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High serum hepcidin is associated with the occurrence of anemia in anti-myeloperoxidase antibody-associated vasculitis with normal kidney function: a cross-sectional study

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Abstract

The etiology of anemia in antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) has not been elucidated. In this cross-sectional study, we tried to investigate the relationship between serum hepcidin and anemia in myeloperoxidase (MPO)-ANCA-AAV. Data of 64 newly diagnosed AAV patients who did not have kidney dysfunction or hemorrhage were analyzed. Serum hepcidin was measured with enzyme linked immunosorbent assay. Twenty-three of 64 patients had anemia. Compared with patients without anemia, patients with anemia had higher Birmingham vasculitis activity score [10 (3, 23) vs. 5 (3, 17), $p=0.020$], lower levels of serum iron (5.83 ± 1.63 vs. 9.76 ± 1.54, $p<0.001$) and higher levels of ferrtin [358.00 (59.85, 1314.10) vs. 151.05 (43.00, 645.30), $p=0.006$]. All 64 patients had increased levels of serum hepcidin compared with normal controls, while patients with anemia had higher serum hepcidin than patients without anemia (85.30 ± 16.92 ng/mL vs. 53.48 ± 13.32 ng/mL, $p<0.001$). In the multivariable analysis, the level of hemoglobin correlated with the levels of serum iron ($r=0.344$, $p=0.026$) and hepcidin ($r=-0.353$, $p=0.022$). Low level of serum iron was related to high level of serum hepcidin ($r=-0.472$, $p=0.001$). Immunosuppressive treatment induced rapid decrease of hepcidin and increase of serum iron on the 1st month, while the recovery of hemoglobin was relatively slow. This study indicated that in MPO-AAV without kidney dysfunction or hemorrhage, the existence of anemia is associated with high level of hepcidin which induces low serum iron and the abnormality of iron utilization.

Keywords Hepcidin · Anemia · Inflammation · Antineutrophil cytoplasmic antibody · Vasculitis

Introduction

Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) are characterized by positive serum ANCA and systemic symptoms [1, 2]. ANCA mainly recognize the myeloperoxidase (MPO) and proteinase 3 (PR3). Anemia is common in active AAV, however, the underlying mechanism of anemia in AAV is complicated. "Renal anemia" which is caused by absolute or relative deficiency of erythropoietin occurs when patients have rapidly progressive glomerular nephritis [3]. "Iron deficiency anemia" is found in patients who have pulmonary or digestive hemorrhage. However, anemia can also be detected in the patients without kidney dysfunction or hemorrhage. So there should be other factors influencing the occurrence of anemia in AAV.

Hepcidin is a 2.7 kDa low molecular weight protein which is very important in iron metabolism and in the pathogenesis of anemia. It is induced by interleukin (IL)-6 during infections or inflammatory diseases and then acts by binding to

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ferroportin, which is an iron exporter present on the absorptive surface of duodenal enterocytes, macrophages, and hepatocytes [4]. It is noteworthy that increased hepcidin can also be observed in patients with decreased estimated glomerular filtration rate (eGFR) [5, 6]. Recently, hepcidin has been reported to be negatively correlated with hemoglobin (Hb) and positively correlated with the clinical scoring system in active AAV [7]. However, although the anemia disappeared when patients got remission, no significant differences of serum hepcidin were found between patients with active AAV and patients in remission. We thought one of the reasonable explanations might be that the authors did not exclude the influence of kidney dysfunction in that study [7]. So whether high level of hepcidin is the reason for anemia in AAV has not been confirmed. In the current study, we tried to investigate the relationship between serum hepcidin and anemia of AAV without kidney dysfunction or hemorrhage.

Methods

Participants

Sixty-four patients (age ≥ 18 years, 26 male and 38 female) with MPO-ANCA positive AAV between January 2013 and August 2018 in the Tianjin Medical University General Hosp

