, decreased iron absorption, or increased iron loss. Hemosiderinuria may account for iron losses as high as 20 mg in 24 h [6]. PNH is characterized by intravascular hemolysis. Unlike extravascular hemolytic processes in which recovery of iron from the metabolized heme molecules through the reticuloendothelial system occurs, recurring, acute, massive and chronic persistent intravascular hemolysis in PNH can result in the intravascular liberation of a large amount of free hemoglobin, which is lost through renal excretion, resulting in excessive urinary losses of iron, a negative iron balance, and rapid depletion of iron stores. In hemolytic PNH, the accompanying iron deficiency was almost certainly due to increased iron loss, although iron intake and absorption were not examined in our patient cohort.

The intravascular hemolysis that occurs in PNH is a consequence of the deficiency of 2 complement regulatory proteins: decay-accelerating factor (DAF; CD55) and membrane inhibitor of reactive lysis (MIRL; CD59). Not all cells are affected; the larger the proportion of affected cells (known as the PNH clone size), the greater the severity of hemolysis [10]. In the present study, we noticed that the high prevalence of iron deficiency was associated with the PNH clone size: 76.3% in classic PNH (PNH clone size 95.06%), 33.0% in PNH/specified bone marrow disorder (PNH clone size 87.57%), and 3.0% in subclinical PNH (PNH clone size 3.90%). Moreover, in many cases of PNH, although no discernible precipitating event can be identified, the paroxysmal nature of the disease originates from the intermittent complement-mediated destruction of red cells, which can be triggered by infections, surgery, blood transfusions, or vaccinations. The long-term history of disease in hemolytic PNH indicates the long-term persistence of a small amount (and even more frequently recurring bouts) of hemoglobinuria and significant iron loss. Both the univariate and multivariate logistic regression analyses in our study indicated that disease duration was one of the risk factors for classical PNH complicated with iron deficiency, consistent with our expectations.

In contrast to the lack of reports of iron deficiency, renal iron deposits in PNH patients have often been reported. Renal damage in hemolytic PNH is associated with chronic hemosiderosis and/or microvascular thrombosis and was observed in 65% of the study population. Some classical PNH patients presented with very low cortical signal intensity on T2-weighted MRI images. Open biopsy of the kidney cortex revealed heavy hemosiderin deposition in the proximal tubular epithelial cells, with scattered interstitial iron deposits [11–18]. The concentration of iron in the kidney can be more than 80 times above normal [19]. Hemoglobin released into plasma forms a complex with haptoglobin (Hp) and undergoes endocytosis after being captured by CD163 surface molecules on macrophages

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or monocytes [20]. Hp critically promotes CD163-mediated Hb clearance at low, but not high (>100 μg/mL), concentrations of 'free' Hb [21]. Plasma hemoglobin levels in patients with PNH are commonly in the range of 0.05–0.2 g/dL and can exceed 1.0 g/dL during severe hemolytic episodes [22]. When the Hp-CD163-dependent pathway and possibly other Hb scavenging systems are saturated, as occurs during chronic hemolysis, the multi-ligand receptors cubilin and megalin expressed in the apical membrane of proximal tubules are thought to mediate renal reabsorption of Hb from glomerular filtrate [23]. Thus, the presence of renal iron deposition suggests longer and more severe intravascular hemolysis and urinary iron loss. As in another chronic intravascular hemolytic disease, SCD (sickle cell disease), the local kidney iron overload is not contradictory to the systemic iron deficiency in hemolytic PNH patients. In the present study, more than 70% of the 114 patients with classic PNH had iron deficiency; however, not even 1 case of iron overload (SF>1000 μg/L) was documented, which also illustrates the issue [24]. We believe that, although kidney damage is prominent, systemic iron deficiency in PNH is more common.

Iron deficiency affects many older infants, young children, adolescents, and pre-menopausal women. In the present study, negative correlations were found between patient age and the prevalence of iron deficiency in classical PNH; specifically, young patients had higher risk of developing iron deficiency.

We found that iron-deficient classical PNH patients has lower hemoglobin levels, reticulocyte counts, and serum-free hemoglobin levels than non-iron-deficient patients. Although cross-sectional investigations can provide insight into correlative but not causative relationships, despite the fact that approximately 80% of the daily required iron is used for erythropoiesis in the bone marrow, we believe that iron deficiency itself further aggravates the inadequate bone marrow hematopoietic compensation and accounts for all the above changes.

Our study has some limitations. First, we used a serum ferritin level lower than 30 μg/L as the criterion for iron deficiency. Compared with the cutoff value of 12 μg/L, the diagnostic sensitivity increased from 25% to 92%, with specificity unchanged at 98%, but some patients may still have been missed. Ferritin is an acute-phase protein that may be increased by many other factors, hiding the actual degree of iron deficiency. Second, the previous use of red blood cell transfusions was not included in the investigation, which may have underestimated the presence of iron deficiency in transfusion-dependent PNH patients. Third, we did not examine the influence of concomitant underlying bone marrow disorders on iron deficiency, which may affect the prevalence of iron deficiency, especially in hemolytic PNH.

Conclusions

The prevalence of and factors associated with iron deficiency in PNH patients were surveyed in a cross-sectional study. The results indicate that PNH patients are at risk of iron deficiency. We found that classic subtype, long disease history, young age, and larger PNH clones were all correlated with iron deficiency. Further studies are needed to thoroughly assess the prevalence and treatment of iron deficiency in this setting.

Acknowledgments

The authors would like to acknowledge Dr. Huijun Wang for carefully conducting the PNH clone testing.

Conflict of interest

None.

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