RESEARCH LETTER

Is iron deficiency anemia always microcytic?

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Introduction Iron deficiency anemia (IDA) is the most common type of anemia worldwide.[1,2] In high-income countries, 6% to 8% of adults have anemia, and 40% to 45% of them suffer from iron deficiency (ID). The latter typically develops as a result od insufficient iron dietary intake, malabsorption, hemorrhage and / or hemoglobinuria, or increased demand for iron. As ID progresses, it turns into IDA, which can be diagnosed based on the manifestations of both anemia and ID.

Of note, anemia of inflammation (AI) makes the differential diagnosis of IDA challenging in numerous cases. It is a frequent (35% of anemia cases) and unique type of anemia. In AI, the inhibition of erythropoiesis (by the tumor necrosis factor and tumor necrosis factor–related apoptosis-inducing ligand) is combined with the blocked iron transport into the blood (from splenic macrophages, duodenal enterocytes, and hepatocytes) because of elevated hepcidin levels (reverse acute-phase reaction). In AI, the serum iron level is generally low, the transferrin level is low (due to reciprocal acute-phase reaction), and transferrin saturation can be normal or, in rare cases, low. The low transferrin level in AI versus high or normal in IDA helps us to differentiate between the 2 types of anemia. In AI, the inhibition of erythropoiesis and blocked iron metabolism are generally proportional, so anemia is regarded as normochromic and hyporegenerative (with a low reticulocyte count).

Iron is essential for hemoglobin (heme) production and only very severe ID would directly inhibit erythropoiesis; hence, anemia associated with IDA is characterized by decreased hemoglobin production and a more or less well-sustained red blood cell (RBC) count.[3]

Decreased mean corpuscular hemoglobin (MCH) concentration also results in the reduction of mean corpuscular volume (MCV). Commonly used laboratory automated analyzers calculate MCV (hematocrit / RBC) and MCH (hemoglobin level / RBC) based on the measured parameters (RBC, hematocrit, and hemoglobin levels).[4] Previous generations of laboratory analyzers used MCV directly for measurements, and IDA was defined as anemia with low MCV, or microcytic anemia.

Red blood cell volume constantly decreases throughout the 100-120-day lifespan of the cell that evolves from a spheroid reticulocyte with an initial volume of 150 to 170 fl to the late form of aged RBCs.[5] Red blood cells in IDA are characterized by reduced cell volume and decreased hemoglobin concentration, generally called hypochromasia. Provided that there is no double pathology including associated severe mechanical intravasal injury or hemolysis, RBC hemoglobin concentration is constant during the RBC lifespan. All the above highlights the role of MCH, and IDA can be characterized by a hypochromic feature rather than a microcytic phenotype.[5,6]

The laboratory of Moritz Kaposi Somogy Country Teaching Hospital analyzes samples from several thousands of patients with anemia per year and we found strong correlations between reduced MCH concentration and ID. We analyzed data on MCV and MCH concentration in 2503 patients with ID including 1733 with IDA and presented the results in this article to demonstrate the significance of MCH concentration compared with MCV in the diagnosis of ID.

Patients and methods The patient population of Moritz Kaposi Somogy County General Hospital (with 1000 beds) was evaluated based on 644 556 samples drawn for complete blood count (CBC) over a 5-year period (2013–2017) (excluding patients below 18 years of age and / or receiving hemodialysis therapy). The vast majority of the tested population was Caucasian-Hungarian and there were almost no cases of moderate-to-severe hemoglobinopathy. Iron deficiency was defined as transferrin saturation ≤20% or a reticulocyte hemoglobin level ≤28 pg,[7-9] or a ferritin level ≤30 μg/l in men and ≤20 μg/l in women.

Results of CBC were obtained using the Sysmex XN-2100i (Hoffmann-LaRoche, Kaposvar, Hungary) laboratory automated analyzer, including hemoglobin levels measured by the sodium lauryl

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TABLE 1 Complete blood count in the study patients with iron deficiency and iron deficiency anemia

Parameter		Women (n = 1836)	Men (n = 667)	Total (n = 2503)
MCH ≤28 pg		1464 (79.7)	527 (79)	1991 (79.5)
MCV ≤80 fl		857 (46.7)	267 (40)	1124 (44.9)
IDA	Total	1241 (67.6)	492 (73.7)	1733 (69.2)
	MCH ≤28 pg	1108 (89.3)	421 (85.6)	1529 (88.2)
	MCV ≤80 fl	707 (57)	209 (42.5)	916 (52.9)
ID without anemia	Total	595 (32.4)	175 (26.2)	770 (30.6)
	MCH ≤28 pg	357 (60)	106 (60.6)	463 (60.1)
	MCV ≤80 fl	151 (25.4)	58 (33.1)	209 (27.1)

Data are presented as number (percentage) of patients.

