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Is Mentzer Index A Reliable Diagnostic Screening Tool For Beta Thalassemia Trait?

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Abstract: ***Objective:*** *Thalassemia trait is commonly seen in Indian population especially in certain communities like Sindhis, Kachchis, Gujaratis& Bengalis. The individuals having thalassemia trait usually have asymptomatic course &have mild microcytic hypochromic anemia. Since the other cause of microcytic anemia is iron deficiency, it is important to differentiate it from and thalassemia trait. Though the definitive diagnosis of thalassemia trait is possible only by Hb electrophoresis, there are certain blood indices which can differentiate between thalassemia trait and Iron deficiency anemia. Mentzer index is such an index. The aim of our study was to evaluate the reliability of Mentzer index in the differentiation of iron deficiency anemia and Thalassemia trait.*

Methods*: This was a prospective study done on 100 patients of pediatric age group of which 60 had iron deficiency anemia and 40 had thalassemia trait. Only those patients who were found to be having iron deficiency anemia by iron studies and patients of thalassemia trait who had been diagnosed by Hb electrophoresis were included in this study. Those patients who had received blood transfusion within 3 months of study were excluded .Mentzer index of all the patients were calculated and the results were analysed.*

Result*: Mentzer index of equal to or more than 13 (≥ 13) indicating iron deficiency anemia and less than 13 indicating thalassemia was found to be reliable.*

Conclusion*: Iron deficiency anemia and thalassemia have different effects on blood indices. In resource poor and developing countries like that of India, it can be used as screening tool. In doubtful cases the diagnosis can be confirmed by Hb Electrophoresis.*

Keywords:*Beta Thalassemia trait, Iron deficiency anemia , Mentzer Index.*

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I. Introduction

Anemia resulting from lack of sufficient iron to synthesize hemoglobin is the most common hematological disease in infants and children. It has been estimated that 30% of the global population suffers from iron deficiency anemia (IDA), and most of those affected, live in the developing countries. Microcytic hypochromic anemia is characterized by decreased hemoglobin, PCV, MCV, MCH, MCHC and normal to increased RDW.

Microcytic anemia in a case of thalassemia results from impaired globin chain synthesis and decreased hemoglobin (Hb) synthesis, resulting in microcytosis and hypochromia. 1.5% of the world's population carries genes for β-thalassemia[1].β-TT is the most common type of hemoglobinopathy transmitted by heredity. It is estimated that about 50% of the world's population with β-TT are in Southeast Asia; it is also common in the Mediterranean region, the Middle East, Southeast Asia, Southwest Europe, and Central Africa [2]. Due to migration and intermarriage of different ethnic populations, β-TT is found in people with no obvious ethnic connection to the disorder.

While the diagnosis of beta thalassemia major usually becomes obvious within initial years of life because of progressive anemia, it is children with beta thalassemia trait who pose a diagnostic dilemma [3].Patients with beta thalassemia trait usually are asymptomatic. Nonetheless, they have pallor on clinical examination and anemia can be detected clinically when these children attend the paediatrician for some other complaints like Upper respiratory tract infection, Acutegastroenteritis or even during immunization visits. It is of utmost importance to differentiate children having microcytic hypochromic anemia due to thalassemia trait from those due to iron deficiency anemia because of obvious implications β-TTwill have on management of these children.[4]

The differentiation in between these 2 conditions can't be done on the basis of blood picture because both of these conditions present with decreased PCV, MCV, MCH, MCHC and normal to increased RDW. Inability to differentiate between these 2 conditions on the basis of blood picture and unavailability and non-

affordability of the tests like Hb electrophoresis and mutation analysis has led some investigators to utilise various indices to differentiate between these 2 conditions [5] .These indices include Mentzer Index, England and Fraser Index, Srivastava Index, Green and King Index, Shine and Lal Index, Red blood cell (RBC) count, red blood cell distribution width (RDW) and red blood cell distribution width index (RDWI)[6]

A definitive differential diagnosis between β-TT and IDA is based on the result of HbA_2 electrophoresis, serum iron levels, and serum ferritin level [7]. However, the aim of this study was to find out the diagnostic value of Mentzer index and to judge it sensitivity and specificity in differentiating betweenβ-TT and IDA.An ideal discrimination index has high sensitivity and specificity; that is, it can detect the maximum number of patients with β-TT (high sensitivity) while eliminating patients with IDA (high specificity).

Mentzer index is calculated using the following formula:
Mentzer index = Mean corpuscular volume (in fL) / RBC count (in Millions per microlitre)

Mentzer originally described the ratio of MCV and RBC count as Mentzer index. A Mentzer index more than 13 is indicative of iron deficiency anemia while an index of less than 13 is suggestive of thalassemia.
Confirmation of β-TT in this study was done by serum electrophoresis carried out by HPLC technique.

