Survey of patients with iron deficiency anemia in haematology outpatient clinic

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Abstract

Background: Iron deficiency anaemia (IDA) is the most prevalent type of anaemia and a common cause for patient referrals to the haematology outpatient clinic. The aim of this study was to determine the number of patients with IDA treated at the Haematology Outpatient Clinic of the UMC Ljubljana in the period of two years, as well as to inquire into the causes for their referrals to the clinic, patient characteristics, their complete blood count results at initial examination, the prescribed therapy, the number and the causes of their follow-up visits. We draw special attention to the IDA onset mechanism, the microcytic anaemia therapy principles and the indications prompting a referral of an IDA patient to the haematology specialist.

Methods: We undertook a retrospective analysis of the medical records of patients who were referred to the Haematology outpatient clinic of the UMC Ljubljana for examination in the two-year period between 1 January 2014 and 31 December 2015 and had been diagnosed with IDA on the basis of their clinical picture and their CBC values. Data were collected with the Hipokrat IT system and statistically evaluated with Microsoft Excel.

Results: In the period relevant for our research, 277 patients of those who were referred to the Haematology outpatient clinic for medical examination were diagnosed with IDA. 11.6 % of these patients were male and 88.4 % female; 62.1 % of the female patients were of childbearing age. IDA was specified as the referral diagnosis in the cases of no more than 39 % of the patients referred to the specialist outpatient clinic, whilst the medical condition of the remaining percentage of patients was not identified by the referring doctor. Comorbidities were observed in 50.2 % of the patients, and for 62.5 % of the patients a follow-up appointment was scheduled by the treating haematologist. Of all patients, 63.5 % were treated with an intravenous iron preparation during their first examination at the outpatient clinic and a transfusion of erythrocytes was administered during such an examination to 4.3 % of the patients.

Conclusion: Patients with IDA were often treated at our Haematology Outpatient Clinic in the relevant two-year period. The data indicates a poor recognition rate of this prevalent type of anaemia. IDA is not a blood disorder and the referral of IDA patients to the Haematology Outpatient Clinic is justified in the case of severe microcytic anaemia, when the patient does not respond to the oral or intravenous iron replacement therapy or if a concomitant change in the CBC persists despite the effective treatment with iron preparations.

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1. Introduction

Iron-deficiency anemia (IDA) is the only anaemia that affects the wealthy and the poor alike. In the developed world it is more common in women of childbearing age with heavy menstrual bleeding (1). Its prevalence is higher in individuals taking non-steroid antirheumatic drugs and proton pump inhibitors, in the latter most probably because of ulcer disease and decreased gastric juice acidity (2). Inadequate nutrition only rarely causes iron-deficiency anaemia (IDA) in the developed world. However, it may occur in individuals following weird diets (1).The causes of IDA can be most bizarre: e.g. this form of anaemia is encountered in people with Munchausen syndrome (3). In the developing countries, it affects mostly children, adolescents and pregnant women as a result of inadequate nutrition and parasitic infections (1). In men and menopausal women diagnosed with IDA, the first step should be ruling out gastrointestinal cancer (4). Treating IDA patients with iron supplements is only a symptomatic measure. It is of key importance to discover and eliminate the cause of the disease. The paper reviews the results obtained over a two-year period for patients referred to the outpatient clinic of the Department of Haematology with the diagnosis of IDA and patients diagnosed with IDA on the basis of history, clinical and laboratory findings. The paper focuses on the recognition of IDA, identification of its causes, oral and intravenous iron supplementation and management of patients who fail to respond adequately to iron supplementation.

2. Material and methods

This retrospective analysis includes the records of 277 patients with the diagnosis of IDA referred to the outpatient clinic of the Department of Haematology between 1 January 2014 and 31 December 2015, including the patients who were diagnosed with IDA on the basis of clinical examination and laboratory tests done in the heamatology clinic. The analysis focused on patient age and gender, referral diagnosis, presence of symptoms and signs of anaemia, haemoglobin levels, erythrocyte levels, mean corpuscular volume (MCV), total iron binding capacity (TIBC), serum ferritin, concomitant blood changes and the presence of menopause in women. In addition, the associated chronic diseases and inflammations that could have led to the onset of anaemia of chronic disease were recorded. The data collected included the patient's comorbidities, inflammatory parameters, urea, uric acid and creatinine levels and liver enzymes. The number of patients scheduled for follow-up examination at the haematology outpatient clinic, the reason for control examination, the treatment modallity prescribed by the patient's GP prior to his/her attendance at the clinic, and the therapy was prescribed on the patient's first visit to the haematology outpatient clinic were also recorded. Table 1 presents the distribution of anaemias by haemoglobin levels. The data were collected using the Hipokrat computer-based information system and statistically evaluated with Microsoft Excel.

