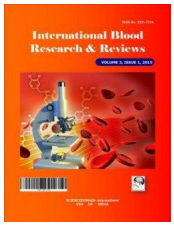

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Variation in Blood Indices in Cases of Anemias Coexisting with HbE from Eastern India

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Authors' contributions

This work was carried out in collaboration between all authors. Author TC had organized the study, observed the results, written the manuscript and answers to the reviewer's queries. Authors SC and AC are the clinical collaborators of this study and hence confirmed the clinical observations. All authors read the manuscript and finally approved it.

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Case Study

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ABSTRACT

Hemoglobin E is one of the most common forms of abnormal hemoglobin, related to hemoglobinopathies in the world. It can result in a heterogeneous group of disorders ranging from asymptomatic to severe anemia with regular blood transfusion dependency. HbE trait and HbE/E are mild disorders, as compared to other form of β globin defect. But when HbE combine with other forms of anemia, it can yield variety of clinical manifestations. Not only these various clinical changes caused by HbE hemoglobinopathy in homozygous or heterozygous forms, but also the standard haematological parameters changes interestingly often leading to misdiagnosis, when other anemia like Aplastic Anemia and Iron Deficiency Anemia are coexisted with HbE allele.
In this paper, we have tried to address how different anemias along with HbE hemoglobinopathy can bring about changes in different hematological parameters. We have categorically tried to address the issue by comparing the specific and relevant hematological parameters of these HbE

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hemoglobinopathy patients, with presence of others forms of anemia, like aplastic anemia, iron deficiency anemia.
This paper can give very significant clues to both the future researchers and clinicians to diagnose the HbE hemoglobinopathy with more certainty and clarity, when other forms of anemia co-existed with HbE.

Keywords: Hemoglobinopathy; thalassaemia; HbE; anemia; Iron Deficiency Anemia (IDA); aplastic anemia.

1. INTRODUCTION

Hemoglobin (Hb) E is one of the most common forms of abnormality of hemoglobin, related to hemoglobinopathies in Eastern India [1,2]. It can show wide spectrum of clinical severity, ranging from almost asymptomatic to severe anemia with requirement of regular blood transfusion. HbE trait and HbE/E are mild disorders, as compared to other form of β globin defect [3,4]. HbE is caused by a substitution of glutamic acid by lysine at codon 26 of the β-globin gene. This mutation also activates a cryptic mRNA splice site, which results in reduced synthesis of the β-E chain and leads to an abnormal hemoglobin. HbE has a weakened α/β interface, leading to some instability during conditions of increased oxidative stress. HbE trait patients may have mild microcytosis without anemia [5], where as thalassaemia is characterized by defects in hemoglobin synthesis, resulting in red blood cells that are abnormally small (microcytic) and contain a decreased amount of hemoglobin (hypochromic) [6]. The capacity of the blood to deliver oxygen to body cells and tissues is thus reduced for thalassaemia patients. HbE allele of one of the β-globin gene often combines with other β-globin mutations, related to β thalassaemia to produce a compound heterozygous condition of HbE-β thalassaemia [7].

Iron deficiency anemia (IDA) is a common anemia (low red blood cell or hemoglobin levels) caused by insufficient dietary intake and absorption of iron, and/or iron loss from bleeding which can originate from a range of sources such as the intestinal, uterine or urinary tract. On the other hand, Aplastic Anemia is a disease in which the bone marrow, and the blood stem cells that reside there, are damaged. This causes a deficiency of all three blood cell types (pancytopenia): white blood cells (leukopenia), red blood cells (anemia), and platelets (thrombocytopenia) [8,9]. Aplastic refers to inability of the stem cells to generate the mature blood cells.

The haematological picture in terms of determining the HbE status may appear as very much confusing when these anemias (iron deficiency anemia, aplastic anemia etc.) co-existed specially in the same patient. For the HbE/E individuals, the red cell morphology may show asymptomatic with very mild anemia and microcytosis [10]. The red cell morphology picture may be similar to other thalassemia traits or mild thalassemia intermedia conditions.

2. STUDY DESIGN

This study is strategically so designed that, it can reveal the picture of variation among the standard hematological parameters routinely evaluated by the haematologist and diagnosis is done on the basis of these values quite frequently. These standard haematological parameters include Hemoglobin (Hb), Mean Cell Volume (MCV), Mean Cell Hemoglobin (MCH), Mean Cell Hemoglobin Concentration (MCHC), Red Cell Distribution Width (Rdw) etc. These were evaluated by Cell Counter (Medonic 530; Merck KGaA, Darmstadt, Germany) and Hemoglobin fractions (HbF, HbA and HbA2/E) were evaluated by High performance liquid chromatography (VARIANT I^{TM}; Bio-Rad Laboratories, Hercules, CA, USA). These values could be deceptive if other hemoglobin associated clinical conditions co-exist along with thalassaemia or other forms of hemoglobinopathies.

