Zinc Protoporphyrin in Anemia of Chronic Disorders

By Jan Hastka, Jean-Jacques Lasserre, Andreas Schwarzbeck, Manfred Strauch, and Rüdiger Heilmann

Hematofluorometric determination of zinc protoporphyrin (ZPP) is a screening method for the assessment of iron deficiency (ID). Chronic disorders are frequently accompanied by anemias of unclear origin, most probably caused by an impairment of iron metabolism. We investigated the relevance of ZPP for the detection of derangements of iron metabolism in anemias of chronic disorders (ACD). In 19 patients with ACD caused by chronic inflammatory non-neoplastic diseases, ZPP was determined and correlated with ferritin, transferrin saturation, and hemoglobin (Hb). Marrow sideroblast counts and semiquantitative grading of the marrow hemosiderin were performed in all patients to exclude ID and to show the decreased iron bioavailability. In all ACD patients who exhibited the typical laboratory findings of disturbed iron metabolism, such as hypocellularity, decreased transferrin saturation, decreased bone marrow sideroblasts, and increased marrow hemosiderin, strongly elevated ZPP levels were found (131 ± 23 μmol/mol heme). ZPP returned to normal after successful treatment of the underlying disease. This is shown in three patients with polymyalgia rheumatica. We conclude that the fluorometric determination of ZPP allows detection and quantification of derangements of iron metabolism associated with chronic inflammatory disorders. By recording the derangements quantitatively, ZPP allows monitoring of therapy of chronic inflammatory diseases. © 1993 by The American Society of Hematology.

MATERIALS AND METHODS

The study was performed during 1988 to 1991 in the III. Med. Klinik and the Department of Nephrology in Mannheim. Nineteen anemic patients suffering from different chronic inflammatory disorders were examined. The group included patients with rheumatoid arthritis (n = 9), polymyalgia rheumatica (n = 3), polymyositis (n = 1), lupus erythematosus (n = 1), tuberculosis (n = 3), sarcoidosis (n = 1), and subacute infective endocarditis (n = 1). Only patients with typical anemias of chronic disorders (ACD)-criteria were included: serum iron level <10.7 μmol/L, transferrin saturation <25%, sideroblast count <30%, bone marrow hemosiderin >2 (6-point scale, 2 = normal). Exclusion criteria were iron deficiency, hemoglobin ≥10 g/dL, and blood transfusion within the last 4 months.

In all patients ZPP, hemoglobin (Hb), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), and serum levels of iron, ferritin, and transferrin were determined. The transferrin saturation (normal value 25% to 50%) was calculated. Iron levels (normal value 10.7 to 32.2 μmol/L) were determined with a multianalysis instrument (SMAC II, Technicon, Tarrytown, NY), transferrin (normal value 2 to 4 g/L) and C-reactive protein (CRP) (normal value <0.5 mg/L) by nephelometry and ferritin (normal value 34 to 310 μg/L for men and 25 to 210 μg/L for women) by enzyme-linked immunosorbent assay. Hb (normal value >13 g/dL for men and >12 g/dL for women), MCV (normal value 80 to 96 fl), and MCH (normal value 28 to 34 pg) were measured using an automatic cell counter (Model CC-180; Sysmex, Kobe, Japan). Erythrocyte sedimentation rate (ESR) (normal value <8/18 mm for men, <11/20 mm for women) was measured by the Westergren method, urinary excretion of the 6-aminoacuvinic acid (ß-ALAS) (normal value <5.5 mg/day) by ion-exchange chromatography.

Bone marrow aspirates were obtained from the sternum or the posterior iliac crest. For the iron examination the aspirates were stained by the Prussian blue reaction and counterstained with hematoxylin. The RBC precursors were evaluated for the presence of iron granulas. Sideroblast count was determined in percent of erythroblasts (normal value 30% to 50%). The iron stores were assessed by a semiquantitative estimation of storage iron, according to a 6-point scale (0 = iron absent; 1 = iron decreased; 2 = normal amount of iron; 3 = iron increased; 4 = iron markedly increased; 5 = iron massively increased).

Blood samples for ZPP measurement were obtained by venipuncture and anticoagulated with EDTA. Measurements were performed
within 2 days of blood sampling. Samples that were not examined on the same day were stored in the refrigerator at 4°C.

ZPP was measured with the Aviv front-face hematofluorometer (Aviv Biomedical Company, Lakewood, NJ). The ZPP measurements were performed with washed erythrocytes; the methodologic details have been described elsewhere.5 Approval was obtained from the Institutional Review Board for these studies. Informed consent was provided according to the Declaration of Helsinki.

