REVIEW ARTICLE

Ann Ibd. Pg. Med 2012. Vol.10, No.2 11-15

THALASSAEMIA IS A TROPICAL DISEASE

T.R. Kotila

Department of Haematology, University College Hospital, Ibadan

Correspondence:
Dr. T.R. Kotila
Department of Haematology,
University College Hospital,
Ibadan, Nigeria.
Email: tkotila@comui.edu.ng

ABSTRACT

Genes for thalassaemias, sickle cell disorders and Glucose-6-phosphate dehydrogenase (G6PD) deficiency are known to be associated with prevalent malaria infection. The prevalence in the heterozygote state for sickle cell anaemia (SCA), G6PD and alpha thalassaemia is between 25-30% in Nigerians but the prevalence for the beta thalassaemia trait (BTT) is low. Under-diagnosis of BTT may arise from the similarity in its clinical manifestation to that of SCA which is of high prevalence in Nigeria and secondly because the hypochromia and microcytosis associated with it may be misdiagnosed as iron deficiency anaemia. There is therefore the need to review this disorder in the light of the wide use of automation in processing a full blood count which will include red cell indices, a good screening method for the thalassaemias. This expectedly will aid easy and early diagnosis of the disorder.

Keywords: Thalassaemia, malaria, red cell indices, misdiagnosis.

INTRODUCTION

Tropical diseases are diseases that are prevalent or unique to the tropical and subtropical regions. Though there are many tropical diseases malaria remains the most common vector-borne disease that is widespread in the tropical and subtropical regions of the world. It is also the strongest known force for evolutionary selection in the recent history of the human genome[1]. Malaria is also the evolutionary driving force behind sickle cell disease, thalassaemia and Glucose-6-Phosphate Dehydrogenase (G6PD) deficiency. The global distribution of thalassaemia encompasses the major malaria prevalent regions of Africa, Asia and Mediterranean regions where malaria was once common. The distributions of the genes associated with malaria are similar in the heterozygote state among Nigerians. The prevalence for sickle cell disease, G6PD deficiency and alpha (α) thalassaemia in the heterozygote state is 25-30%[1-3], it is not until recently that the prevalence of beta (β) thalassaemia trait was found to be similar[4]. It is therefore likely that there is an under-diagnosis of the thalassaemia in the African setting mostly because of the lack of the required diagnostic facilities. This however, should not preclude physicians from entertaining the diagnosis, hence the need to discuss these disorders.

The distribution of á thalassaemia though worldwide is restricted in clinicaly severity. The clinically severe type which is associated with hydrops fetalis and HbH disease is found mostly in South East Asia and occasionally in the Mediterranean region. The deletional form in contrast to those due to point mutation is of lesser clinical severity and has a more globally distribution. The only type of α thalassaemia found in Nigerians till date is the $-\alpha^{3.7}$deletion (5), recently 300 chromosomes were screened for á thalassaemia and only the $-\alpha^{3.7}$ deletion was detected with 42% being heterozygote and 9% homozygote (in press). The implication of this is that the α thalassaemia present in Nigerians is of little clinical significance. Beta thalassaemia on the other hand is almost always of clinical significance though the severity differs too and it is therefore classified clinically into thalassaemia major, intermedia and minor. If the prevalence of β thalassaemia is as high as recently stated[4], then the disease and its complications are being misdiagnosed[6]. There is a need therefore to review this subject with a view to understand the subtle ways in which it may be misdiagnosed. This communication will discuss mostly the epidemiology, pathogenesis, clinical presentation and management of β thalassaemia. The diagnosis of the disorder was discussed alongside that of other haemoglobinopathies extensively in an earlier communication[7]

Epidemiology

It is estimated that 1.5% of the world's population are carriers of β thalassaemia with an estimated 60,000 new carriers born each year[8]. Southeast Asia accounts for about 50% of the world's carriers while Europe and the Americas jointly account for 10-13% of the world carriers[9]. Beta thalassaemia is widespread

throughout the Mediterranean with uneven distribution in Greece and Italy, but it is less common at the western end of the Mediterranean and appears to be little in France except in those of Italian or Spanish descent[10]. The disorder is however common in the Middle East and west Asia, and it is probably the commonest inherited haemoglobin disorder in India. Sickle cell disease on the other hand is believed to dominate the haemoglobinopathies in south of the Sahara, while β thalassaemia is reported to be between 3-7% in most of North Africa[10].