The following reference levels were used in the study:

- Haemoglobin 120–160 g/L for women and 130–180 g/L for men (5)
- Haematocrit 0.30–0.47 for women and 0.40–0.54 for men; MCV 82–98 fL; RBC $4{,}2–5{,}4 \times 10^{12}$/L for

women and 5,4–6,3 × 10^{12}/L for men; WBC 3.9–11.1 × 10^{9}/L; platelets 157–384 × 10^{9}/L (6).

- Serum iron:10.7–28.6 µmol/L; ferritin 10–120 µg/L for women and 20–300 µg/L for men; TIBC 44.8–80.6 µmol/L; increased CRP > 5 mg/L; creatinine 44–97 µmol/L; elevated AST 3-fold the upper limit (0.52 µkat/L) for women and 3-fold the upper limit (0.58 µkat/L) for men; increased ALT 3-fold the upper limit (0.56 µkat/L) for women and 3-fold the upper limit (0.74 µkat/L) for men (7).

The study was approved by the Medical Ethics Committee of the Republic of Slovenia on 14 Nov.2017 (no.0120–583/217/5).

Tabela 1: Razdelitev anemij glede na vrednost hemoglobina.

Type of anaemia	Hb levels
mild	100–120 g/L (women) 100–130 g/L (men)
moderate	70–100 g/L
severe	< 70 g/L

3. Results

The analysis included data for 277 patients seen for IDA at the outpatient clinic of the Department of Heamatology between 1 January 2014 and 31 December 2015. There were 32 men (11.6 %) and 245 women (88.4 %), of these 172 (62.1 %) were women of reproductive age and 73 (26.3 %) were menopausal women. The median age of men was 66.5 years (range 21–87 yrs) and the median age of women 44 years (range 18–94 yrs). Table 2 shows mean RBC parameters. The majority of the referred patients had Hb levels in the range of mild or moderate anaemia. In slightly less than one fifth of the examined patients, Hb levels were within reference range. Figure 1 indicates the classification of anaemias by Hb levels.

Other referral diagnoses included: sweating, monoclonal spike, malaise, monoclonal immunoglobulin of undetermined significance, suspected myelodysplastic syndrome (MDS), suspected thalassemia, pancytopenia, chronic anaemia, macrocytosis, B12 deficiency, peripheral neuropathy, suspected haemolytic anaemia, positive Coombs test, jaundice and others.

Twelve patients (4.3 %) were referred to the clinic for an urgent exmination.

Table 2: Mean RBC indices and iron levels

Laboratory parameters	Women	Men
Mean Hg levels (g/L)	100,5 (σ = ± 20,4)	101,5 (σ = ± 23,3)
Mean RBC count (10^{12}/L)	4,18 (σ = ± 0,62)	4,13 (σ = ± 0,95)
Mean serum iron levels (µmol/L)	8,3 (σ = ± 10,9)	
Mean ferritin levels (µg/L)	21,6 (σ = ± 70,5)	
Mean TIBC (µmol/L)	71,3 (σ = ± 10,6)	

TIBC –total iron binding capacity; σ- standard deviation (SD)

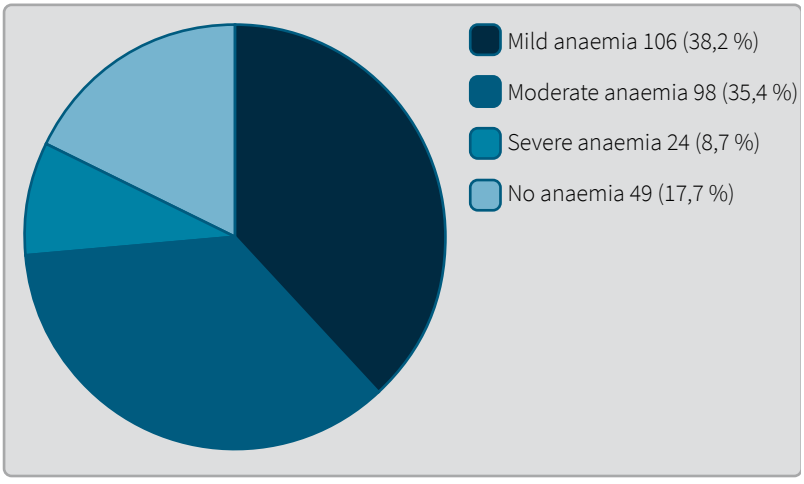

Figure 1: Classification of anaemias by Hb level. N = 277

One of these had mild, seven had moderate and six severe anemia.