RESULTS

Table 1 summarizes the parameters of iron metabolism in the 19 ACD patients analyzed. The mean ZPP was markedly increased (131 ± 23 μmol/mol heme, range 92 to 180 μmol/mol heme). The mean and the SD of Hb, MCV, and MCH were 8.9 ± 0.6 g/dL, 84.6 ± 3.7 fl, and 27.9 ± 1.3 pg, respectively. Serum iron (x̄ = 3.4 ± 1.1 μmol/L), transferrin (x̄ = 178 ± 24 mg/dL) and transferrin saturation (x̄ = 15.2% ± 3.8%) were decreased. The sideroblast counts were decreased in all patients (x̄ = 11.5% ± 3.8%; range 6% to 16%) and ferritin levels were markedly elevated (x̄ = 642 ± 212 μg/L). Also, the storage iron in the bone marrow was increased to grade 3 in 8 patients and grade 4 in 11 patients. Urinary excretion of the δ-ALS was within the normal range in all patients (x̄ = 2.8 ± 1.2 mg/die; range 1.1 to 5.2 mg/die), which excluded hepatic porphyria and lead poisoning.

All of these parameters, including ZPP, returned to normal on successful treatment of the underlying chronic inflammatory disease. This is illustrated by three patients with polymyalgia rheumatica and ACD who showed a complete recovery after therapy (Table 2).

The clinical course of one of these three patients (patient no. 1) is described in the following in detail, to demonstrate the practical value of ZPP in treatment of chronic inflammatory diseases. Patient no. 1. A 55-year-old woman presented with severe ACD in the course of a polymyalgia rheumatica. Treatment with 100 mg prednisone led to a continuous increase of Hb, which was accompanied by a decrease of ESR, ferritin, storage iron in the bone marrow, and ZPP and by an increase of transferrin saturation. With a gradual reduction of the prednisone dose to 60 mg, symptoms reappeared, whereas the ZPP was persisting at about 100 μmol/mol heme. An increase of the prednisone dose led to a disappearance of symptoms and a further decrease of ZPP. Other parameters, such as ESR, CRP, Hb, ferritin or transferrin saturation, were not sufficiently sensitive to reflect quick changes of disease activity. An episode of acute angina tonsillaris (days 60 to 70) led to another increase of ESR and CRP; ZPP was not influenced. After the angina subsided, ESR and CRP returned to normal (with the same prednisone dose). Because of stomach trouble, the patient was treated additionally with azathioprine, and the prednisone dose was reduced. Six months later the patient had completely recovered (Hb 16.0 g/dL, ZPP 37 μmol/mol heme, ESR 7/23, CRP 4 mg/L, Fe 11 μmol/L, ferritin saturation 29%, ferritin 25 μg/L).

DISCUSSION

Up to now, a complicated procedure was necessary to diagnose iron derangements in ACD. In addition to the commonly used "iron parameters," such as ferritin, serum iron, and saturation of transferrin, an examination of Prussian blue-stained marrow smears, including the estimation of storage iron and evaluation of the sideroblast count, had to be performed. Thus, the diagnosis was invasive, rather expensive, and required a hematologist. In spite of this extensive diagnostic workup, only severe ACD cases could be detected and a quantification was not possible. Therefore, the ACD diagnosis in most cases was not really proven but only postulated.

The determination of ZPP is a simple screening procedure for the detection of iron deficiency.17,21,27,28 In our present

### Table 1. Parameters of Iron Metabolism in 19 ACD Patients

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Abbreviations: Fe, serum iron; Fer, ferritin; Sat, saturation of transferrin; SBC, sideroblast count; BM, bone marrow hemosiderin.
study, we demonstrate that ZPP can further be applied to
detect and describe the pathophysiologic defect, ie, impaired
iron bioavailability underlying the anemia of chronic inflam-
matory disorders.

The 19 patients with chronic inflammatory diseases in our
study showed anemias that were accompanied by hypofer-
remia, decreased saturation of transferrin, increased ferritin
levels, and increased storage iron in the bone marrow. The
inadequate supply of iron to the erythroid marrow in spite
of increased hemosiderin was reflected by a decreased count
of sideroblasts. These derangements of iron metabolism,
which prove an impaired iron bioavailability, are the typical
findings in ACD, as first described by Cartwright and Lee.3

As a consequence of the impaired iron supply for the
eythropoiesis, all our ACD patients showed markedly in-
creased ZPP levels despite the increased bone marrow he-
obosiderin. These results demonstrate that the increased in-
corporation of zinc into protoporphyrin IX is independent of
the cause of the impaired iron supply, because any dis-
turbance in the iron metabolism ultimately leads to a de-
creased production of Hb and an increase of ZPP. The path-
way that leads to the production of ZPP instead of heme in
the case of iron deficiency works also in the presence of
the impaired iron bioavailability in ACD. By this means, ZPP
determination allows the rapid detection and quantification
of derangements of iron metabolism in chronic inflammatory
disorders.

