Clinical profile of heart failure in Beta-Thalassaemia Major (ß-TM): Case studies with current consideration and future perspectives

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ABSTRACT

Background: Cardiac involvement is a major cause of mortality in Beta-Thalassaemia Major (ß-TM) patients. Despite many advances in therapeutic management of ß-TM, cardiac involvement remains the primary cause of mortality in ~70% of the cases. Chronic iron overloading results in thalassaemic cardiomyopathy, leading to diastolic dysfunction and overt heart failure (HF). Serial electrocardiography (ECG), 2D-echocardiography (2D-ECHO) and cardiovascular magnetic resonance (CMR) help in early detection and risk stratification of ß-TM patients, to prevent complications, such as arrhythmias and sudden cardiac death. An established network of care between thalassaemia centres and local health providers is essential for optimal management.

Case presentation: We report 2 cases of HF in ß-TM of varied etiology, and different approaches undertaken for its early diagnosis and treatment.

Conclusion: It is important to differentiate various phenotypes of cardiomyopathy in ß-TM. Since, the management of each varies accordingly. ß-TM patients require a multi-disciplinary approach that includes HF specialists, haematologist, hepatologist, endocrinologist, psychologist, transfusion experts and nursing personnel to maximise benefits from the application of the modern HF therapeutic strategies in evaluation, monitoring and treatment. SAHeart 2022;19:14-18

INTRODUCTION

Beta-thalassaemias are a group of inherited, autosomal recessive disorders, manifested by low or absent synthesis of ß-globin chains in haemoglobin (Hb) tetramer, resulting in variable clinical phenotypes, often ranging from asymptomatic cases to severe anaemia. Thalassaemia is one of the most common genetic disorders with nearly 5% of the world's population carrying globin chain variants. Three main forms of thalassaemia such as heterozygotes, homozygotes ß$^{+}$ and homozygotes ß^{0} have been described.[1]

Lately, a significant improvement in survival of Beta- thalassaemia major (ß-TM) patients has been documented. In the mid-1960s, only 37% of patients with ß-TM were alive at the age of 16 years. However, 3 decades later, a 95% survival was recorded.[2] Before the introduction of chelation therapy, the most common cause of death in ß-TM patients was heart failure (HF). After its introduction, the occurrence of HF has been delayed by a decade.

Despite many advances in therapeutic management of ß-TM, cardiac involvement remains the primary cause of mortality in ~70% of the cases.[3] Here we describe 2 cases of HF in ß-TM with varied etiology, and approach undertaken, for its early diagnosis and treatment.

Case 1

A 30-year-old female, diagnosed with ß-TM since childhood, on well-monitored blood transfusions and iron chelating therapy of deferoxamine, presented with progressive onset of dyspnoea on exertion (NYHA class II). No significant medical or surgical history in the past was known. On examination, vitals were normal. Jugular venous pressure (JVP) was elevated (8cm). Pallor was present. Chest auscultation revealed no S3, but had crepitation in bilateral basal lung fields. Hb was 5.5gm/dL. Serum ferritin level was 2 450ng/mL. Blood glucose level, kidney, liver, thyroid functions, and viral markers were normal. ECG showed sinus tachycardia with left ventricular hypertrophy. Chest X-ray was normal.

2D-echocardiogram (2D-ECHO) showed global hypokinesia with LV ejection fraction of 35%. Left atrial (LA) and left ventricular (LV) dimensions were increased with mild mitral regurgitation (MR). Right atrium (RA), right ventricular (RV) size and function were normal. Type-I diastolic dysfunction with mild pulmonary hypertension (ePASP 36mmHg) was observed. Myocardial strain imaging revealed global longitudinal strain (GLS) of 21% (normal) and global circumferential strain (GCS) of 22% (reduced).

The liver iron concentration (LIC) by CMR was 6 800µg/g dry weight and 1 100µg/g wet weight. CMR showed T2* value of 30ms and global hypokinesia with LV ejection fraction (LVEF) 36% (Figure 1A). MRI-gadolinium enhancement showed small multifocal areas of fibrosis in sub-epicardial region of the left ventricle (<5% of total mass) without restriction (Figure 1B, 1C).

Patient was initially treated with intravenous furosemide to control HF. Anaemia was corrected. She was stabilised on oral furosemide, spironolactone, ivabradine and bisoprolol. Intensive chelation with deferoxamine (DFO) was now continued 24 hours a day and 7 days a week. 2D-ECHO repeated at discharge showed significant improvement, with LVEF of 45%. Monitoring of ferritin was advised every 2 - 3 months and LIC every 6 - 12 months. She is on a regular follow up and is currently asymptomatic.

Case 2

A 29-year-old male, a known case of ß-TM presented with exertional dyspnoea (NYHA class III) for the last 5 days. Patient was receiving regular blood transfusions, but with unsupervised, irregular iron chelating therapy. She had a past history of hepatitis-C infection for the last 8 years, not on treatment. On examination, patient was tachypnoeic (respiratory rate of 25/min) with oxygen saturation of 92%. Heart rate was 108bpm, regular with BP = 100/70mmHg. JVP was elevated (10cm), hepatojugular reflex was present with pallor, icterus and bilateral pedal oedema. On chest auscultation S3 gallop was present with coarse crepitations at the base of both lungs. Liver was enlarged, tender with shifting dullness present.

