Cardiac Complications in Non-Transfusion Dependent Thalassaemia

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Abstract

Among the haemoglobinopathies non-transfusion dependent thalassaemia (NTDT) are more common than the major patients. Bangladesh is located within the thalassaemia belt, moreover, Hb-E is prevalent here. So, the burden of non-transfusion dependent haemoglobinopathies is pretty massive. Due to less severe presentation and unawareness of general people, most patients with NTDT present with complications. On the other hand, cardiac complications are the major causes of death in these patients, and, negligence in early treatment increases the death. This review discusses haemoglobinopathies in general, followed by pathogenesis, clinical features and management of cardiac complications.

Key Words: Non-Transfusion Dependent Thalassaemia (NTDT), Cardiac Complications

Introduction to Haemoglobinopathies

As a group, thalassaemia represents the most common single gene disorder. Thalassaemia are heterogeneous group of disorders characterised by reduced production of globin chain(s), and thus haemoglobin. Thalassaemia classically are classified into major, intermedia and minor (or trait), which denote severity of the disease; more recently these are classified into two groups: transfusion dependent (TDT) and non-transfusion dependent (NTDT) thalassaemia. All thalassaemia major patients are TDT and all intermedia patients are NTDT, irrespective of patient's genetics and Hb electrophoretic pattern. It should be remembered that, TDT and NTDT labelling implies patients present condition and may vary from time to time throughout his or her lifetime.¹

Depending on Hb electrophoresis and genetics thalassaemia are classified into large groups: alpha-thalassaemia and beta-thalassaemia, which denotes absence or reduced production of respective Hb globin chain. There are of course many complex forms like delta-beta thalassaemia, heterozygosity of abnormal Hb with thalassaemia, and HbE inheritance. Due to variable penetrance of hundreds of mutations responsible for thalassaemia, disease severities are also variable. HbE state is unique among other Hb disorders in the respect that, a single genetic mutation, G (guanine) to A (adenine) at codon 26, which is

translated into substitution of amino acid lysine in place of glutamic acid in the globin chain, causes production of not only an abnormal beta chain, but also, production of Hb in reduced amount. That is why it is a thalassaemic haemoglobinopathy disorder. The highest prevalence of the structural variant haemoglobin E is observed throughout India, Bangladesh, Thailand, Laos, and Cambodia where carrier frequencies may reach as high as 80%.^{2,3}

If NTDT is correlated with Hb electrophoretic and genetic pattern, this will include, in broad headings, beta-thalassaemia intermedia, HbE/beta-thalassaemia (mild and severe forms) and HbH disease (alpha-thalassaemia intermedia).⁴⁻⁶ The world-wide annual number of births for the NTDT form of α -thalassaemia, α -thalassaemia intermedia or haemoglobin H disease, is approximately 10,000.^{7,8}

Epidemiology of haemoglobinopathies in Bangladesh

According to Uddin et. al., among the 600 anaemic patients in Bangladesh, β -thalassaemia minor was found in 21.3%. Incidence of HbE- β -Thalassaemia and HbE trait, were 13.5 and 12.1%, respectively. HbE disease was found in 9.2%, Hb D/S trait in 0.7%, β -thalassaemia major 0.5%, and δ - β -thalassaemia 0.5%.⁹ In another study by Khan et. al., among 735 school children in Bangladesh showed a 4.1% prevalence of the beta-thalassaemia trait and a 6.1% prevalence for the HbE trait.¹⁰

In a latest report of 2019, significant variation is found in the prevalence of haemoglobinopathies among the general population of different divisions of Bangladesh (Table 1). In this report HbE trait is found to be much higher than beta-thalassaemia trait.¹¹

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Table 1: Carrier Frequencies in Studies of Different Populations Amalgamated from Several Sources. [Report of DGHS, Bangladesh February 2019]