Pathogenesis

The imbalance between the α and β globin chains of haemoglobin results in thalassaemia. The reduced amount or absence of beta globin chains in β thalassaemia result in a relative excess of unbound alpha globin chain that precipitate in erythroid precursors in the bone marrow, this interferes with maturation of the red cells and its destruction in the bone marrow (ineffective erythropoesis), it also results in marrow expansion. The resultant hypertrophy of erythroid marrow is characterized by deformation of the bone of the face, it could also result in osteoporosis with pathologic fracture of long bones. The red cell membrane is not unaffected since structural abnormalities of the membrane cause premature destruction of the red cells hence a shortened life span. Peripheral haemolysis contributing to anaemia is less prominent in thalassaemia major than in thalassaemia intermedia, and occur when alpha globin chains induce membrane damage to the red cell. The resulting anaemia stimulates the production of erythropoietin with consequent intensive but ineffective expansion of the bone marrow which causes the said bone deformities (frontal bossing, with enlarged maxilla). Prolonged severe anaemia along with increased erythropoetic drive result in extramedullary erythropoesis and hepatosplenomegaly, it can also result in the formation of erythropoetic masses which may primarily affect not only the spleen and the liver, but also the lymph nodes and spine[11]. Haemolysis sometimes results in gallstones but this also occurs more commonly in thalassaemia intermedia than major[12]. Although individuals with thalassaemia intermedia are at risk of iron overload, secondary to increased intestinal absorption, hypogonadism, hypothyroidism and diabetes are not common in them.

Clinical Presentation

The clinical findings in β thalassaemia is similar to what is found in sickle cell disease, this will explain the difficulty in differentiating between patients with sickle cell disease and β thalassaemia on clinical grounds in this environment where the incidence of sickle cell anaemia is high. Clinical findings in â thalassaemia also depend on whether the patient is poorly transfused (untreated) or on a regular transfusion programme, since the excess iron from regular transfusion compounds the scenario in the well transfused patient. Findings in untreated or poorly transfused individuals with thalassaemia major, as seen in some developing countries, are growth retardation, pallor, jaundice, poor musculature, hepatosplenomegaly, leg ulcers, and development of masses from extramedullary haemopoesis and skeletal changes that result from expansion of the bone marrow[11]. Regular transfusion on the other hand leads to iron overload and related endocrine complications which includes failure of puberty, diabetes mellitus and insufficiency of the parathyroid, thyroid, pituitary and less commonly the adrenal glands. It may also result in dilated cardiomyopathy, liver fibrosis with or without cirrhosis. The patients are also classified into thalassaemia major, intermedia or minor depending on the regularity with which they require blood transfusion. Thalassaemia major patients will often require blood transfusion in the first two years of life and may not survive if not on regular blood transfusion. Thalassaemia intermedia patients will only require transfusion later in life and may not require regular transfusion while thalassaemia minor patients are often asymptomatic with mild anaemia but could sometimes have moderate anaemia. Patients with thalassaemia intermedia frequently develop leg ulcers and have an increased predisposition to thrombus formation especially if splenectomised in contrast to thalassaemia major patients. Such events include deep vein thrombosis, portal vein thrombosis, stroke and pulmonary embolism[13].

Diagnosis

The thalassaemias generally are classified as hypochromic and microcytic anaemia. Hence the mean corpuscular volume (MCV) reported in femtoliters is a key diagnostic indicator even though the pattern of mean corpuscular haemoglobin (MCH) is usually similar to that of MCV. Virtually all automated haematology analyzers now provide a measurement of MCV that is both precise and accurate. In most adult populations it ranges from 80-100fl. Thalassaemic individuals have a reduced MCV; studies have suggested that the MCV may predict the mutation and thus severity[14] and that a value of 72fl is maximally sensitive and specific for a presumptive diagnosis of β thalassaemia[15]. The Red cell distribution width (RDW) is a measure of the degree of anisocytosis (variation in red cell size). Iron deficiency which is also a cause of microcytic anaemia is characterized by an increase in RDW while the thalassaemias in contrast, produce a uniform microcytic red cell population

without a concomitant increase in RDW. Therefore, the RDW provides useful information as an adjunct to diagnosis but is not useful as a single indicator. The red blood cell (RBC) count is also a useful diagnostic adjunct because the thalassaemias produce microcytic anaemia with an associated increase in the RBC number. Other causes of microcytic anaemia, including iron deficiency and anaemia of chronic disease are more typically associated with a decrease in the RBC number that is proportional to the degree of decrease in haemoglobin concentration[16]. An elevated HbA2 is the hallmark of the classic beta thalassaemia trait (BTT) while HbF is raised by about 1-3% in one third to half of the people with BTT[17].