On physical examination at the haematology outpatient clinic, pallor was the only sign of anaemia reported. It was documented in 145 (52.3 %) patients.

Table 4 shows that anaemia was frequently associated with other CBC changes.

Table 5 indicates that at least one concomitant condition was present in 139 referred patients (50.2 %).

Three or more associated diseases were diagnosed in 35 (12.6 %) patients with IDA.

In the group of patients with a history of chronic diseases, 54 (19.5 %) patients had increased CRP, five (1.8 %) showed abnormal liver transaminase levels, and one female patient had elevated urea and creatinine levels. ACD associated with IDA was diagnosed in four female patients (1.4 %).

A total of 173 (62.5 %) patients were scheduled for a follow-up appointment with the haematologist. Of these, 133 (48 %) attended for follow-up examination after iron supplementation. The haematologist ordered additional diagnostic procedures for IDA in 144 (52 %) cases.

One hundred and sixty-three (58.8 %) patients had been treated for IDA in the past or were taking iron supplements at their first appointment at the clinic. Oral iron supplements were taken by 144 (52 %) patients; 30 (10.8 %) were treated by intravenous iron supplementation and nine (3.2 %) patients by transfusion of red cell concentrate (RCC). For the rest of the patients no data are available. Of all the patients examined, 210 (75.8 %) received treatment or instructions for treatment. Of these 176 (83.9 %) were treated with intravenous iron preparations, and 12 (5.5 %) with transfusion of RCC. Nine (30 %) patients who were given intravenous iron supplement at their first visit to the outpatient clinic received repeat dose of intravenous iron when seen at the haematology outpatient clinic. Fourty-one (28.5 %) patients initially treated with oral iron supplements continued to take iron per os after their follow-up examination. At follow-up examination, nine (2.9 %) patients received a transfusion of RCC.

Table 3: shows the most common GP referral diagnoses of patients diagnosed with IDA at the heamatology outpatient clinic.

Referral diagnosis	n = 277 (%)
Iron-deficiency anaemia	108 (39)
Microcytic anaemia	77 (27,8)
Anaemia	30 (10,8)
Leukopenia	5 (1,8)
Thrombocytopenia	5 (1,8)
Iron deficiency	4 (1,4)
Bicytopenia	4 (1,4)
Normocytic anaemia	4 (1,4)
Other diagnoses	40 (14,6)

Table 4: Classification of anaemias by concomitant changes in CBC

Concomitant change in CBC	n = 277 (%)
Leukopenia	21 (7,6)
Leukocytosis	16 (5,8)
Thrombocytopenia	20 (7,2)
Thrombocytosis	46 (16,6)
Pancytopenia	4 (1,4)

4. Discussion

IDA is the most common anaemia and is not regarded as a true blood disorder. The study showed that 277 patients with IDA – i.e.2.7 patients per day – were treated at the Department of Haematology over a 2-year period. There was a predominance of women of reproductive age. The most likely reason for anaemia in this population is menstrual blood loss.

Absorption of iron is limited to 1 to 2 mg daily and most iron needed for erythropoiesis is provided through metabolic switch of macrophages that phagocytose senescent erythrocytes (1). In clinically significant iron deficiency, depletion of bodyiron stores is reflected in the blood by a decrease in serum ferritin levels (8). Depletion of iron stores leads to disturbances in haemoglobin synthesis and production of hypochromic microcytic erythrocytes in the bone marrow. As indicated by Figure 2, clinically significant forms of iron deficiency develop gradually.

Table 5: Comorbidities in IDA patients

Concomitant disease/condition	n = 277 (%)
Type 2 diabetes	23 (8,3)
Autoimmune disorder*	23 (8,3)
Hypothyroidism	18 (6,5)
Cancer	8 (2,9)
Heart failure	8 (2,9)
Occult GI bleeding	6 (2,2)
Pregnancy	5 (1,8)
Chronic renal failure	3 (1,1)
Other	69 (24,9)

* ulcerative colitis, Chron's disease, rheumatoid arthritis, Hashimoto thyroiditis, coeliac disease, Sjögren syndrome, systemic sclerosis, type1 diabetes.

It is estimated that women of reproductive age lose 1 to 3 mg of iron daily; the intake of iron is often inadequate to maintain iron balance (1). In addition to heavy menstrual bleeding, the most common causes of IDA in the developed world include gastrointestinal bleeding, impaired iron absorption and unusual fad diets (1). In developing countries, IDA most commonly occurs as a result of poor nutrition in people living in poverty.