ital were enrolled. All the patients fulfilled the Chapel Hill Consensus Conference classification [8]. These patients were in active stage of AAV and did not receive any immunosuppressive therapy or blood purification therapy before admission. All patients enrolled were anti-MPO antibody positive because patients with positive anti-PR3 antibody were rare in our hospital. In the current study, the sample size was determined using the GPower program with 80% power and 95% confidence interval (effect size 0.5, allocation ratio 1/1.2). At least 15 patients were needed in anemia group and 18 patients were needed in non-anemia group for achieving at least 80% power. Therefore, at least 33 patients were needed in this study. At last, 64 consecutive adult patients were enrolled in this retrospective study. Exclusion criteria were coexistence of kidney dysfunction [estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m^2], hemorrhage, systemic lupus erythematosus or other autoimmune diseases, hematologic diseases, diabetes, tuberculosis, hepatitis, cirrhosis, pregnancy, malignancy, infection at onset of the disease, or positive antiglomerular basement membrane antibody. For the measurement of hepcidin and IL-6, 18 samples of normal blood were collected to establish the normal cut-off values. All these normal samples were obtained from 18 people who did physical examination in our hospital in 2018 (normal group). To exclude the influence of the age and sex, the mean age of normal controls was set to be 65 ± 10.5 years and the ratio of male and female was set to be 8 /10. All controls had been demonstrated to be healthy before the selection.

Clinical and laboratory information

Clinical and laboratory data were collected as follows: gender, age (years), time from onset (days), with/without weight loss, with/without fever, organs involvement (with/without), Birmingham Vasculitis Activity Score (BVAS) [9], Hb (g/L), mean corpuscular volume (MCV, fL), mean corpuscular hemoglobin (MCH, pg), mean corpuscular hemoglobin concentration (MCHC, g/L), ferrtin (ng/mL), white blood cell (WBC, 10^9/L), platelet (PLT, 10^9/L), Hematuria (red blood cell/μL), proteinuria (mg/24 h), serum creatinine (μmol/L), albumin (Alb, g/L), erythrocyte sedimentation rate (ESR, mm/h), ANCA level (Ru/mL), C-reactive protein (CRP, mg/dL), complement 3 (C3, mg/dL), complement 4 (C4, mg/dL), rheumatoid factor (RF) elevation (with/without), ferrtin (ng/mL), serum iron (μmol/L). Anemia was defined as Hb < 120 g/L for male and Hb < 110 g/L for female.

Measurement of hepcidin and IL-6

The assays for the quantification of hepcidin and IL-6 in human serum were done with enzyme linked immunosorbent assay kits (catalog DHP250 and D6050; R&D Systems). Serum hepcidin and IL-6 were also measured for 18 normal controls to establish the normal cut-off values (mean + 2 standard deviation).

Statistical analyses

Differences of quantitative parameters between two groups were assessed using the t test (for data that were normally distributed) or nonparametric test (Mann–Whitney *U* test, for data that were not normally distributed). Differences of quantitative parameters among three groups were assessed using one-way ANOVA test (for data that were normally distributed) or nonparametric test (for data that were not normally distributed). Significance was considered when *p* values was lower than 0.05. The software SPSS, version 19.0 for Windows (IBM, Chicago, IL, USA), was used for statistical analysis.

Results

Patients with anemia had more active disease than patients without anemia

Among all 64 patients, 23 patients had anemia on admission (anemia group, with the average Hb 95.91 ± 10.43 g/L),

while the other 41 patients did not have anemia (non-anemia group, with the average Hb 131.88 ± 11.99 g/L). Comparison of all clinical and laboratory parameters between patients with and without anemia were shown in Table 1. The activity of AAV (BVAS) of patients with anemia was significantly higher than that of patients without anemia [10 (3, 23) vs. 5 (3, 17), $p = 0.020$]. The mean corpuscular volume (MCV) in patients with anemia was smaller than that in patients without anemia, but the difference was not significant ($p = 0.186$). Compared with patients without anemia, patients with anemia had lower levels of Alb ($p < 0.001$) and serum iron ($p < 0.001$), higher levels of PLT ($p = 0.040$), ESR ($p < 0.001$), CRP ($p < 0.001$) and ferrtin ($p = 0.006$). There were no differences of other laboratory parameters between patients with and without anemia.

Patients with anemia had higher levels of serum hepcidin than patients without anemia

Compared with normal controls, all 64 patients had increased levels of serum hepcidin, while patients with anemia had higher levels of serum hepcidin than patients without anemia (85.30 ± 16.92 ng/mL vs. 53.48 ± 13.32 ng/mL, $p < 0.001$). Similar to the results of hepcidin, patients with anemia had higher levels of serum IL-6 than patients without anemia (51.47 ± 14.83 pg/mL vs. 32.83 ± 14.52 pg/mL, $p < 0.001$), but there was some overlap of the serum IL-6 between patients and normal controls, especially for patients without anemia (Fig. 1).