The iron status of multi-transfused patients can be assessed by several methods but serum ferritin has in general been found to correlate with body iron stores[18], being an acute phase reactant it is however influenced by other factors such as inflammatory disorders, liver disease and malignancy. Despite this, serial measurements of serum ferritin remain a reliable and the easiest method to evaluate iron overload and efficacy of chelation therapy[11]. Determination of liver iron concentration in a liver biopsy specimen shows a high correlation with total body iron accumulation and is considered the gold standard for the evaluation of iron overload[19]. However, liver biopsy is an invasive procedure which may be associated with complications.

Thalassaemia patients often have significant iron stores either from blood transfusion or increased absorption from the gut, but this iron could be unavailable for haemopoesis. Methods to quantify the iron content of the heart and liver are therefore important in monitoring the course of iron accumulation and the effect of chelation therapy. The magnetic resonance T2* technique is now widely used for the evaluation of myocardium and liver iron[20] values less than 20ms indicate iron overload, it is considered severe when it is less than 10ms and is associated with systolic and diastolic ventricular dysfunction[21]. It was recently reported that the relative risk for heart failure with cardiac T2* values less than 10ms versus values greater than 10ms was 160 and that heart failure occurred in 47% of patients within 1year of cardiac magnetic resonance imaging when T2* was less than 6ms[22].

Major Complications

Heart: Heart complications are the first cause of death in thalassaemia major and it is the consequence of iron overload. Patients with thalassaemia intermedia with less severe haemosiderosis are less prone to cardiac problems. Heart complications found in most patients include congestive cardiac failure, chronic pericardial changes and valvular problems.

Pulmonary hypertension is also a common cause of secondary right heart failure.

Thromboembolic: Thromboembolic complications are frequent in thalassaemia and are four times more frequent in thalassaemia intermedia than in major, with more venous events occurring in thalassaemia intermedia and more arterial events occurring in thalassaemia major[23]. It has been suggested that the presence of a chronic hypercoagulable state could be due to the procoagulant effect of the phospholipids exposed on the surface of the damaged circulating red blood cells.

Endocrine: Endocrine problems are less common in thalassaemia intermedia than in thalassaemia major, but the frequency reported is highly variable, and depends on the severity of the anaemia and the degree of iron overload. Hypogonadism is the most frequent endocrine complication, affecting female more than male patients[24]. This is followed by diabetes and hypothyroidism, reported in 24% and 5.7% of thalassaemia intermedia patients respectively[21]. Delayed puberty is not unusual, as are irregular menses. Oligospermia and azoospermia affect more than one half of men with thalassaemia[25]. Pregnancy is also burdened with complications.

Bone Disease: Osteoporosis is a common cause of morbidity in patients with α thalassaemia with a prevalence as high as 50%[26]. This is sometimes associated with pathological fracture, the prevalence of which is clustered in mid adulthood in thalassaemia major patients[27], it is related to vitamin D deficiency and low bone mineral density. Endocrine complications in addition to progressive marrow expansion, iron and desferrioxamine toxicity on bones, as well as liver disease contribute to the complex mechanism of osteoporosis in thalassaemia patients[28].

Treatment Options

Blood Transfusion: Patients with thalassaemia major are transfusion dependent but this is not so in thalassaemia intermedia. The most difficult therapeutic choice that needs to be made when treating a patient with thalassaemia intermedia is whether or not to initiate a chronic transfusion programme[29]. Sometimes transfusion becomes necessary during infection induced aplastic crisis. The consequences of withholding transfusion are medullary and extramedullary hyperplasia. It should also be noted that transfusion regimen initiated in childhood to favour growth, can be discontinued after puberty. Conversely, some adults who have remained transfusion independent for two or more decades gradually develop severe anaemia, requiring regular blood transfusion.

Chelation: Since the body has no effective means of effectively removing iron, the only way to remove excess iron is to use iron chelators. The major step forward in improving survival and reducing complications was the introduction, in the 1960s of the chelating agent deferoxamine, initially used as an intramuscular injection but later as a subcutaneous infusion. Two oral chelators, deferiprone and deferasirox, have recently become available, making therapy easier and more efficacious. Compliance, although improved by the switch to oral therapy, still presents a problem and is the major obstacle to effective prevention of iron overload. The orally active chelators seem to be more effective in gaining access to the chelatable iron pool of cardiomyocytes, binding labile iron, and attenuating reactive oxygen species formation[30].

