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Microcytic anemia is frequently due to iron deficiency (IDA) or thalassemia.

Other causes are Anemia of chronic disease (rheumatoid arthritis, Hodgkin lymphoma) and hereditary or acquired sideroblastic anemia or lead poisoning. Both diseases are endemic; represent a problem of public health particularly in the developing countries.

The World Health Organization (WHO) has recently highlighted their growing concern about anemia, affecting an estimated 2000 million people, 50% of the cases caused by iron deficiency. Iron deficiency remains the most prevalent micronutrient deficiency worldwide [1].

Iron deficiency is one of the leading risk factors for disability and death worldwide; it may result from insufficient iron intake or menstrual blood loss in women of childbearing age, or chronic blood loss in the gastrointestinal tract in the case of elderly subjects. The consequences for affected individuals and the economic productivity of societies are substantial.

The high prevalence of iron deficiency in the developing world has substantial health and economic costs, including poor pregnancy outcome, impaired school performance and decreased productivity. WHO estimates that 39% of children younger than 5 years, 48% of children between 5 and 14 years, 42% of all women, and 52% of pregnant women in developing countries are anaemic, with half of them having iron deficiency anemia. According to WHO, the frequency of iron deficiency in developing countries is about 2-5 times that of anaemia. Iron deficiency is also common in women and young children in industrialized countries [2].

Nutritional iron deficiency arises when physiological requirements cannot be met by iron absorption from diet. Human life cycle includes two phases in which optimal nutritional iron is critically important: pregnancy and early childhood. Pregnancy because of the risk of maternal death, preterm labor, low birth weight, and neonatal mortality and early childhood due to adverse effects on cognitive, motor, and emotional development that may only be partially reversible. In elderly persons anemia may be caused by a variety of potentially contributing etiologies: nutritional, anemia of chronic inflammation or renal disease [3].

Microcytic anemia in the case of thalassemia results from impaired globin chain synthesis and decreased Hemoglobin (Hb) synthesis.

Structural Hb variants are typically due to point mutations in a globin gene that produces a single amino acid substitution in a globin chain. Thalassemias, in contrast, result from quantitative underproduction of globin chains.

Inherited Hb disorders such as Hb variants and thalassemias were originally characteristic of the tropics and subtropics but are now common worldwide. Non-endemic countries such as Northern Europe and North America are also facing health issues due to Hb disorders as a result of demographic changes caused by migration of ethnic minority groups with a high frequency of mutations [4].

Because heterozygotes have a survival advantage after malaria infections, the inherited hemoglobinopathies are the most common monogenetic diseases and approximately 7% of the world population is carrier of such disorders. The prevalence of Hb disorders ranges from 0.3 to 25 per 1000 live births and Hb disorders are considered as a significant health care problem worldwide.

Thalassemia syndromes are among the most common genetic disorders worldwide, with 1.7% of the world's population carrying thalassemic genes. In endemic countries the risk of homozygosity is high and there it represents a major public health problem. The  $\beta$ -thalassemias have an estimated annual incidence of symptomatic individuals of 1 in 100,000 throughout the world and 1 in 10,000 people in the European Union. Data from recent epidemiological surveys indicate that in Europe there are approximately 15,000 subjects with transfusion-dependent thalassemia major [5].

Most of the Hb variants and thalassemias are of limited clinical relevance, but severe forms of thalassemia may produce serious clinical manifestations and may result in disabilities and even death in the first years of life.

The laboratory challenge is to detect the clinically significant Hb disorders and to identify them accurately. Since the pioneering study of Pauling in 1949, in which the different electrophoretic mobilities of sickle cell anemia (Hb S) and normal Hb were described, nearly 1100 Hb variants and 400 thalassemias affecting the  $\alpha$ ,  $\beta$ ,  $\gamma$  and  $\delta$ -globin chains have been identified.