In this paper, we have tried to show, by taking four different cases, how these standard haematological parameters vary when other anemias like Aplastic Anemia and Iron Deficiency Anemia coexisted with HbE allele. First case sited in this paper, is a case of typical Aplastic Anemia, whereas the second case is of a patient who is an HbE trait/ carrier and also has Aplastic Anemia simultaneously. Comparing the haematological parameters in between these two cases can reveal interesting observations. Third case is a typical example of an Iron Deficiency Anemia patient, who is not inheriting any

β thalassaemia specific allele. In connection to this, our fourth selected case is of a HbE trait boy, who is also having Iron Deficiency Anemia. It will be really interesting to observe the differences between the standard haematological parameters in the selected cases.

3. CASE REPRESENTATIONS

3.1 Case I (Typical Aplastic Anemia)

A male child of 16 years old with normal beta globin gene along with Aplastic anemia also showed thalassaemia major like blood transfusion dependency, though he was showing exactly opposite hematological indices like normal MCV, MCH and MCHC values (Fig. 1), in compare to β thalassaemia. His diagnosis of Aplastic Anemia was confirmed by bone marrow biopsy and karyotyping. For this case, the most important part is his increased HbA2 and HbF values. Here, both parents are 'Normal', not having any type of 'thalassaemia trait'. So, the son is definitely not β thalassaemic. The son is 'Aplastic', with high HbF & HbA2, like thalassaemia major patient, may be wrongly diagnosed as β thalassaemia.

3.2 Case II (Aplastic Anemia with HbE Trait)

A male child of 11 years old with HbE/+ along with aplastic anemia showed thalassaemia major like blood transfusion dependency. Though he was HbE/+, there was no sign of microcytic, hypochromic RBCs. Rather, his RBCs was completely normocytic and normochromic (high MCV and MCH values) (Fig. 2). This is probably due to aplastic anemia, which is co-existed in him and made his RBC indices (MCV, MCH, MCHC etc.) very much normal. But, aplastic anemia also causes very much decrease in hemoglobin level (Hb= 4.7 g/dl). So, overall, the hematological and clinical picture of the boy with these two conditions like aplastic anemia and HbE trait is really interesting to follow. His hemoglobin is 4.7 g/dl, with MCV 100 fL, MCH 42.5 pg. and transfusion dependency is like thalassaemia major.

3.3 Case III (Typical Iron Deficiency Anemia)

A male child of 12 years, when came to our clinic for diagnosis, showed the classical symptoms of anemia. But, when his HPLC was done, it looked like normal (Fig. 3). Though mutation study was not done for the child, but the absence of β thalassaemia or others forms of inherited hemoglobin disorder was reconfirmed by performing HPLC of the both the parent (Fig. 3). But, the boy was definitely anaemic, which was evident from the total estimated hemoglobin (Hb = 8.3 g/dl). MCV and MCH show normocytic indices of RBCs. That's why, serum ferritin was tested and without any surprise, it was found to

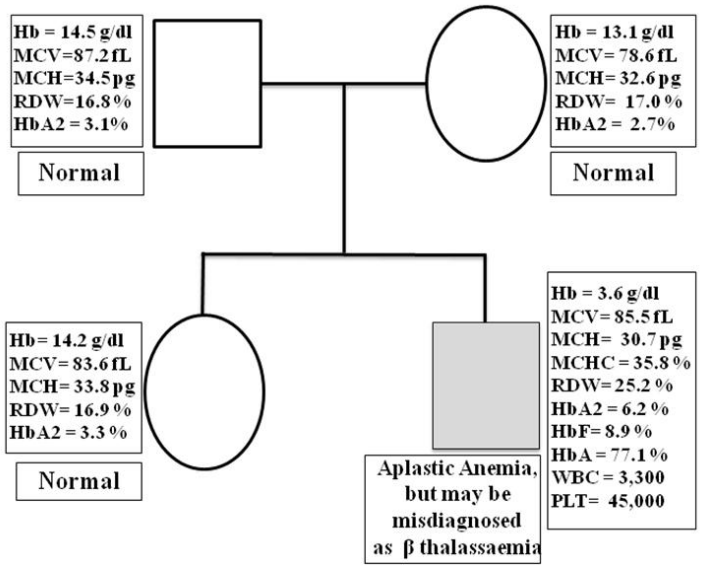

Fig. 1. Pedigree chart of a family having an Aplastic Anemia son with normal β globin, as evident from hematological data of parents and elder sister