ZPP is not a simple parameter of iron deficiency but rather a
screening parameter of iron deficient erythropoiesis, sur-
veying all steps of the iron metabolism from iron uptake to
its utilization. Thus, the ZPP determination can serve as a
kind of "end point control" of the whole iron metabolism, which
detects real iron deficiency as well as derangements of
iron metabolism in chronic inflammatory and neoplastic
diseases,30 in sideroblastic disorders, eg, myelodysplasias,31
or after lead poisoning22-26 (Fig 1). The only possible source
of error recognized so far seems to be the congenital eryth-
ropoietic porphyria and the protoporphyria caused by the
fact that free erythrocyte porphyrin is fluorescent at a wave-
length closely related to the wavelength of ZPP, resulting in
measurement of falsely high ZPP levels in the test system
reported so far.32-35 The only possible source of error recog-
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ria and the protoporphyria caused by the fact that free erytro-
cyte porphyrin is fluorescent at a wavelength closely related
to the wavelength of ZPP, resulting in measurement of falsely
high ZPP levels in the test system used.30 However, these
tremely rare diseases do not play a significant role in clinical
practice and can easily be excluded by typical signs in patient
history and laboratory findings.

Whereas lead-intoxicated patients show the most increased
ZPP levels, up to 1,000 μmol/mol heme,32-35 the values ob-
served in chronic inflammatory disorders are less increased
and, even in the most severe cases, range below 200 μmol/
mol heme. In patients with myelodysplastic syndromes we
observed even in refractory anemia with ring sideroblasts

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<th>MCV fl</th>
<th>MCH pg</th>
<th>Fe μmol/L</th>
<th>Fer μg/L</th>
<th>Sat %</th>
<th>ESR mm</th>
<th>CRP mg/L</th>
<th>SBC %</th>
<th>Pre mg</th>
<th>Aza mg</th>
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Abbreviations: Pre, prednisone; Aza, azathioprine; ND, not determined.
ZINC PROTOPORPHYRIN IN ACD

levels below 80 amol/mol heme.\(^{31}\) The different ZPP levels measured in the different sideroachrestic anemias indicate that the derangements of iron metabolism are probably induced by different pathomechanisms. Thus, ZPP could be a tool to classify the sideroachrestic anemias according to the degree of ZPP synthesis. The significance of such classification requires further study.

In chronic inflammatory disorders, the degree of the disturbances of iron metabolism depends on the severity and activity of the underlying disease. By recording these disturbances quantitatively through ZPP determinations, chronic diseases and their response to therapy can be monitored inexpensively, quickly, andatraumatically. The normalization of the iron metabolism after a successful therapy of the underlying disease is accompanied by a normalization of ZPP. This may be of clinical relevance in patients with chronic inflammatory diseases such as polymyalgia rheumatica or rheumatoid arthritis as well as in patients with chronic infectious diseases such as tuberculosis.

It was reported recently that ZPP has a moderate inhibitory effect on the in vitro erythropoiesis.\(^{33,38}\) After addition of ZPP a decrease in bone marrow erythroid colony-forming units and erythroid burst-forming units growth has been observed. This could be an additional effect in the multifactorial pathogenesis of the hematopoietic disturbances in ACD. The possible aim of this effect could be the reduction of the iron deficient erythropoiesis by a self-limiting feedback mechanism.

In contrast to conventional inflammatory parameters, such as ESR or CRP, ZPP values are not influenced by acute inflammations. In patients with acute inflammatory diseases, such as bronchitis, influenzal infections, pneumonia, meningitis, enteritis, angina tonsillaris, and erysipelas without iron deficiency, normal ZPP levels were measured.\(^{39}\)

We suggest that the ZPP determination can be used in routine practice as a simple method to detect and quantify derangements of iron metabolism in chronic inflammatory disorders.

**Fig 1.** ZPP as a screening parameter of the iron metabolism. Normal ZPP values (<40 amol/mol heme) exclude an iron-deficient erythropoiesis; the iron metabolism is intact. Increased ZPP indicates an iron-deficient erythropoiesis, which can be caused by different pathogenetic mechanisms, as illustrated by the arrows. ZPP detects real iron deficiency as well as derangements of iron metabolism with impaired iron availability caused by chronic inflammatory diseases, myelodysplasias, or lead poisoning.

**REFERENCES**

34. Lamola AA, Yamane T: Zinc protoporphyrin in the erythrocytes of patients with lead intoxication and iron deficiency anemia. Science 186:936, 1974
Zinc protoporphyrin in anemia of chronic disorders

J Hastka, JJ Lasserre, A Schwarzbeck, M Strauch and R Hehlmann