In women with menorrhagia disorders of primary haemostasis should be considered (9). Von Willebrand disease affects approx.1 % of the general population and more than 5 % of women with menorrhagia (10). Women with heavy menstrual bleeding have a higher prevalence of abnormal platelet function (9). Further diagnostic testing in pre-menopausal women with IDA is the domain of a GP or a gynaecologist. Even in young women IDA may be brought about by occult gastrointestinal bleeding. Screening for blood in the stool should be done at least six times in a row.

One-third of the IDA patients seen in the haematology outpatient clinic were older males and menopausal females in whom IDA is very likely due to gastrointestinal diseases (1). Gastrointestinal diagnostic testing in this population is imperative (4). Endoscopic procedu-

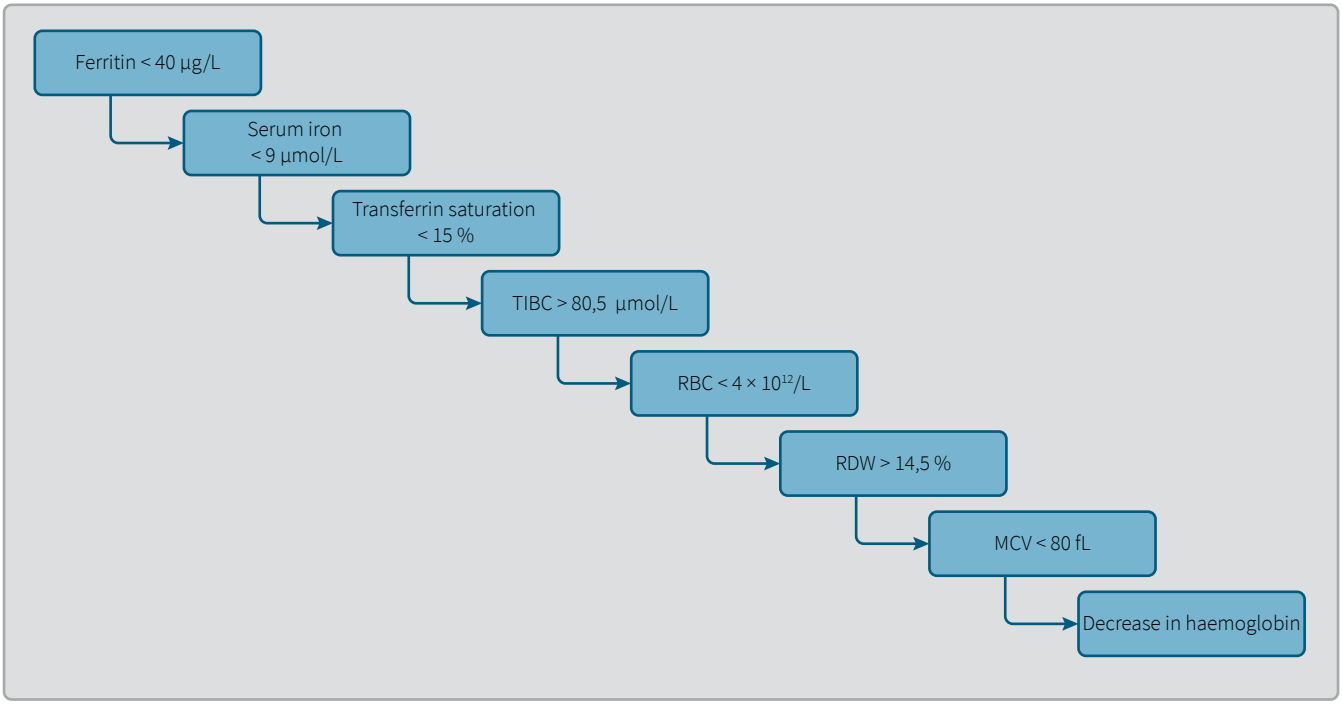

Figure 2: Changes of laboratory patameters on the onset of negative iron balance.
TIBC–total iron binding capacity; RDW–red cell distribution width. Source: Alleyne et al. (8).

res are done to rule out gastrointestinal malignancies, mucosal inflammation, ulcers and angiodysplasia (1). Another cause of IDA may be haemorrhoidal bleeding. After ruling out gastrointestinal haemorrhage, impaired iron absorption that may be due to *Heliobacter pylori* infection, coeliac disease and chronic inflammatory bowel diseases should be considered in all age groups. IDA due to bleeding in the urinary tract is rare. History of unusual dietary patterns and medication should be reviewed in both sexes (11). IDA may occur as a result of the therapy with non-steroid anti-rheumatic drugs, salicylates, warfarin, clopidogrel, heparin, glucocorticoids and proton pump inhibitors (1). Anaemia is a symptom rather than a disease and it is necessary to determine its aetiology.