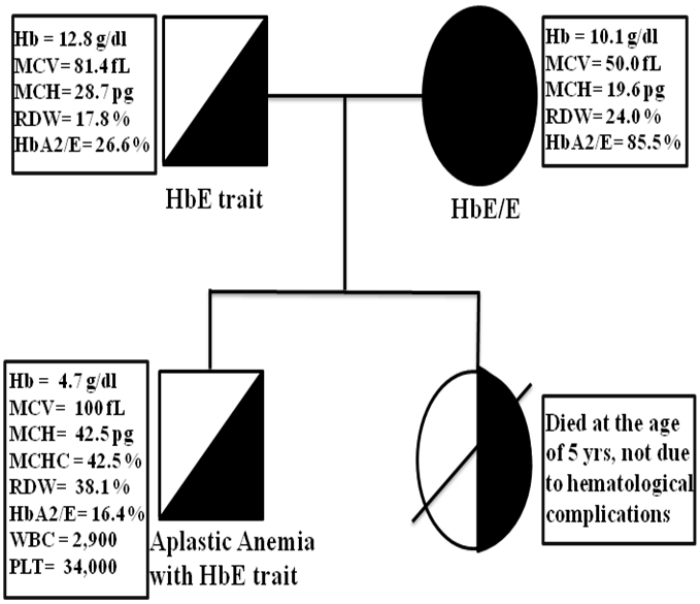

Fig. 2. Pedigree chart of a family having HbE trait son with Aplastic Anemia, HbEE mother and HbE trait father

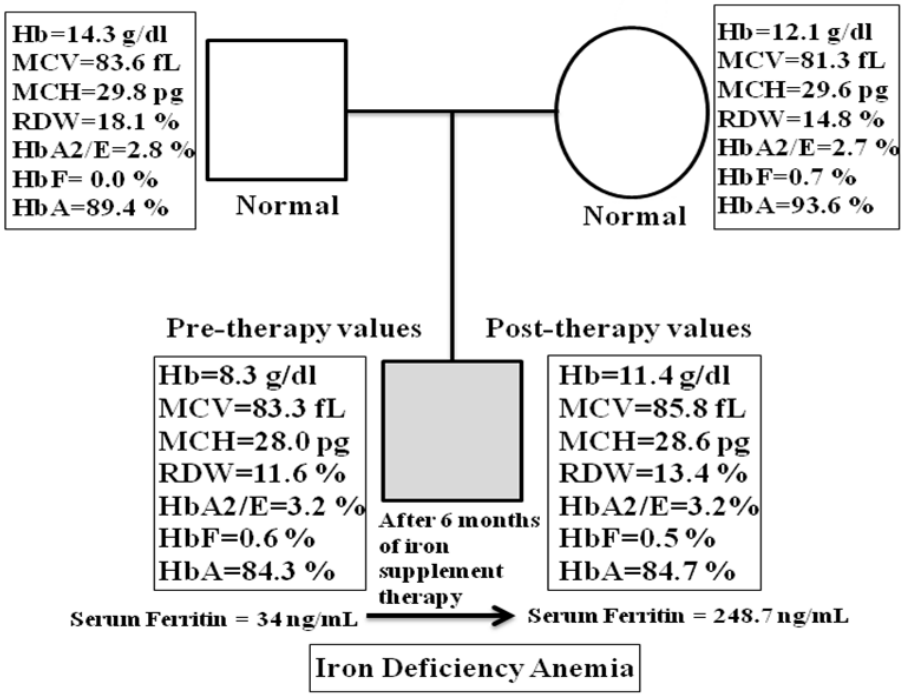

Fig. 3. Pedigree chart of a family having Iron deficiency anemia son from normal parents and also showing hematological profile of the son before and after 6 months of iron supplement therapy

be 34 ng/mL. Iron supplement therapy was implemented and after 6 months of iron supplementation the hemoglobin was increased to 11.4 g/dl from 8.3 g/dl. So, a total of 3.1 g/dl increase in total hemoglobin level was seen by implementing iron supplementation. In the Fig. 3, pre therapy values indicates the hematological indices before starting the iron supplementation