In the univariate correlation analysis, the level of Hb positively correlated with the level of Alb and serum iron, and negatively correlated with the level of BVAS, PLT, proteinuria, ESR, CRP, ferrtin, IL-6 and hepcidin. In the multivariable analysis that included all the above mentioned parameters, the level of Hb still correlated with the levels of serum iron ($r = 0.344$, $p = 0.026$) and hepcidin ($r = -0.353$, $p = 0.022$), but did not correlated with other parameters (Table 2).

Low serum iron was related to high serum hepcidin

Among all 23 patients who had anemia, 13 had decreased serum iron (< 5.4 μmol/L), while no one of 41 patients who did not have anemia had decreased serum iron ($p < 0.001$). Serum iron correlated with the level of Alb ($r = 0.583$, $p < 0.001$), Hb ($r = 0.860$, $p < 0.001$), BVAS ($r = -0.335$, $p = 0.007$), ESR ($r = -0.635$, $p <= 0.001$), CRP ($r = -0.544$, $p < 0.001$), ferrtin ($r = -0.518$, $p < 0.001$), IL-6 ($r = -0.671$, $p < 0.001$) and hepcidin ($r = -0.782$, $p < 0.001$) in the univariate correlation analysis. In the multivariable analysis,

Table 1 Comparison of the clinical and laboratory parameters between patients with and without anemia

	Patients with anemia (23)	Patients without anemia (41)	*p* value
Age (years)	67.04 ± 14.51	64.95 ± 9.70	0.541
Sex (male/female)	7/16	19/22	0.291
Time from onset (days)	45 (14, 90)	60 (30, 90)	0.532
BVAS	10 (3, 23)	5 (3, 17)	0.020
eGFR (mL/min/1.73 m^2)	93.68 ± 34.67	102.08 ± 26.70	0.283
Hemoturia (RBC/μL)	3.00 (1.00, 359.20)	7.20 (1.00, 329.50)	0.511
Proteinuria (mg/24 h)	223.20 (45.00, 4671.30)	113.50 (11.50, 900.00)	0.073
MCV (fL)	89.25 ± 6.78	91.60 ± 4.78	0.186
MCH (pg)	29.65 ± 2.56	30.07 ± 1.70	0.591
MCHC (g/L)	332.46 ± 14.85	328.60 ± 9.82	0.397
WBC (10^9/L)	9.06 (2.66, 20.16)	7.88 (3.51, 18.13)	0.520
PLT (10^9/L)	338.21 ± 148.40	267.63 ± 69.01	0.040
ESR (mm/h)	66 (27, 141)	33 (6, 62)	< 0.001
Alb (g/L)	29.65 ± 3.21	38.35 ± 6.07	< 0.001
Serum iron (μmol/L)	5.83 ± 1.63	9.76 ± 1.54	< 0.001
Ferrtin (ng/mL)	358.00 (59.85, 1314.10)	151.05 (43.00, 645.30)	0.006
CRP (mg/dL)	7.46 (0.25, 18.10)	1.44 (0.10, 18.70)	< 0.001
ANCA level (Ru/mL)	106.00 (21.10, 238.02)	76.00 (22.43, 289.11)	0.226
C3 (mg/dL)	105.35 ± 24.49	104.04 ± 22.73	0.844
C4 (mg/dL)	24.58 ± 7.27	24.85 ± 7.22	0.903

Alb albumin, *ANCA* antineutrophil cytoplasmic antibodies, *BVAS* Birmingham vasculitis activity score, *C3* complement 3, *C4* complement 4, *CRP* C-reactive protein, *eGFR* estimated glomerular filtration rate, *ESR* erythrocyte sedimentation rate, *Hb* hemoglobin, *MCH* mean corpuscular hemoglobin, *MCHC* mean corpuscular hemoglobin concentration, *MCV* mean corpuscular volume, *PLT* platelet, *RBC* red blood cell, *WBC* white blood cell