Thalassemias are characterized by insufficient or absent synthesis of the globin chains. An imbalanced production of one of the globin chains leads to accumulation and precipitation of unpaired globin chains and consequently to ineffective erythropoiesis and hemolysis. Characteristically, patients affected with  $\alpha$ - or  $\beta$ -thalassemia show microcytic hemolytic anemia.

Clinically, three main forms have been described: thalassemia major, intermedia, and minor. Individuals with thalassemia major usually show severe anemia within the first 2 years of life and require regular transfusions during their whole life. This therapy leads to iron overload and complications including endocrine complications (growth retardation, failure of sexual maturation, diabetes mellitus, and insufficiency of the parathyroid, thyroid, pituitary, and less commonly, adrenal glands), myocardopathy, liver fibrosis, and cirrhosis.

Prognosis for individuals with  $\beta$ -thalassemia has improved substantially in the past 20 years following recent medical advances in transfusion, iron chelation, and bone marrow transplantation therapy. However, cardiac disease remains the main cause of death in patients with iron overload.

Usually, patients with thalassemia intermedia develop moderate anemia later in life and do not require regular transfusions. Main clinical features in these patients are hypertrophy of erythroid marrow with enhanced medullary and extramedullary hematopoiesis and its complications. Thalassemia minor is clinically asymptomatic, but some subjects may have moderate anemia and some splenomegaly.

While the majority of patients show significant microcytosis and some have borderline anemia, the hallmark of  $\beta$ -thalassemia minor is an increase of Hb A<sub>2</sub> that distinguishes it from other microcytic conditions like iron-deficiency.

The diagnosis of  $\beta$ -thalassemia involves measuring HbA<sub>2</sub> concentration of lysed red cells via high-performance liquid chromatography (HPLC), with an ion-exchange column or electrophoresis methods. The HPLC measurement is considered the "gold standard" and is useful for assessing sensitivity and specificity of other testing methods.

Differentiation between thalassemic and non-thalassemic microcytosis has important clinical implications, because each has entirely different cause, pathogenesis, prognosis and treatment.

As in all chronic diseases prevention is important for the overall management of the disease; the real danger of non-diagnosis or misdiagnosis of the carriers of thalassemia trait is the potential homozygous offspring: appropriate screening, detection of patients and counselling of couples at risk are the most important

procedures for reducing morbidity and mortality of thalassemia patients.

IDA and thalassemia have different etiologies, which result in typical profiles of the hemogram: erythrocytosis and microcytosis in thalassemia carriers, anisocytosis in iron deficiency. Nevertheless, the profiles may show considerable overlap and hence it is difficult to recognise a carrier in daily practice based on individual parameters of the hemogram only.

A discriminant formula or index based on red cells parameters derived from automated blood cell analyzers, with a high level of specificity and sensitivity for detecting thalassemia trait, would be a useful tool in the investigation of microcytic anemia. In particular in geographic areas where nutritional deficiencies and thalassemia do occur with high prevalence, such discriminant indices are of great interest [6].

The usefulness of these indices is to detect  $\beta$ -thalassemia carriers with a high probability. Therefore, the best index must have the highest sensitivity possible, in order to detect (almost) all  $\beta$ -thalassemia carriers. On the other hand, specificity must be good enough to avoid the measurement of HbA<sub>2</sub> in samples that do not need to undergo further analysis (false positives).

Suspicious samples can be selected for HbA<sub>2</sub> analysis, to confirm the presumptive diagnosis of the disease.  $\beta$ -Thalassemia can be diagnosed with confidence when raised HbA<sub>2</sub>, erythrocytosis, microcytosis and normal serum ferritin are present.

In the developing countries, where these diseases are endemic, represent a problem of public health; but in the developed countries with the general budgetary reductions, the presumptive identification of Hemoglobin disorders must rely on inexpensive methods of detection, to allow an efficient use of the resources. RBC indices are useful tools, adding in the selection of highly suspicious samples for further analysis, more sophisticated and expensive.

RBC indices can be calculated from data reported by the analyzers so every laboratory can apply this strategy, improving productivity, adding value and quality to the Laboratory reports.

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