Division	Number tested	Heterozygote β ; n (%)	AE; n (%)	EE; n (%)
Barisal	77	2 (2.6)	4 (5.2)	2 (2.6)
Chittagong	260	17 (6.5)	20 (7.7)	1 (0.4)
Dhaka (including present Mymensingh)	475	12 (2.5)	39 (8.2)	4 (0.8)
Khulna	159	2 (1.3)	8 (5.0)	0 (0.0)
Rajshahi	338	14 (4.1)	44 (13.0)	0 (0.0)
Rangpur	116	5 (4.3)	31 (26.7)	7 (6.0)
Sylhet	14	1 (7.1)	1 (7.1)	0 (0)
Total	1439	53 (3.7)	147 (10.2)	14 (1.0)

Complications of haemoglobinopathies

Complications in thalassaemia are myriad. There is no check and balance or negative feedback mechanism that might control production of unaffected globin chain. So, unaffected globin chains are produced in normal amount, and failure to bind to affected type of globin chain leads to deposition of the extra unaffected globin chains in the cytoplasm of red cells, i.e., alpha chains are deposited and precipitated in case of beta thalassaemia and vice versa. Precipitation of excess globin chains leads to pathologic changes in the cell membrane and premature lysis of red cells. As a result, there are features and complications of haemolytic anaemia (anaemia, jaundice, splenomegaly, gall stones and haemolytic or aplastic crises).¹²⁻¹⁶ Pathologic changes in cell membrane also induce thrombotic tendency and leg ulcers.

Death of red cell precursors in marrow causes ineffective erythropoiesis, and efforts to cope with body's demand leads to massive erythropoietic activity which ends up with bony deformities and weakening, and even compression syndromes (paraplegia due to spinal cord compression, or loss of visual acuity or visual fields caused by optic nerve compression). Extra medullary haemopoietic masses may also cause pleural effusions and upper airway obstruction.

Due to insatiable crave for iron, absorption of dietary iron from the gut is markedly increased; combined with inherent lack of iron excretion mechanism in human body, iron deposits in various viscera like liver, heart and endocrine organs. Cardiac complications are the leading cause of death in thalassaemia.

Pathophysiology of Cardiac Complications

Due to less severe presentation, NTDT patients may be unaware of the disease condition; moreover, due to fear of transfusion dependency, cost of blood transfusion, iron deposition and cost of iron chelation, and alloimmunity to red cells, many patients may avoid transfusion until grave condition. So, heart failure due to anaemia is not uncommon.

The other complication is due to iron deposition in cardiac myocytes. Even in the absence of regular red cell transfusion in NTDT, iron deposition level in many patients is like that of TDT by third or fourth decades. It may reach 3-4 mg/day or as much as 1,000 mg/year.¹⁷ The effect of cardiac hemosiderosis is twofold: functional and electrical abnormalities. Functional abnormalities are characterized by stiffening of heart which results in diastolic failure, and, reduced contractility of cardiac myocytes leading to systolic failure. Heart failure due to iron deposition in thalassaemia is usually biventricular, which is different from right heart failure from pulmonary hypertension (vide infra). Electrical abnormality due to siderosis in the heart, on the other hand, causes arrhythmias; which may be due to defect in the Purkinje system or due to atrial fibrillation. Enlargement of heart chambers due to heart failure may also lead to morbid arrhythmias.

Incidence of pulmonary hypertension is greatly increased in NTDT, which is much more than TDT. The incidence rate is widely variable depending on diagnostic criteria. If it is based on tricuspid valve regurgitant jet velocity (TRV) exceeding 2.5-2.8 m/s, corresponding to a pulmonary arterial systolic pressure exceeding 30-35 mm Hg, with or without symptoms, the incidence is markedly increased (10-78.8%, averaging about 30%).¹⁸ But strict diagnostic criteria like right heart catheterization and consideration of hyperdynamic circulation in anaemia reduces the incidence to 2.1% only. Still it is higher in head to head comparison with TDT patients (4.8% vs. 1.1%).⁸ The aetiology of pulmonary hypertension is inconclusive and is still at the level of hypothesis. It is thought that free haemoglobin from haemolysis consumes free nitric oxide, which is a potent vasodilator, from circulation. As a result, there is vasoconstriction in pulmonary vasculature leading to increased pressure.^{19,20} Hypercoagulability of blood of thalassaemic patients may also contribute to recurrent small pulmonary embolisms leading to pulmonary hypertension.