II. Materials And Methods

In this prospective study, we selected 100 patients of the paediatric age group of which 60 patients suffered from iron deficiency anemia and 40 patients suffered from beta thalassemia trait. The diagnosis of iron deficiency anemia was done on the basis of blood picture and iron studies carried out on a 5- part cell differential counter BC 5300 Mindray and the diagnosis of beta thalassemia major was done on the basis of increased HbA2 (>3.5%) levels estimated by serum electrophoresis carried usingBio-Rad A 5 which uses HPLC technique. The samples were obtained during the course of routine analysis and collected in EDTA anticoagulant tubes at LataMangeshkar Hospital, Nagpur and were outsourced to S.K Pathology Laboratory, Bilaspur for further confirmation by Hb electrophoresis. The EDTA samples were transported in a cold ice pack container with thermometer to ensure steady optimum temperature. Patients with β-TT and concomitant iron deficiency may show normal HbA2 levels. Therefore, none of the subjects in the present study had both IDA and β-TT and were excluded from the study.

Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and Youden's index were calculated for each measure using the following formulae:
Sensitivity = [true positive ÷ (true positive + false negative)]×100,
Specificity = [true negative ÷ (true negative + false positive)]×100,
PPV=true positive (true positive + false positive)×100,
NPV=true negative(true negative + false negative)×100,
Youden's index=(sensitivity + specificity)−100.

1. **Inclusion criteria**
   a) Children already diagnosed with iron deficiency anemia or thalassemia trait on the basis of blood picture, iron studies and Hb Electrophoresis.
   b) Children of age 12 and below.
2. **Exclusion criteria**
   a) Age more than 12 years.
   b) Coexistence of other hematological condition like autoimmune hemolytic anemia, aplastic anemia or lead intoxication.
   c) Coexistence of β-TT and IDA in the same patient.
   d) History of blood transfusion in near past

III. Result

The peripheral blood examination of 100 patients who were included in this study revealed microcytic hypochromic anemia. The diagnosis of microcytic hypochromic anemia was further confirmed by evaluating the blood samples run through a 5- part cell counter which revealed decreased Hb, PCV, MCV, MCH and MCHC. The confirmation of iron deficiency anemia was done by conducting iron studies to rule out other differential causes. The diagnosis of thalassemia trait was done on the basis of increased Hb A2 on Hb electrophoresis.

Total number of patients afflicted with β-TT and IDA are shown in Fig (1)

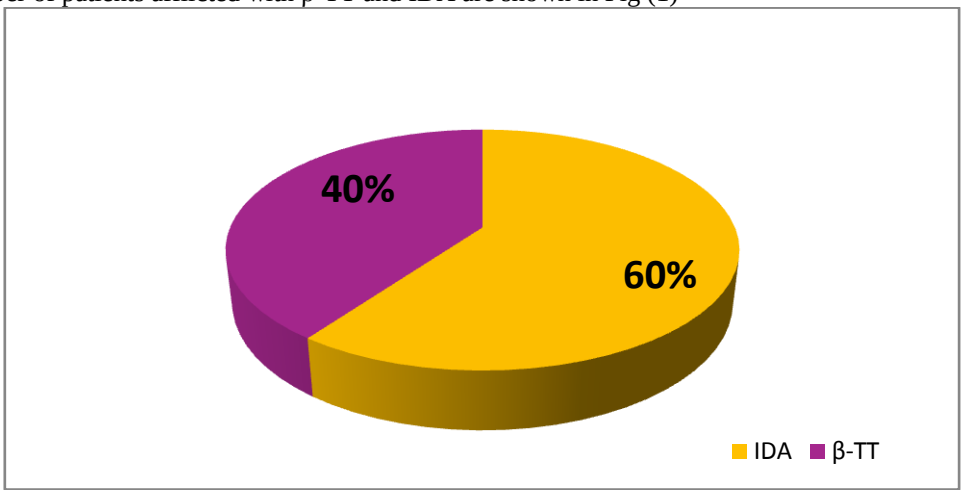

Figure (1) – Total number of patients

An analysis of the presenting signs and symptoms of patients was also done. The most common clinical feature of patients suffering with iron deficiency anemia was found to be fatigue (58.3%), followed by breathlessness (20%), irritability (13.3%), anorexia (5%) and 3% were asymptomatic. It was found that most of the patients suffering from beta thalassemia trait were asymptomatic (60%). However, some of them presented with fatigue (20%), irritability (10%), breathlessness (7.5%) and anorexia (2.5%). Overall, most common presenting feature was fatigue which accounted for 43% involving a total of 43 patients. The data is represented in Fig 2.

