

Presentation of a Computing System and Algorithm for Differentiating Beta Thalassemia Trait from Iron Deficiency Anemia

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Abstract

The prevalence of beta thalassemia trait (BTT) is estimated to be 240/000/000 cases around the world, and these patients are centralized in the thalassemia world belt map (TWBM). Marriage of the couples with BTT can result beta thalassemia major in their next generation. Any country located in the TWBM has applied a kind of screening test to find the symptomless cases of BTT and impose some preventive conditions for the marriages of the couples who both have BTT. The most efficient screening tools in this way are those that can differentiate the two most common microcytic anemia which are BTT and iron deficiency (ID) anemia. For example, NESTROFT (Naked Eye Single Tube Red Cell Osmotic Fragility Test) has been used as a screening tool in the India. Unfortunately, none of the current screening tests has sufficient sensitivity or specificity. We compared the red blood cell (RBC) indices of 250 patients with BTT and 250 cases with ID in the city of Esfahan in Iran from 2011 to 2016. We used an algorithm, as a novation, in the form of a software that its inputs were RBC indices. And found significant differences between the BTT calculation results and the results of the ID anemia. To find out the specificity and the sensitivity of our new screening tool we put the data of 100 patients with BTT and 100 patients with ID in the algorithm and estimated a sensitivity of 93% and a specificity of 94% for diagnosis of BTT from ID.

Keywords: Beta thalassemia trait, Iron deficiency anemia, Screening, Software

INTRODUCTION

Beta thalassemia trait (BTT) is the potential source for beta thalassemia major in the next generation of these patients. BTT cases are centralized in the thalassemia world belt map (TWBM) [1] such as Iranians (Fig.1). The latter disease is a cause of sever morbidity and also mortality in the patients living in TWBM [2].



Figure 1: The thalassemia world belt map is shown.

In some parts of Iran the prevalence of BTT is between 4% to 8% [3]! This has made the health organization of Iran and the countries that are in the high risk locations, to codify some screening protocols to find the symptomless cases of BTT and impose some preventive conditions for the marriages of the couples who both have BTT. Iron deficiency (ID) anemia is

also a major health problem in developing countries [4] and it is the most important microcytic anemia which should be differentiated from BTT in screening programs. The definitive diagnostic tests for BTT and ID anemia are Polymerase chain reaction (PCR) [5] and bone marrow aspiration biopsy [6] respectively. But these tests are expensive, time wasting, not easily accessible and invasive (for bone marrow aspiration). And so cannot be used as screening tests. Different screening protocols have been codified by different countries, such as Naked Eye Single Tube Red Cell Osmotic Fragility Test (NESTROFT) which is used in India [7]. This test although sensitive, is not specific

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for BTT [8]. In Iran screening is performed in several steps. At first a patient is studied with a cell blood count (CBC) test. If microcytosis is discovered in the CBC, the most common microcytic conditions are tried to be differentiated from each other that are BTT and ID anemia. The second step varies. It may be an iron therapy and rechecking the CBC after several weeks (diagnostic therapy). Hemoglobin electrophoresis, and serum ferritin measurement may be the other alternatives. These protocols can neither be used to make a definitive diagnosis, nor are they easily achievable for screening purposes! On the other hand, coexistence of BTT and ID anemia is not impossible and interpretation of these tests will be more difficult [9, 10]. Being as an active phase protein [11] makes ferritin non sensitive for diagnosis of iron deficiency [12]. Some of the researchers have presented their own formulas that are acclaimed to be as differentiators between BTT and ID anemia, such as Mentzer Index, England and Fraser Index, Srivastava Index, Green and King Index, and Shine and Lal Index [13]. The input of these formulas are RBC indices and the results are net numbers as cutoff points of differentiations. But none of these formulas has gained a verification to be accepted as a screening tool [14].

MATERIALS AND METHODS

Retrospectively we reviewed the CBC reports of 250 adult patients with BTT and 250 adult patients having ID anemia, in the city of Esfahan from 2011 to 2016. The cases in which coexistence of both anemias had occurred had not been differentiated from the pure cases of BTT or ID anemia. The used coulter counters were Hycel Diagnostic type CA 4001 and Sysmex KX 21. Confirmatory tests performed for BTT and ID anemia were hemoglobin electrophoresis and low serum ferritin respectively. Each RBC index was compared between the two groups. For example, the distribution curves of the RBC count of BTT and ID anemia in Esfahan adult people were drawn as that is seen the Fig.2. For any patient who had microcytic anemia with a specified RBC count, the probability of BTT and ID anemia could be calculated with integral methods. For example, if someone had a RBC count of 6.3 M/ μ L, the probability of BTT and ID were calculated as 94.5% and 0.5% respectively (the remained 5% was calculated as the probability of the other rare microcytic anemia such as glucose-6-phosphate dehydrogenase deficiency with a prevalence of 2.1% in Tehran [15], vitamin B6 deficiency and etc.). The same process was done for other RBC indices too. These were hemoglobin (Hb), hematocrit (Hct), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC) and red cell distribution width (RDW).

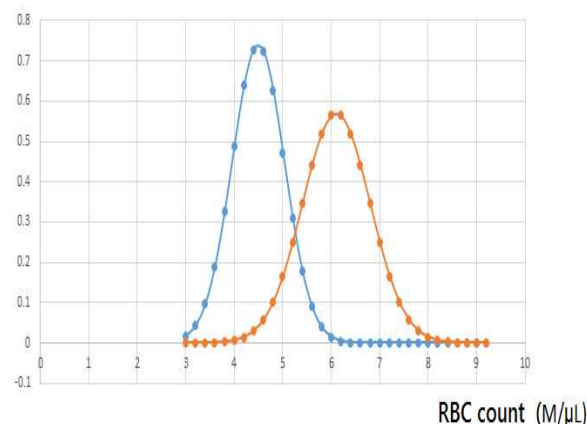


Figure 2: Distributions of the RBC counts are compared in BTT (the orange line) and ID anemia (the blue line), based on the study that was made in the Esfahan adult people.

So we had 7 pairs of calculated probabilities for BTT and ID anemia. Estimation of the resultant in each series of 7 data with multiple regression method, enabled us to find the final result as percentage of each anemia. We inserted all of those calculative stages in a software named Microcytic Anemia Screening Software (MASS) that was innovated by us. The inputs of this software were RBC indices and, if there was any microcytic anemia, its outputs were the calculated probabilities of BTT and ID anemia in Esfahan adult people.

RESULTS

To study the efficiency of our software, we chose 100 adult patients having BTT and 100 adults with ID anemia in Esfahan, and examined our software based on the data that these patients had. The false positive rate, false negative rate, sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of our software were calculated, and summarized in the Table 1.

Table 1: The false positive rate, false negative rate, sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of this software are shown for BTT and ID in Esfahan.

	false positive	false negative	sensitivity	Specificity	PPV	NPV
BTT	6%	7%	93%	94%	91.8%	94.7%
ID	7%	6%	94%	93%	94.7%	91.8%

DISCUSSION

The software we presented as ((MASS)), has several advantages for screening of the BTT cases in many countries. It can be available easily anywhere, it is inexpensive, and also its sensitive and specific results are quickly accessible. It should be noted that the distribution of the different RBC

indices in BTT and ID anemia may be different in the distinct cities of each country. For example, the distribution shown in Fig.2 is for Esfahan and no other city! So for having precise results in each part of the world some needed data should be reflected to us, and we would edit a specific software for that particular point of the world. It is also important to know that MASS has been produced for screening of the adults and because that normal RBC indices differ in various stages from infancy to adulthood^[16], patients under 12 years old should not be screened by our software.

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