As indicated by Table 3 mean Hb levels in the men and women studied bordered between mild and moderate anaemia. Mean serum iron concentration was expectedly decreased, mean serum ferritin was at the lower border of normal and mean TIBC was within the range of reference levels. Interestingly, nearly one-fifth of the patients had normal Hb levels at their first appointment at the haematology outpatient clinic, which may be explained by the fact that the triage haematologist gives treatment instructions based on the enclosed laboratory results to the patient's GP prior to his/her examination at the clinic.

A surprisingly large proportion of patients in the study were referred as urgent cases. In half of them, Hb levels were within the range of moderate anaemia and in one female patient they were even suggestive of mild anaemia.

Table 4 shows that a little less than half of the patients were referred to the haematology outpatient clinic with the diagnosis of IDA. In only one-tenth Hb levels were within the range of severe anaemia. Indications for referral

of IDA patients to the haematologist included: severe macrocytic anaemia (Hb < 70 g/L), unclear differentiation of IDA from ACD and other abnormalities in CBC that persist despite iron supplementation and increase in the Hb levels.

IDA remains a condition with low recognition rate. As many as one-third of patients were referred to the clinic with the diagnosis of microcytic anaemia, which is surprising considering the fact that IDA is known to be by far the most common cause of microcytic anaemia. In addition to low Hb levels and the associated microcytosis, the evidence of reduced body's iron stores (decreased serum iron and decreased serum ferritin levels) is necessary to confirm the diagnosis of IDA (1,11). MCV is considered a nonspecific index as the presence of normocytic anaemia does not exclude iron deficiency (12). A combination of IDA and vitamin B12 or folate deficiency should also be considered. In addition to IDA, the differential diagnosis of microcytic anaemia should include ACD and thalassemia minor (11).

ACD is a form of anaemia seen in chronic diseases, chronic infection, chronic inflammation and malignancy (11). It is characterised by elevated levels of the hormone hepcidin, which inhibits intestinal iron absorption and release of iron from body iron stores. Laboratory findings therefore include low serum iron, elevated serum ferritin and, frequently, decreased TIBC concentration. Serum ferritin is not a relevant parameter in the assessment of body iron stores in ACD (13).

Beta thalassemia minor is the most common haemoglobinopathy in Slovenia (14). It affects mostly individuals with Mediterranean and Balkan ancestors. In the future its prevalence is likely to increase with international migration flows. Patients with beta thalassemia minor, as a rule, experience no clinical symptoms. They have mild anaemia (Hb levels of around 100 g/L) pronounced microcytosis (MCV of 60–70 fl) and normal RBC count (15). Typically, there is a disproportion between Hb levels and pronounced microcytosis. Examination of the peripheral blood smear reveals target erythrocytes and basophilic punctation of erythrocytes, with prevailing dacriocytes and ovalocytes (16). In patients with suspected thalassemia minor, haemoglobin electrophoresis is used instead of unpleasant endoscopic examinations to confirm abnormal findings.

Once the diagnosis of microcytic anaemia is made, the patient's body iron status, i.e serum iron, serum ferritin and TIBC levels, should be determined (11). Patients with IDA have low serum iron and serum ferritin and high TIBC concentrations. Reduced ferritin is the most reliable parameter used to confirm IDA (17). Normal ferritin levels in the serum with concurrent low serum iron levels do not rule out IDA, as IDA may be associated with ACD (11,13).

Iron homeostasis is a process regulated mainly by hepcidin, a hormone present in the liver (11). Elevated plasma levels of iron induce secretion of hepcidin from the liver. By binding to the transmembrane iron transporter ferroportin it causes its degradation and thereby inhibits iron release from the duodenum and delivery from the reticuloendothelial system in the blood. Chronic inflammations and infections enhance hepcidin secretion from the liver and reduce the levels of serum iron, which is stored in adequate amounts in the body. The condition is known as functional iron deficiency. It is differentiated from manifested iron deficiency by high levels of storage iron, confirmed by high serum ferritin concentration.