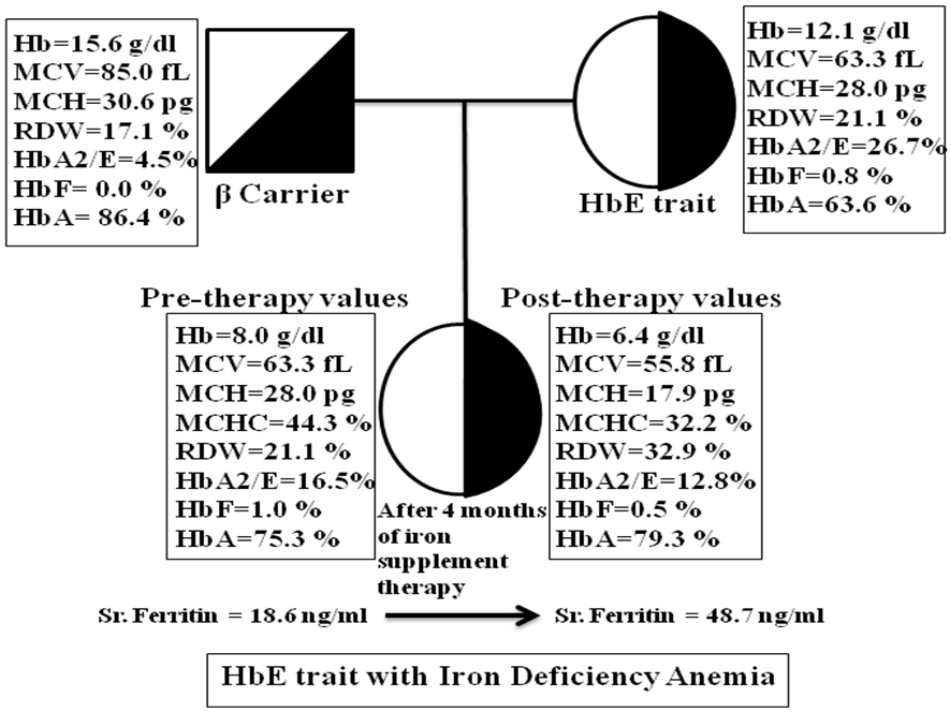

Fig. 4. Pedigree chart of a family having HbE trait with iron deficiency anemia daughter, HbE trait mother, β carrier father and also showing hematological profile 4 month before and after Iron supplement therapy

therapy and post therapy values indicates the hematological indices after 6 months of continuation of iron supplementation.

3.4 Case IV (Iron Deficiency Anemia with HbE Trait)

A female child of 14 years old with HbE/+ along with Iron deficiency anemia showed thalassaemia intermedia like clinical condition with occasional blood transfusion history. Though mutation study was not performed for the child, but to reconfirm her hemoglobinopathy status, HPLC of both parents was performed. Her Her father was found to be beta trait and mother was HbE/+. The daughter was HbβE/+ like her mother, but showed low hemoglobin value due to coinheritance of iron deficiency anemia along with HbE (Fig. 4). Iron deficiency anemia was quite evident as serum ferritin level was found to be 18.6 ng/ml and clear evidence of microcytosis (MCV=63.3 fL) and with an iron supplementation therapy for 4 months her hematological indices showed interesting variation from the pre-therapy values. After therapy, the only improvement was seen in serum ferritin values. t got changed from 18.6 ng/ml to 48.7 ng/ml.

4. INTERESTING OBSERVATIONS IN CASES

Case I may probably be reported as Beta thalassaemic, if only HPLC data is observed. But, that would be completely wrong diagnosis. If the CBC is followed carefully, it can be predicted that, it is normocytic normochomic anemia, so it can't be thalassaemia. Now the interesting things happen in case II, when two opposite conditions, one trying to make RBC microcytic (which is presence of HbE hemoglobinopathy) and other normocytic (which is presence of Aplastic Anemia) in the same patient. But actually, what we can see is the increase in mean corpuscular volume of RBC (MCV=100). We can also see the higher MCH and hemoglobin, which means the patient who is inheriting two opposite conditions together, actually remains clinically better than the one who inherits only one condition (here Aplastic Anemia). This fact is found to be very much interesting to point out.

Among case III and case IV, case III is a typical iron deficiency anemia patient. So, we can observe major improvement in hematological indices and clinical profile after iron

supplementation therapy. But, similarly for case 4, who is similar iron deficiency anemia patient, but, also co-inheriting the HbE allele, showed completetely different response to iron supplementation therapy. Her hematological picture became worse after iron supplementation, though serum ferritin got improved little bit. But no significant clinical improvement was seen in her. So, for patients who inherits other alleles, related to hemoglobinopathies including thalassaemia (Here HbE) along with iron deficiency, for them iron supplementation may not give positive results always. This point found to be very much interesting to us in the selected cases.