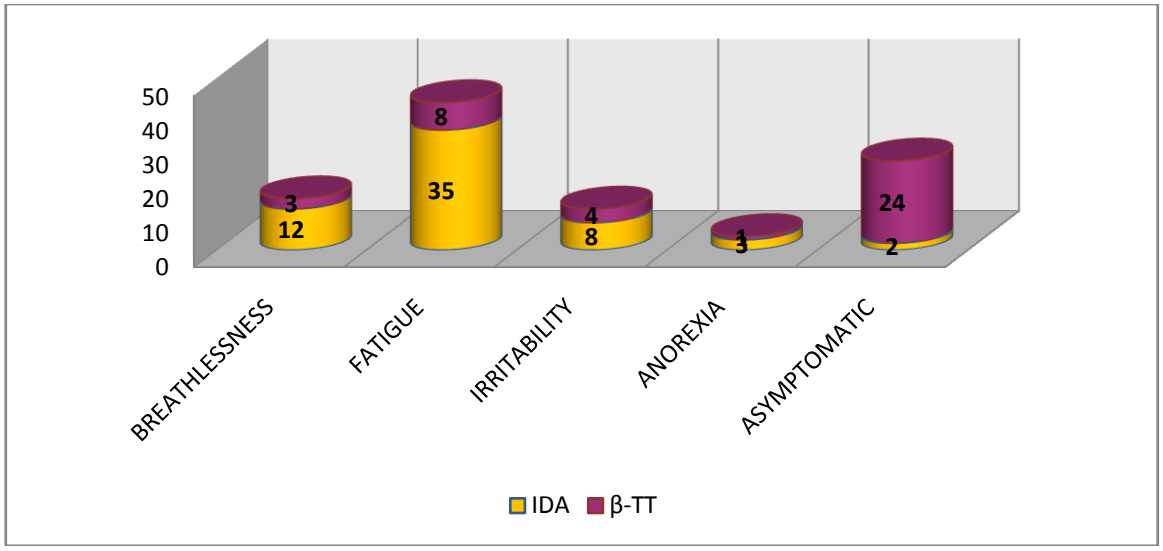

Figure (2)- Presenting symptoms of patients

Various blood indices of all the cases were calculated and studied using a 5- part cell counter. Mentzer index was calculated for all the 100 patients of Iron deficiency anemia & Beta thalassemia trait. A Mentzer index of ≥ 13 was considered to be pointing towards IDA and an index of < 13 was considered to be of thalassemia trait. Out of 60 patients of IDA, 45 patients had Mentzer index of ≥ 13 and 15 had <13. Out of total 40 patients of Beta thalassemia trait. 34 patients had a Mentzer index of < 13 and 6 patients had index ≥ 13. Mentzer index for both has been depicted in Fig (3).

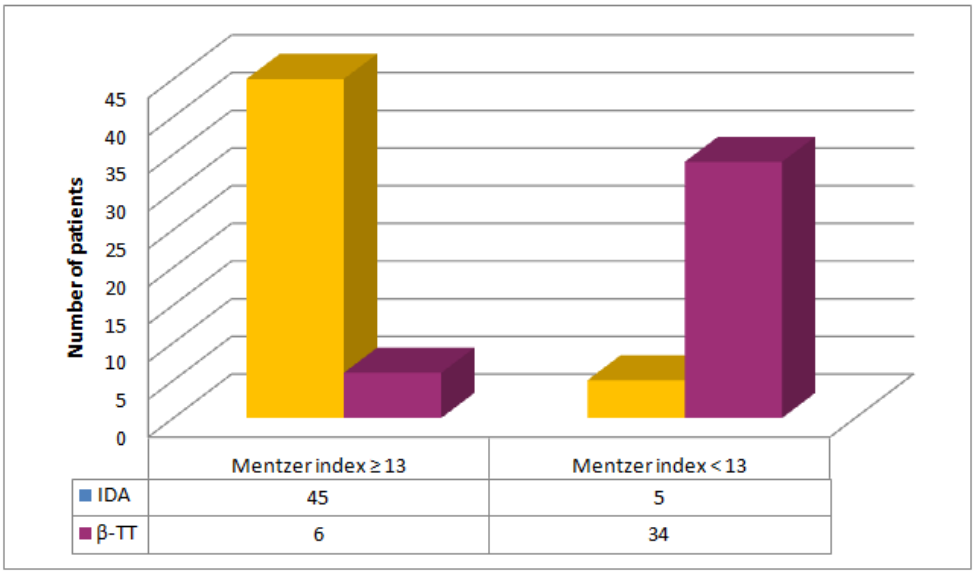

Figure (3) – Mentzer index for β-TT and IDA

The sensitivity, specificity, positive predictive value, negative predictive value & Youden's index were calculated for both Iron deficiency anemia and Beta thalassemia trait using the formulae as stated above in the description. The values have been tabulated below in table 1:

Table 1

PARAMETERS FOR MENTZER INDEX	IDA	β-TT
Sensitivity (%)	90	85
Specificity (%)	85	90
PPV (%)	88.2	87.1
NPV(%)	87.1	88.2

Sensitivity is the probability that a test will indicate 'disease' among those with the disease while specificity is the fraction of those patients without disease who will have a negative test result. Mentzer index was found to be more reliable to detect true positive cases for Iron deficiency anemia with a sensitivity of **90 %** whereas it was more specific to pick the true negative cases of Beta thalassemia trait with a specificity of **90 %.** The positive predictive values for IDA &β-TT were 88.2 % and 87.1 % respectively. The negative predictive value for IDA &β-TT were 87.1 % and 88.2 % respectively.

Youden's index was also calculated using the formula : (Sensitivity + Specificity) – 100 , which came out to be **75.**

IV. Discussion

β-TT and IDA are among the most common causes of microcytic anemia encountered in India. Distinguishing β-TT from IDA has important clinical implications because each disease has an entirely different cause, prognosis, and treatment. Children are predisposed to iron deficiency because of dietary insufficiency, growth and helminthic infestations. On the other hand, beta thalassemia trait is usually asymptomatic which is caused by mutation in one beta globin gene. Beta thalassemia accounts for a major disease load in Southeast Asia especially in India. In India, the communities which are majorly inflicted are Sindhis, Gujaratis, Punjabis, Prajapatis, Bengalis and Kachchis due to presence of higher number of thalassemia trait patients [8]. Misdiagnosis of β-TT has consequences for potential homozygous offspring leading to beta thalassemia disease.

The presenting symptoms of patients suffering from Iron deficiency anemia and Beta thalassemia trait are usually similar consisting mostly of fatigue, breathlessness, anorexia, angular stomatitis & irritability. However, most of the patients of β-TT remain asymptomatic and present with symptoms in their later age.

The diagnosis of iron deficiency anemia depends upon reduced PCV, MCV, MCH, and MCHC but is confirmed by carrying out iron studies. The classical findings seen in iron deficiency anemia are reduced serum ferritin and serum iron along with increased total iron binding capacity. The diagnosis of thalassemia is dependent upon demonstration of increased HbA2 levels in blood (> 3.5%) on Hb electrophoresis and mutation analysis [9]

There have been many investigators who have used different mathematical indices to distinguish β-TT from IDA using only a complete blood count. This process helps to select appropriate individuals for a more detailed examination; however, no study has a single index which was 100% specific &/or 100% sensitive. Elevated RBC count might be associated with erythrocytosis. We observed that the RBC count increased at the initiation of iron therapy in patients with IDA and decreased by the end of therapy.

In 2009, Ehsani et al. showed that the best discrimination index according to Youden's criteria was the Mentzer index (90.1%), followed by the Ehsani et al. index (85.5%). In their study, the Mentzer and Ehsani et al. were able to correctly diagnose 94.7% and 92.9% of cases, respectively [10].

Though the definitive tests for iron deficiency anemia and thalassemia are iron studies and Hb electrophoresis respectively, it is difficult to perform these tests in all patients having microcytic hypochromic anemia as they are costly. The HbA_2 analysis is however considered to be the gold standard for diagnosing thalassemia. It is for this reason that Mentzer index as a diagnostic screening tool was studied to differentiate between iron deficiency anemia and thalassemia trait. [11]

The diagnosis of β-TT involves measuring the HbA_2 concentration of lysed RBCs via HPLC. Several studies have shown that iron deficiency directly affects the rates of HbA_2 synthesis in bone marrow; therefore, 16–20 weeks of iron therapy should be instituted, after which a repeat serum iron with electrophoresis is done to confirm improvement in the HbA_2 levels [12].

V. Conclusion

Beta thalassemia trait and iron deficiency anemia are conditions causing microcytic hypochromic anemia. Though the definitive diagnosis depends upon iron studies and Hb electrophoresis, in cases where these studies are not possible Mentzer index can be used to screen the patients. In our study Mentzer index proved to be a reliable tool in differentiating between the two showing a sensitivity and specificity of 90% & 85% for Iron deficiency anemia and 85 % & 90% for Beta thalassemia trait respectively. Hence, Mentzer index can be used as a reliable diagnostic screening tool, however a confirmation by electrophoresis will be needed. The calculated Youden's index was significant with a value of 75 %.

Compliance with ethical standards

Funding – This study was not funded.

Conflict of interest – There was no conflict of interest by any of the author.

Ethical approval: This article does not contain any studies with human participants or animals performed by any of the authors.

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