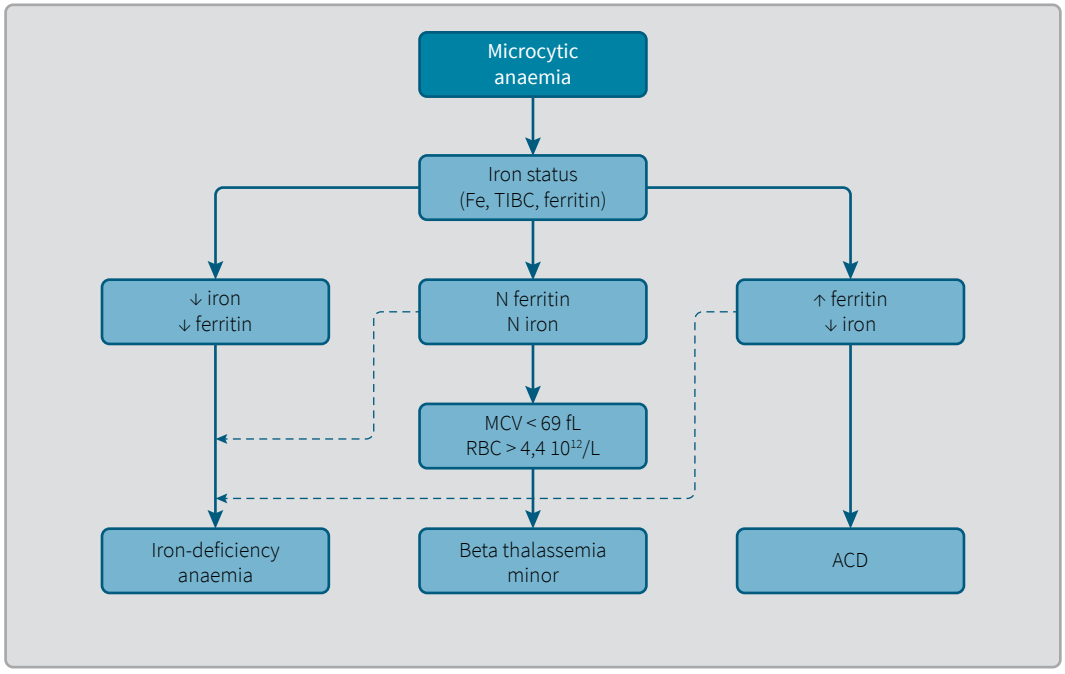

Figure 3: The proposed diagnostic workup for microcytic anaemia
MCV – mean corpuscular volume, RBC– red blood count, TIBC– total iron binding capacity.

As concluded by clinical studies, patients with chronic diseases have iron deficiency when their ferritin levels drop below 100 µg/L (18). There is, however, some discrepancy between the authors. According to some investigators (2,19) ferritin concentration associated with iron deficiency is 200 µg/L. Final recommendations are still awaited. In Slovenia, patients with ACD are treated with iron supplements when their ferritin levels drop below 100 µg/L. These patients do not respond to oral iron replacement, therefore invariably intravenous therapy is used (19,20).

One-third of the patients studied presented with concomitant chronic diseases. The laboratory parameters that help us determine the combined aetiology of microcytic anaemia include: transferrin saturation, soluble transferrin receptor levels, reticulocyte haemoglobin content and hepcidin levels (19). It is possible to measure those parameters in the laboratory of the Department of Haematology but are not routinely done.

Low serum iron levels indicate iron deficiency. Serum iron, however, is not a reliable index of body iron stores because of the role played by the individual's diet. After patient with IDA ingest food high in iron, serum iron can rise. Misled by these results, the physician may assume that the patient's iron stores are adequate, yet in the absence of ACD, low ferritin concentration are the key index of the body's stores of iron. Because of fluctuations caused by diurnal variation, serum iron levels are the highest in the morning and at noon, and decrease gradually in the afternoon (21). Iron is an ideal food source for microorganisms, therefore individuals with high levels of serum iron are prone to infections and septic conditions (35,36).

Patients who present to the haematology outpatient clinic often provide results of blood tests and serum iron determination without data of serum ferirtin concentration. This information is of key importance in the management of patients with IDA and should therefore

always be included in the patient's referral medical documentation.

Clinical presentation of anaemia is well known, but it is of primary importance to obtain information on the speed of onset of the disease. Patients with chronic anaemia, even those with severe microcytic anaemia, are often free of symptoms. The authors have experience in treating Jehowah's Witnesses who attended for follow-up examinations until their Hb levels were less than 40 g/L. Pallor was documented in only half of the study patients seen in the haematology clinic. It is a matter of the haematologist's subjective judgement. This sign is only rarely mentioned in the patient's record. Haematologists, faced with overcrowded waiting rooms, work fast and may therefore be inaccurate. Iron replacement therapy is instituted also in patients who complain of severe fatigue, exertional dyspnea and palpitations.