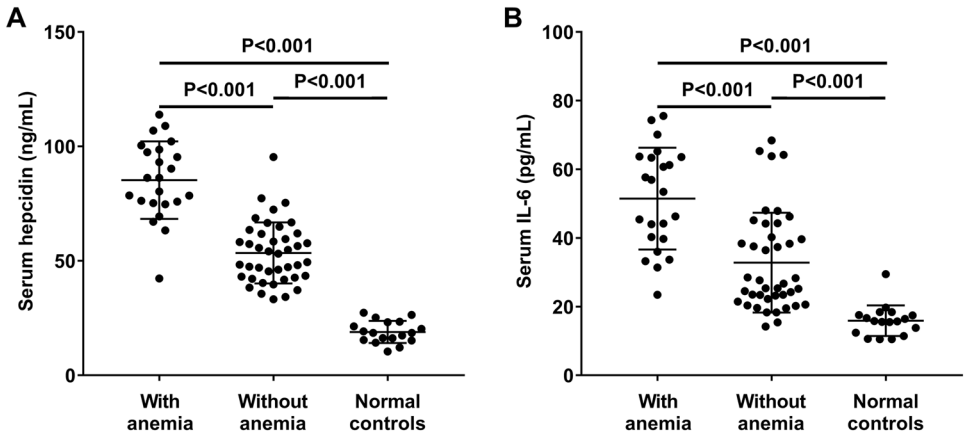

Fig. 1 Comparison of the serum hepcidin and IL-6 among 23 patients with anemia, 41 patients without anemia and 18 normal controls. Compared with normal controls, all patients had increased levels of serum hepcidin, while patients with anemia had higher levels of serum hepcidin than patients without anemia (**a**). Patients with anemia also had higher levels of serum IL-6 than patients without anemia (**b**)

Table 2 Correlation analysis of the relationship between hemoglobin and other parameters

	Univariate analysis			Multivariate analysis		
	R value	*p* value	95% confidence interval	*R* value	*p* value	95% confidence interval
BVAS	− 0.350	0.005	− 0.542 to − 0.111	0.102	0.519	− 0.238 to 0.397
PLT (10^9/L)	− 0.325	0.009	− 0.562 to − 0.059	0.012	0.939	− 0.246 to 0.305
Proteinuria (mg/24 h)	− 0.275	0.035	− 0.421 to − 0.115	− 0.106	0.503	− 0.321 to 0.178
Alb (g/L)	0.615	< 0.001	0.503 to 0.728	0.274	0.079	− 0.048 to 0.530
ESR (mm/h)	− 0.677	< 0.001	− 0.787 to − 0.531	− 0.275	0.078	− 0.504 to − 0.014
CRP (mg/dL)	− 0.529	< 0.001	− 0.662 to − 0.363	0.071	0.657	− 0.199 to 0.295
Ferrtin (ng/mL)	− 0.423	< 0.001	− 0.632 to − 0.187	0.132	0.405	− 0.205 to 0.472
Serum iron (μmol/L)	0.860	< 0.001	0.809 to 0.905	0.344	0.026	0.041 to 0.543
IL-6 (pg/mL)	− 0.632	< 0.001	− 0.758 to − 0.460	− 0.079	0.617	− 0.449 to 0.287
Hepcidin (ng/mL)	− 0.769	< 0.001	− 0.849 to − 0.664	− 0.353	0.022	− 0.603 to 0.002

Alb albumin, *BVAS* Birmingham vasculitis activity score, *CRP* C-reactive protein, *ESR* erythrocyte sedimentation rate, *PLT* platelet

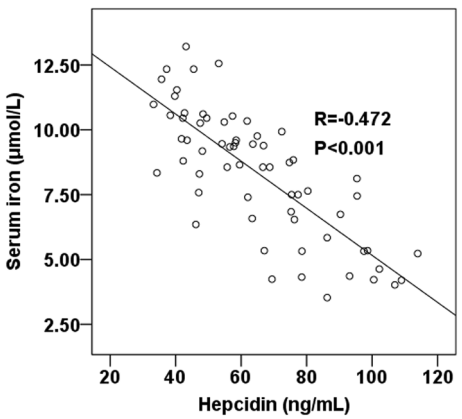

Fig. 2 Correlation between serum iron and serum hepcidin for all patients in active AAV. In the multivariable analysis, serum iron negatively correlated with the hepcidin

serum iron only correlated with Hb ($r = 0.377$, $p = 0.008$) and hepcidin ($r = -0.472$, $p = 0.001$) (Fig. 2).