Intracardiac thrombus formation is another complication in thalassaemia. Due to atrial fibrillation and hypercoagulable state, thrombus may be formed in left atrium, which, when dislodged may culminate into stroke or other

embolic catastrophes. Acute myocarditis, found in 5% thalassaemia major patients, is less common in NTDT.²¹

Clinical Features of Cardiac Complications

Cardiac complications present with breathlessness, palpitation, easy fatigability, exertional dyspnoea, dependent oedema, and, sometimes chest pain. On examination, the patient is anaemic, dyspnoeic, may be cyanosed, tachypnoeic and tachycardiac. Depending on side of heart failures, there are various combinations of low volume pulse, which may be irregular, bilateral basal crepitations over lung fields, gallop rhythm on cardiac auscultation, and raised jugular venous pressure, shifted apical pulsation with or without enlarged tender liver. In the past, death usually occurred within 1 year of developing heart failures without adequate chelation therapy. Presently, 5-year survival is estimated to be 48%. Outcome is significantly poorer if arrhythmia persists with heart failure and/or myocarditis.²²

Investigations for Cardiac Complications

12-lead ECG is mandatory as initial cardiac evaluation. Early change is prolonged P-R interval, i.e., first degree heart block. Later, S-T segment depression and ventricular ectopic beats are seen which indicates more serious myocardial damage. If patient complains of intermittent palpitation but ECG fails to detect arrhythmia, 24-hours or longer ambulatory ECG may be done (Holter monitor).

Echocardiography detects functional status of heart muscle, competency of the valves, any intracardiac thrombus and type of heart failure (right or left, systolic or diastolic). It should be remembered that, by the time echocardiography or Holter monitor detects a defect, clinical heart disease is imminent or has already occurred. Annual echocardiography and assessment of TRV (vide supra) are recommended for high risk patients. That is why studies are undergoing to anticipate clinical heart disease by assessing cardiac iron deposition noninvasively. Mitigated acquisition (MUGA) scan is another test to assess systolic function of heart, but lacks widespread availability.

Cardiac iron deposition can be assessed noninvasively by R2 or T2* magnetic resonance imaging (MRI) of heart.²² This test is also available for liver iron evaluation. The best way to measure cardiac iron is biopsy of heart muscle, but this is not practical. Due to irregular requirement of blood transfusion, iron accumulation is slow in NTDT; thence regular monitoring is advised after the age of 10 years, which is the age at which iron-related morbidity starts to be of concern.²³ Due to complex

correlation between ferritin level in serum and extent of iron store, the former does not reflect the level of iron overload in NTDT.^{17,25}

Management of Cardiac Complications

Management of cardiac complications includes immediate measures for arrhythmia and heart failure, and of course, vigorous iron chelation to sustain the improvement of heart disease. Immediate measures may involve emergency cardiac team to revert arrhythmias, electrically or pharmacologically, and to stabilize the failing heart. At the same time transfusion of red cell concentrate may be needed to maintain a pretransfusion haemoglobin level between 10-12 gm/dL. Diuretics, beta-blockers (with or without alpha-blocking activity), angiotensin converting enzyme inhibitors (ACEI) and anti-arrhythmic drugs may be needed for indefinite period depending on symptoms, investigation findings and response to therapy.

All 3 iron chelators are effective removing cardiac irons, though recent study shows superiority of deferiprone over desferrioxamine. Despite poor correlation between ferritin level and extent of iron overload (vide supra), ferritin level can be measured easily and is taken as a standard to initiate and follow up chelation therapy, which is usually started at ferritin 800 ng/ml, and is continued till 300 ng/ml, which is the upper level of reference range.²⁶ After bone marrow transplantation is done, another treatment modality is phlebotomy to remove extra iron from the body, as well as from heart, which improves cardiac functions. Both heart transplantation and combined heart-liver transplantation are successfully done in end-stage heart failure.

Conclusion

Patients with NTDT do not generally require regular blood transfusions. However, as they grow, they develop a host of complications because of: ineffective erythropoiesis, haemolysis, chronic anaemia and iron overload. Cardiac complications are the major cause of death in NTDT and negligence in early treatment increase the death which can be prevented or adequately treated when caught at an early stage of disease. Timely intervention is of paramount importance to prevent irreversible complications.

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