Iron deficiency was diagnosed for ferritin levels ≤30 µg/l in men and ≤20 µg/l in women or transferrin saturation <20%, or reticulocyte hemoglobin levels <28 pg.

Abbreviations: ID, iron deficiency; IDA, iron deficiency anemia; MCH, mean corpuscular hemoglobin; MCV, mean corpuscular volume

sulfate method, RBC count by the impedance test, and reticulocyte levels by flow cytometry. Iron parameters were tested on the COBAS 8000 c502--es (Roche, Kaposvar, Hungary) immunochemistry analyzer. Serum iron levels were measured by the FerroZine method at 552 nm, and the results were provided in mmol/l. The first threshold was 6.6 mmol/l for women and 11 mmol/l for men (later, the threshold for women was changed to 11 mmol/l). Ferritin levels were measured using the electrochemiluminescence immunoassay, and transferrin levels were determined by immunoturbidimetry. Transferrin saturation was calculated based on the following formula: serum iron level / transferrin level × 3.98. The results were presented as percentage, and values of 20% or greater were considered abnormal.

Anemia was diagnosed in patients with hemoglobin levels ≤130 g/l in men and ≤120 g/l in women.[10]

Statistical analysis In addition to the descriptive statistical method, the χ^2 test was used to compare dichotomous variables. Statistical analysis was performed using the open-source R statistical software package, version 3.1.2 (The R Foundation for Statistical Computing, Kaposvar, Hungary). A *P* value less than 0.05 was considered significant.

Ethics Ethical approval was granted by the Research Ethics Committee of Moritz Kaposi Somogy County General Hospital. As it was a retrospective data analysis, written patient consent was not required.

Results During our 5-year retrospective study, 644 556 samples were analyzed for CBC, and the sex ratio among patients was 365 271 women to 279 285 men. Iron parameters were concurrently tested in 35 398 patients—23 321 women and 12 077 men.

In the 35 398 individuals in whom iron parameters were measured, MCH and MCV values were compared: MCH concentration was at 28 pg or lower in 8915 patients, and 4039 of them (45.3%) had an MCV of 80 fl or less. In the 26 483 cases with an MCH concentration exceeding 28 pg, 150 (0.6%) had an MCV of 80 fl or less.

Serum iron levels were measured in 30 830 patients (20 867 women and 9963 men). Transferrin saturation was also tested in 2938 patients (1972 women and 966 men). Data on ferritin levels were available in 2551 patients (1680 women and 871 men). Reticulocyte hemoglobin concentration was measured in 5117 patients (2835 women and 2282 men). Detailed study results are shown in **TABLE 1**.

Among 2503 patients with confirmed iron deficiency, 1733 (69.4%) were identified as having IDA. A total of 1241 women (67.6%) and 492 men (73.7%) were diagnosed with IDA.

As many as 1529 patients with IDA (88.2%; 1108 women [89.3%] and 421 men [85.6%]) had an MCH concentration of 28 pg or lower. A total of 916 patients with IDA (52.9%; 707 women [57%] and 209 men [42.5%]) had an MCV of 80 fl or less. In terms of IDA, hypochromia was more frequent (P <0.001) compared with microcytosis.

Discussion Currently, IDA is primarily defined as microcytic anemia.[11] The results of our retrospective analysis highlight the significance of MCH concentration among the parameters measured with commonly used automated hematology analyzers. While hypochromia occurred in nearly 90% of patients with IDA cases, microcytosis was found only in 53%. Reticulocyte hemoglobin levels were shown to be essential among the measured reticulocyte parameters. The concentration of MCH is secondary to its alterations, and it may theoretically play an important role among other CBC parameters. This retrospective analysis provided evidence supporting the potential significance of MCH in the diagnosis of IDA.

ARTICLE INFORMATION

CONFLICT OF INTEREST None declared.

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