Serum hepcidin recovered faster than Hb after immunosuppressive therapy

All patients received corticosteroid combined with immunosuppressive treatment. No patients were treated with commercial erythropoietin or iron supplement. Remission was defined by the absence of clinical activity (BVAS = 0). After treatment, 10 out of 23 patients who had anemia were followed up for at least 3 months. Among these 10 patients, 6 patients got complete remission within 1 month, while the other 4 patients got complete remission within 3 months. As shown in Fig. 3, the serum levels of both IL-6 and hepcidin decreased significantly on the 1st month for all 10 patients no matter whether complete remissions were achieved or not, while the serum iron increased significantly on the 1st month for all 10 patients no matter whether complete remissions were achieved or not. There was no obvious change of the levels of IL-6, hepcidin and serum iron from the 1st month to the 3rd month. The recovery of Hb was relatively slow. There was only s slight improvement of Hb on the 1st month, while

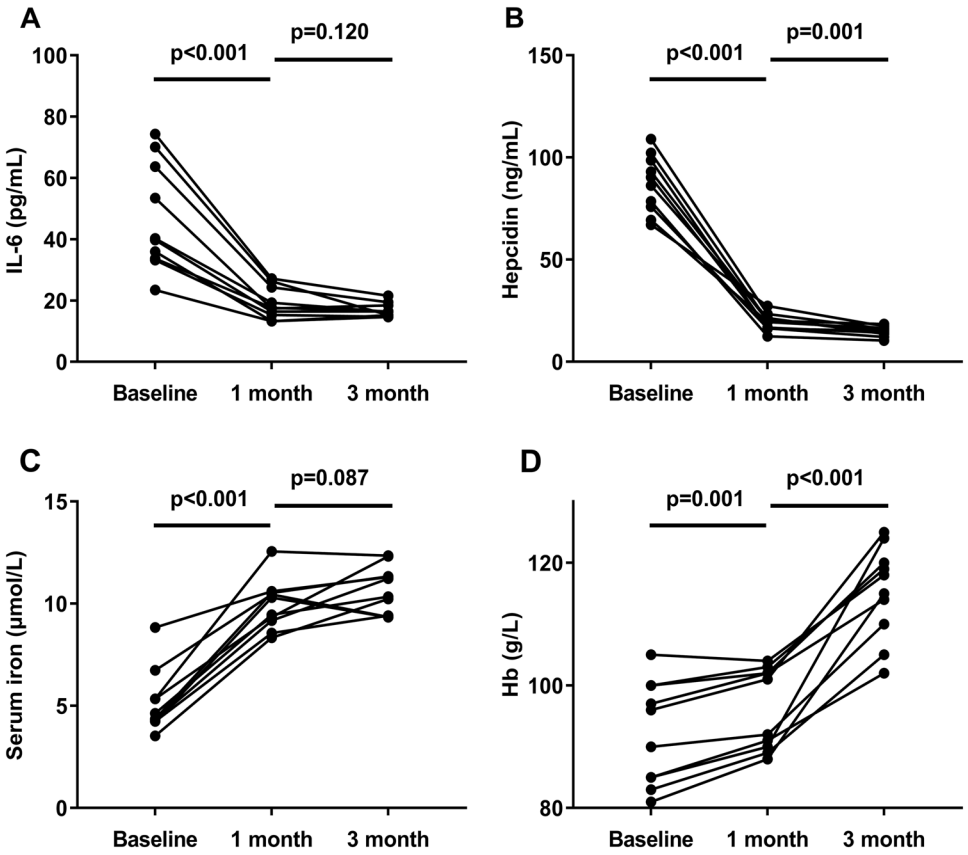

Fig. 3 Changes of IL-6 (**a**), hepcidin (**b**), serum iron (**c**) and Hb (**d**) at different time points for 10 patients who had anemia and were followed-up. Ten out of 23 patients who had anemia were followed up after treatment for 3 months. The serum levels of both IL-6 and hepcidin decreased significantly on the 1st month, while the serum iron increased significantly on the 1st month. There was only s slight improvement of Hb on the 1st month

the Hb returned gradually to near normal level on the 3rd month.