Stem Cell Transplantation: Haemopoetic stem cell transplantation is available for patients who have a related or unrelated HLA-identical donor. The probability of cure ranges from 90-95% for recipients of grafts from relatives[21] to 80-85% for those receiving grafts from an unrelated donor, although the probability even in these cases approaches 90% when donor matching is as strict as that between HLA-identical siblings[31]. The transplant related mortality, even in the best conditions, average 5%, a risk that is worth running probably only in severe transfusion dependent disease.

Gene Therapy: This offers a potential cure for β thalassaemia and would represent an ideal alternative to both conventional therapy and bone marrow transplantation. Gene therapy however poses some challenges among which is the instability and poor expression of retroviral vectors carrying the human β-globin cassette. Considerable progress has now been made using lentiviral vectors which stably transmit the β-globin expression cassette.

Other forms of treatment used in sickle cell disease are equally beneficial in thalassaemic patients. HbF reactivation by 5 azacytidine, Butyrate and Hydroxycarbamide (Hydroxyurea) has been found to be equally effective in thalassaemia patients. Even though Hydroxyurea has been approved for use in sickle cell disease but not in thalassaemia it is being administered all over the world with impressive results. Recombinant Human Erythropoetin (rHuEPO) can increase haemoglobin level in some patients with thalassaemia intermedia but the effect is transient and the drug is expensive, the subcutaneous administration is also inconvenient. The most commonly used dose is 5-10 times higher than the dose used for anaemia in chronic renal failure[29]. Treatment with antioxidant is not uncommon in thalassaemia patients because oxidative damage is believed to be a main contributor to cell injury in these patients. The daily use of folic acid is also advised in thalassaemia patients since there is increased folate utilization caused by increased erythropoesis.

Survival

Thalassaemia used to be a paediatric disease, but the median age of patients has now increased because of increased survival and birth rate reduction. Individuals who have not been regularly transfused usually die before the second-third decade while those who have been regularly transfused and treated with appropriate chelation live beyond the age of 40. Cardiac complications are the cause of death in 71% of patients with thalassaemia major[11]. Population screening, genetic counseling and the availability of prenatal diagnosis have also been extremely effective in controlling the disease.

CONCLUSION

The thalassaemias are under-diagnosed in the African setting even though genes for the thalassaemias are among the genes that are associated with malaria infection. Reasons attributed to this include firstly, the similarity between its mode of presentation and that of sickle cell disorders which are very prevalent in the environment. Secondly, the hypochromic microcytic anaemia commonly associated with it may be misconstrued as iron deficiency anaemia. The required confirmation by genetic studies especially in an epidemiological survey is also absent. These pitfalls are however insufficient reasons not to entertain the diagnosis especially when the red cell indices are suggestive of the diagnosis.

REFERENCE

1. **Kwiatkowski DP.** How malaria has affected the human genome and what human genetics can teach us about malaria. Am J Hum Genet 2005; 77:171-192
2. **Omotade OO,** Kayode CM, Falade SL, Ikpeme S, Adeyemo AA, Akinkugbe FM. Routine screening for sickle cell haemoglobinopathy by electrophoresis in an infant welfare clinic. West Afr J Med.1998;17:91-94
3. **Ademowo OG,** Falusi AG. Molecular epidemiology and activity of erythrocyte G6PD variants in a homogenous Nigerian Population. East Afr Med J 2002;79:42-44
4. **Kotila TR,** Adeyemo AA, Mewoyeka OO, Shokunbi WA. Beta Thalassaemia trait in Western Nigeria. Afr. Health Sci 2009;9:46-49