5. DISCUSSION

Anemia is very hard to define clinically, as there are too many conditions viz. pathophysiological, clinical, subclinical, inherited, which can cause anemia. The only characteristic feature in anemia, is the fall in haemoglobin level, compare to normal. But along with this, anemia can be represented with all forms of RBC size, microcytic, normocytic and macrocytic (Fig. 5). Thalassaemia, iron deficiency anemia are the examples of microcytic hypochromic anemia. Aplastic anemia, myelophthisic anemia, and myelofibrosis are examples of normocytic and normochromic anemias. Folate deficiency, vitamin B12 deficiency, alcohol abuse, myelodysplastic syndromes and reticulocytosis can cause macrocytic anemia. As the cause of development of anemia is diverse, so hematological indices vary greatly with pathophysiological, clinical, subclinical and inherited causes when two or more causes coexist, it influences RBC indices differently.

Here in this paper, we have observed the variation of the hematological indices in HbE hemoglobinopathy patient, with the coexistence of other forms of anemia like iron deficiency anemia, aplastic anemia. The cases strategically taken to compare the HbE hemoglobinopathy in presence of others forms of anemia. Typical aplastic anemia patient was clinically compared with a patient, who has HbE trait coexisted with aplastic anemia, as both condition is known for causing anemia with different RBC size (HBE causes microcytosis and in aplastic anemia RBCs remain normocytic). The standard hematogical parameters like hemoglobin (Hb), MCV, MCH, MCHC, RDW shows interesting variations in aplastic anemia with HbE patients in compare to the typical aplastic anemia patient. If case III (typical iron deficiency anemia) and case IV (iron deficiency anemia with HbE trait) can be compared, we can see interesting difference of effect of iron supplementation therapy in both patients. Typical iron deficiency anemia patient (case III) showed significant improvement after iron supplementation therapy. But, the patient, who inherit HbE trait along with iron deficiency anemia (case IV) didn't show much sign of improvement in haematological indices, except mild increase in serum ferritin level. So, presence of HbE can bring about interesting changes in response criteria to iron supplementation therapy for the iron deficiency anemia patients, if coexisted together.

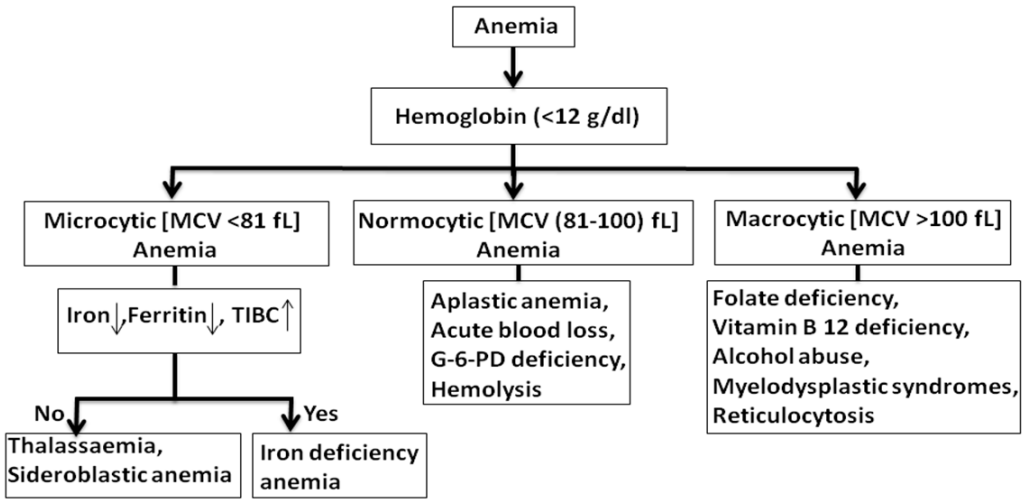

Fig. 5. Clinical pathway for determination of anemia

6. CONCLUSION

The presence of other clinically relevant conditions (different anemias) along with HbE hemoglobinopathy can bring about interesting changes in values of clinical parameters. So, most often the HbE may be misdiagnosed if other anemia coexisted along with HbE. We have categorically tried to address the issue by comparing the specific and relevant clinical parameters of these HbE haemoglobinopathy patients, with presence of others forms of anemia, like aplastic anemia, iron deficiency anemia. The interesting and clinically significant changes of these hematological parameters in HbE cases along with the presence of other forms of anemia, can be interesting to follow and can give very significant clue to both the future researchers and clinicians to diagnose the disease with more certainty and choose appropriate therapeutic interventions.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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