Discussion

Hepcidin was initially identified as a peptide with antimicrobial properties [10, 11]. It contributes in the defense against extracellular infection by reducing serum iron levels, as iron availability is necessary for bacterial growth and enhances oxidative stress. Then hepcidin was proved to be a key regulator of iron homeostasis in the pathogenesis of anemia in chronic disease [12, 13]. Previous studies demonstrated an IL-6-induced increase of hepcidin expression through a complex of the IL-6 receptor and gp130 dependence manner [14–16]. Consistent with these studies, we found serum IL-6 increased in active AAV [17–19]. We also found higher IL-6 levels in the patients with anemia compared with patients who did not have anemia. Besides IL-6, there were higher levels of ferritin, CRP, BVAS and ESR in patients with anemia. This suggested that the patients with higher hepcidin levels also had higher inflammatory burden. Interestingly, no differences of the serum C3 and C4 were found between two groups. In the pathogenesis of AAV, the activation of complement system is considered to be more important than the inflammatory level because the activation of alternative complement system is closely associated with the injury of kidney. So we speculate that the existence of anemia in AAV is caused by high level of inflammation and might not be related to the status of complement system.

Increased hepcidin level is related to decreased iron bioavailability. In the current study, patients with anemia had high serum hepcidin, low serum iron and high serum ferritin. Ferritin level is a good indicator of iron stores. In iron deficiency anemia, ferritin is always lower than normal level, while its level may increase irrespective of iron stores in many chronic diseases [20–23]. In the current study, the levels of ferritin of patients with anemia were higher than that of patients without anemia. This should be interpreted as the increased synthesis of ferritin in AAV. Although the difference was not significant, the MCV in patients with anemia was smaller than that in patients without anemia. This also indicated the anemia of the patients might be caused by the abnormality of iron utilization.

The outcome of AAV is very poor without an effective therapy. The mechanism of anemia is multifactorial in AAV because of the complicated pathogenesis of AAV. Patients with chronic kidney dysfunction have renal anemia caused by deficiency of erythropoietin. Anemia caused by blood loss is another interference factor which should be ruled out when investigating the anemia of AAV because hemorrhage may lead to absolute iron deficiency. This study

demonstrated that high serum hepcidin was the main cause of anemia in AAV with normal kidney function and no bleeding, and high level of hepcidin was associated with high level of inflammation. In remission stage, the recovery of hepcidin was earlier than that of hemoglobin. Since the measurement of serum hepcidin is feasible in clinical work, the recovery of anemia after treatment can be predicted by detecting the change of serum hepcidin level.

Treatment of AAV consists of the induction of remission followed by maintenance therapy. Anemia has been demonstrated to be associated with a poor prognosis in many diseases. However, we did not found any influence of anemia on the prognosis because all patients got remission within 3 months in our study. Longer follow-up might be needed to draw a conclusion. Serum hepcidin can be influenced by the application of erythropoietin or iron supplement. To avoid the interference of the serum hepcidin, all patients in this study did not receive erythropoietin or iron treatment. We found the serum hepcidin recovered faster than Hb after immunosuppressive therapy. The serum levels of both IL-6 and hepcidin decreased significantly in all patients on the 1st month no matter whether BVAS had got 0 or not. This result was contrary to the study of Přikryl et al. in which no significant differences of serum hepcidin were found between patients with active AAV and remission [7]. A reasonable explanation should be that we did not included patients with kidney dysfunction. Patients with decreased eGFR, especially the patients who are dialysis-dependent, are usually accompanied by increased inflammation levels and serum hepcidin. Although it is still unclear whether kidney function is independently associated with serum hepcidin level, the small molecular size of hepcidin suggests that renal clearance may be a major pathway of its elimination.

Study limitations

The main drawback of this study is the small sample. To avoid the influence of kidney dysfunction or hemorrhage on the serum hepcidin, only patients with relatively moderate disease were enrolled. Study with larger sample size is needed in future. Besides, lacking of the results of bone marrow puncture was another drawback for judging the iron metabolism exactly.

Conclusions

Anemia in MPO-AAV without kidney dysfunction or hemorrhage is a kind of anemia of chronic disease. The existence of anemia is associated with high level of hepcidin which induces low serum iron and the abnormality of iron utilization.

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Author contributions CT: data collection and manuscript writing. XPC: study design, interpretation of data, manuscript writing. HSY: study design, statistical analysis and interpretation of data. GS: data collection, manuscript writing/approval. JJY: statistical analysis, manuscript writing/approval. YTK: study design and data collection. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interests. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Ethics approval and consent to participate Written informed consent to participate in the study was acquired from all participants. The protocol was approved by the ethical committee of Tianjin Medical University General Hospital (IRB2013-001-01) and this research was in compliance of the declaration of Helsinki.

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