5. **Falusi AG,** Esan GJF, Ayyub H, Higgs DR. α Thalassaemia in Nigeria: its interaction with sickle cell disease. Eur J Haematol. 1987; 38:370-375
6. **Kotila TR.** When the inheritance of two heterozygote states become a diagnostic problem: Misdiagnosis of the sickle cell trait. Nig. J Med. 2007;16 No2: 173-176
7. **Kotila TR.** Guidelines for the diagnosis of the haemoglobinopathies in Nigeria. Ann Ibd Post Med. 2010;8:25-29
8. **Rathod DA,** Amarjeet K, Patel V *et al.* Usefulness of cell counter-based parameters and formulas in detection of β thalassaemia trait in areas of high prevalence. Am J Clin Pathol. 2007;128:585-589
9. **Angastinotis M.** Epidemiology In: Galanello R, Eleftheriou A, Traeger-Synodinos J *et al* eds. Prevention of Thalassaemias and other haemoglobin disorders. Vol I. Nicosia, Cyprus: Thalassaemia International Federation Publication; 2005:10-13
10. **Weatherall DJ,** Clegg JB. The thalassaemia syndrome. 2001; 4th edn. Blacwell Scientific Publications, Oxford
11. **Galanello R,** Origa R. Beta thalassaemia. Orphanet J Rare Dis. 2010;5:11-21
12. **Galanello R,** Pira S, Barella S *et al* Cholelithiasis and Gilbert's syndrome in homozygous beta thalassaemia. Br J Haematol 2001;115:926-928
13. **Taher AT,** Otrock ZK, Uthman I *et al.* Thalassaemia and hypercoagulability, Blood Rev 2008;22:283-292
14. **Rund D,** Filon D, Strauss N *et al.* Mean corpuscular volume of heterozygotes for β-Thalassaemia correlates with the severity of mutations. Blood1992;79:238-243
15. **Lafferty JD,** Crowther MA, Ali MA *et al.* The evaluation of various mathematical RBC indices and their efficacy in discriminating between thalassaemic and non-thalassaemic microcytosis. Am J Clin Pathol 1996;106:201-205
16. **Clarke GM,** Higgins TN. Laboratory investigation of haemoglobinopathies and thalassaemias: Review and Update. Clin Chem 2000;46:1284-1290
17. British Committee for Standards in Haematology. Guidelines for investigation of the α and β thalassaemia traits. J Clin Pathol 1994;47:289-295
18. **Brittenham GM,** Cohen AR, McLaren CE *et al.* Hepatic iron store and plasma ferritin concenteration in patients with sickle cell anaemia and thalassemia major. Am J Haematol 1993;42:81-83
19. **Angelucci E,** Brittenham GM, McLaren CE *et al.* Hepatic iron concentration and total body iron stores in thalassaemia major. N Engl J Med 2000;343:327-331
20. **Anderson LJ,** Holden S, Davis B *et al.* Cardiovascular T2-star (T2*) magnetic resonance for the early diagnosis of myocardial iron overload. Eur Heart J 2001;22:2171-2179
21. **Borgna-Pignatti C.** The life of patients with thalassaemia major. Haematologica 2010;95:345-348
22. **Kirk P,** Roughton M, Porter JB *et al.* Cardiac T2* magnetic resonance for prediction of cardiac complications in thalassaemia major. Circulation. 2009;120:1961-1968
23. **Taher A**, Isma'eel H, Mehio G *et al.* Prevalence of thromboembolic events among 8860 patients with thalassaemia major and intermedia in the Mediterranean and Iran. Thrombosis and Haemostasis 2006;96:488-491
24. **Papadimas J,** Goulis DG, Mandala E *et al.* Beta thalassaemia and gonadal axis: a cross-sectional clinical study in a Greek population. Hormones 2002;1:179-187
25. **De Sanctis V,** Katz M, Wonke B. Semen parameters in patients with homozygous β thalassaemia. Infertility 1989;12:167
26. **Voskaridou E,** Terpos E. New insight into the pathophysiology and management of osteo-porosis in patients with β thalassaemia. Br J haematol 2004;127:127-139
27. **Haidar R,** Musallam KM, Taher AT. Bone disease and skeletal complications in patients with β thalassaemia major. Bone 2011;48:425-432
28. **Toumba M,** Skordis N. Osteoporosis syndrome in thalassaemia major: An overview. J Osteoporos 2010;201:537-544
29. **Borgna-Pignatti C.** Modern treatment of thalassaemia intermedia. Br J Haematol 2007;138:291-304
30. **Glickstein H,** El RB, Link G *et al.* Action of chelators in iron loaded cardiac cells: accessibility to intracellular labile iron and functional consequences. Blood 2006; 108:3195-3203
31. **La Nasa G,** Argiolu F, Giardini C *et al.* Unrelated bone marrow transplantation for beta thalassaemia patients: the experience of the Italian bone marrow Transplant group. Ann NY Acad Sci 2005;1054:186-195