Table 4 shows that many study patients with anaemia had concomitant CBC abnormalities. IDA is often accompanied with changes of CBC (22), the most common being reactive thrombocytosis. It was present in one-sixth of the study patients. The exact causative mechanism of reactive thrombocytosis in patients with IDA is unknown (23). Some studies explain it as a synergistic effect of erythropoeitin on platelet formation (24). It makes sense that patients presenting with anaemia and thrombocytosis have a peripheral smear test to rule out the presence of IDA. According to the literature data reactive leukopenia is encountered in 2–17 % of IDA patients (25,26). It tends to be mild with iron levels of 3.0×10^9/L or higher (22). In this review, leukopenia was recorded in 7 % of cases. A similar proportion of patients had thrombocytopenia, which, according to the literature, is less frequently associated with IDA (27,28). In patients with a combination of anaemia and thrombocytopenia it is necessary to consider thrombotic microangiopathy or any of its forms, such as thrombotic thrombocytopenic purpura and haemolytic uremic syndrome, chracterised by typical clinical manifestations and abnormal laboratory findings. A few cases of pancytopenia have been documented, yet the disorder rarely occurs in patients with IDA (29). Low counts of all blood cells are more often found in megaloblastic anaemia (30). Iron supplementation usually makes all the aforementioned changes in CBC disappear. If IDA goes away but other abnormal CBC findings persist, the patient needs further haematologic evaluation to exclude possible concomitant blood disorders (22).

A surprisingly large number of patients were invited to attend for a follow-up examination, in our opinion, the majority of them for no clear reason. Following a patient with IDA is the domain of the patient's GP.

Prior to their visit to the haematology outpatient clinic more than half of the patients were taking iron supplements. IDA is invariably treated with iron replacement. Oral iron is the first-choice treatment for haemodynamically stable IDA patients (1). The recommended dosage for adult patients is 200 mg divided into morning and evening doses. The duration of iron replacement therapy is three months. Haemoglobin levels are expected to increase by 20 g/L over three weeks (1 g/L daily) (20,31). In order to fill up iron stores, treatment with iron supplements at a dose of 100 mg daily is continued for further three to six months (32).

For better iron absorption iron supplements should be taken on an empty stomach or at least two hours after meals, together with vitamin C (1). Some authors recommend taking iron supple-

ments with a meat-based meal (11). Iron absorption is impaired by a simultaneous ingestion of calcium (milk and dairy products), tannin (black tea, some herbal teas, red wine), phytates (cereals, grains) and caffeine (33).

Gastrointestinal problems that may be caused by iron supplements are the most common reason for unsuccessful therapy (11). Taking iron on a regular basis is more important for the effective therapy than the choice between two- and three-valent iron supplements (1). Some manufacturers recommend slow-release formulations, yet from these preparations iron is released in the digestive tract distal to the duodenum where no absorption takes place (1). The principal site for iron absorption if the upper gastrointestinal tract, i.e. in the upper half of the duodenum. Side-effects of therapy are therefore more pronounced. Iron supplements cause black stools, yet faecal occult blood tests are negative (1).

The newer understanding of the role of hepcidin has led to changes in the treatment with oral supplements. Recent studies showed that a single daily dose of iron increases hepcidin levels in blood and decreases absorption of iron from subsequent doses. The effect of hepcidin may be apparent for up to 48 hours (37). The present recommended dosing scheme will probably be a single daily dose of iron supplement taken on alternate days (38). Further clinical research are needed in this field. Currently, standard dosing of oral iron is recommended as described in this paper.

If a 4- to 6-week treatment with elemental iron of 100 mg daily fails to increase haemoglobin levels by 10 g/L, the diagnosis of refractory IDA is made (20). Common causes of refractory IDA include: coeliac disease, autoimmune atrophic gastritis, gastritis caused by *H.pylori* infection and iron refractory iron deficiency anaemia (IRIDA), a hereditary form of IDA (20). IDA is the most common extraintestinal manifestation of coeliac disease. It occurs as a result of a combination of impaired iron absorption and occult bleedings (20). Gastric hypoacidity in autoimmune atrophic gastritis impairs oral iron solubility (20). Clinical studies have confirmed the connection between refractory IDA and gastritis caused by *H.pylori* infection. A clear mechanism behind the effect of this microorganism on iron uptake, occult bleedings and gastric juice alkalisation is yet unknown (20). Eradication of *H.pylori*

Table 6: Oral iron preparations for the treatment of IDA

Brand name	Substance	Packaging	Dosage*
Ferrum Lek®	trivalent iron oxide	30 × 100 mg chewable tablets 100 ml of syrup 50 mg/5 ml	1–3 tbs/day 10–30 ml/day
Eisensulfat Lomapharm®	two-valent ferrous sulphate	20 x, 50x, 100x 100 mg tablets	1 tb/12 hours
Legofer®	trivalent iron proteinsukcinalat	150 ml of syrup 40 mg/15 ml	7.5–15 ml/12 hours
Tardyfer®	two-valent iron sulphate	30 × 80 mg tablets	1–2 tbs/day

* dosage for adults with overt iron deficiency

infection and simultaneous iron replacement therapy have proved effective in treating IDA in most cases (34). IRIDA is a rare hereditary condition caused by mutations in TMPRSS6 gene which encodes matriptase 2 enzyme (1), affecting the regulation of hepcidin secretion. This disease is characterised by very high hepcidin levels that impair absorption of iron from the digestive tract. Iron status in hypochromic microcytic anaemia in similar to that in ACD: serum iron levels are very low, while serum ferritin is normal or even elevated. Absence of inflammatory signs differentiates it from ACD. It affects more commonly children and young adults.

Indications for intravenous iron therapy include: intolerance of iron preparations, refractory anaemia associated with iron deficiency, refusal of transfusion based on religious reasons (Jehovah's Witnesses), filling up of iron stores before treatment with erythropoieitin (1). Intravenous iron therapy causes a fast increase in iron serum haemoglobin and is therefore used in IDA patients scheduled for surgery, as well as in women in the second and third month of pregnancy with severe anaemia, and in patients with blood coagulation disorders bleeding from the gastrointestinal tract. Fear of allergic reactions to intravenous iron administration comes from the past when dextran-containing iron preparations were used for intravenous iron replacement (39). Dextran was most often responsible for adverse reactions in these patients. Iron supplements used today contain no dextran and allergic reactions are very rare. Giving the patient intravenous iron supplements in the health care centre is an entirely safe procedure, therefore referral to the haematologist is not justified (40). Costs of treatment are covered under the national health insurance scheme. Intravenous iron replacement in the first trimester of pregnancy is avoided because of a lack of safety studies (40).

Transfusion of red cell concentrates (RCC) in IDA is symtpomatic and

Table 7: Intravenous iron preparations for the treatment of IDA

Brand name	Substance and carrier	Packaging	Dosage*
Ferrologic®	trivalent iron oxide (saccharated)	20 mg/ml 5-ml ampoules	100–200 mg/day to 3 times a week, or max.500 mg once a week
Iroprem®	trivalent iron carboxymaltose	50 mg/ml 10-ml vials 2-ml vials	max.1000 mg/day once a week
Venofer®	Trivalent iron oxide (saccharated)	20 mg/ml 5-ml ampoules	100–200 mg/day to 3 times a week or max.500 mg once a week

*total cummulative dose of IV iron is calculated as follows:

Ferrologic® and Venofer®

Total amount of iron to be administered (mg) = body mass (kg) x (target Hg concentration – actual Hb concentration (g/l) × 0.24* + amount of iron needed to fill up body iron stores (500 mg)

Iroprem®

Patients with BMI 35 kg to < 70 kg; Hb < 10 g/dl: 1,500 mg, Hb ≥ 10 g/dl: 1,000 mg

Patients with BMI ≥ 70 kg; Hb < 10 g/dl: 2,000 mg, Hb ≥ 10 g/dl: 1,500 mg.

should be reserved for patients with severe clinical problems (1). RCC transfusion is beneficial for healthy individuals with haemoglobin concentrations below 60 g/L. Anaemia is not well tolerated by patients with heart disease; cardiac patients with haemoglobin concentration of less than 100 g/L had higher mortality rates (41). RCC transfusion is usually given after acute bleeding regardless of the site of bleeding. Also, it is administered to patients with major chronic haemorrhage in whom haematopoesis cannot compensate for blood loss, i.e. patients with hereditary haemorrhagic telangiectasia (1). RCC transfusion is indicated in patients with heart failure and chronic renal or liver diseases, and in patients with other chronic conditions who have a higher threshold for transfusion, dependent on symptoms and signs of anaemia. RCC transfusion always worsens the course and outcome of treatment of primary disease.

In patients receiving RCC transfusion, iron supplementation should be instituted, as a rule, via the intravenous route (42). Erythropoietin has no place in the treatment of IDA.

Iron supplements used in IDA patients in Slovenia (43):

- Oral iron supplements are listed in Table 6.
- Intravenous iron preparations are listed in Table 7

5. Conclusion

IDA is a common reason for referring patients to the haematology outpatient clinic. The results of this study show that most of the patients seen in the clinic were women of childbearing age. The majority of patients with IDA received intravenous iron replacement. The results indicate that microcytic anaemia is a condition with low recognition rate. Referral to the haematology outpatient clinic is justified if the patient has severe symptomatic microcytic anaemia (Hb < 70 g/L) or if concomitant changes in the CBC persist despite iron supplementation and with increase in Hb levels.

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