ECG showed sinus tachycardia with right axis deviation. Hb was 7.0gm/dL. Serum ferritin level was 2 830ng/mL. 2D-ECHO showed global LV hypokinesia with ejection fraction of 20%. Right atrium was enlarged and reduced RV function with features of ventricular restriction. Moderate mitral and tricuspid regurgitation (TR), moderate pulmonary hypertension (ePASP = 52mmHg) with dilated and non-collapsing inferior vena cava (2.1cm). Myocardial strain imaging (MSI) revealed GLS of -10% (reduced) and GCS of -15% (reduced).

CMR showed LIC of 8 125µg/gm dry weight and 1 800µg/g wet weight with evidence of iron overload in liver (Figure 2A) and pancreas (Figure 2B). CMR indicated severe restrictive pattern of LV and RV with T2* of 3.9msec. CMR gadolinium enhancement showed extensive fibrosis in the sub-epicardial and sub-endocardial regions of the ventricular myocardium (~20% of LV and RV mass) (Figure 2C).

The response to all medical therapies (furosemide, spironolactone, ramipril, ivabradine, dual iron chelating agents and inotropic supports) was inadequate with progressive worsening of symptoms. In spite of all our efforts, patient succumbed due to refractory HF and multiorgan dysfunction. Based on our case studies, we discuss below the current considerations of HF in ß-TM patients.

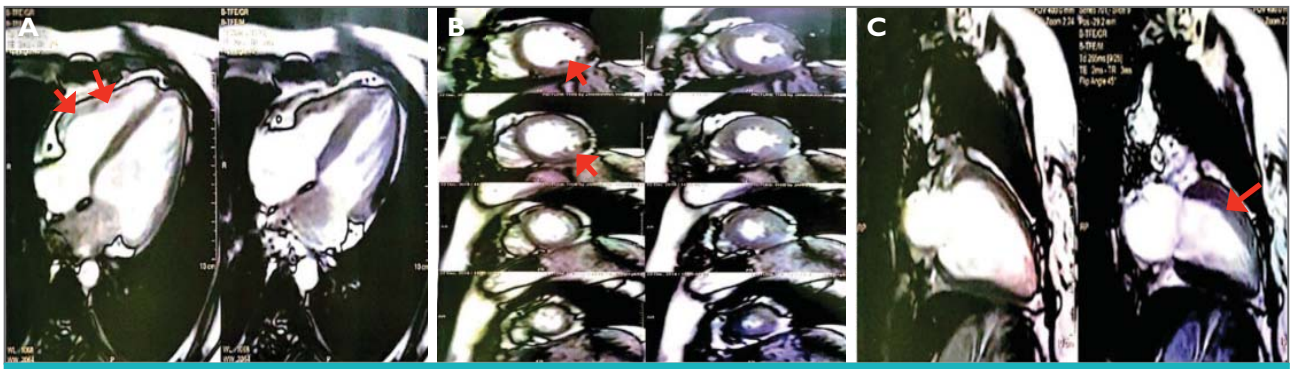

FIGURE 1: CMR showing global hypokinesia with LVEF 36% (A). MRI-gadolinium enhancement showed small multifocal areas of fibrosis in sub-epicardial region of the left ventricle (B, C) (arrows) with no restriction.

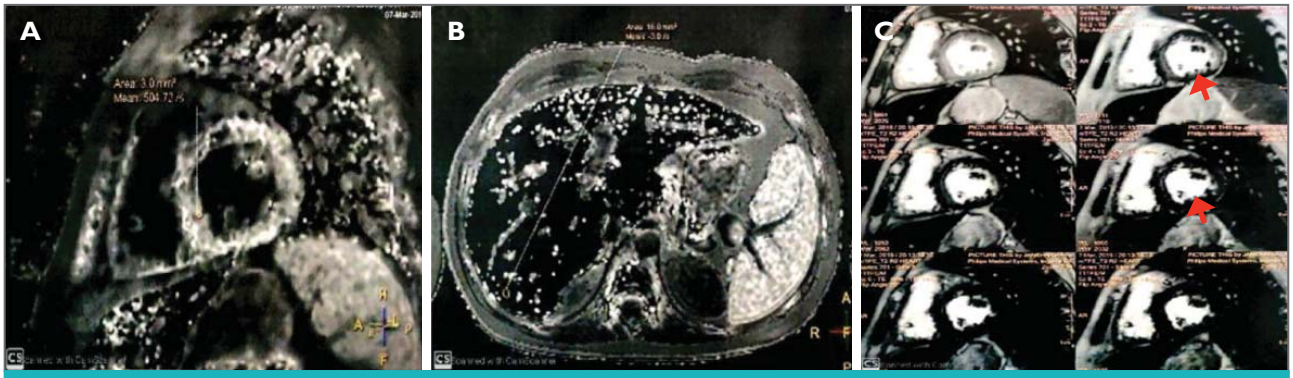

FIGURE 2: CMR showing evidence of iron overload in liver (A) and pancreas (B). CMR-gadolinium enhancement showing extensive fibrosis in the sub-epicardial and sub-endocardial regions of the ventricular myocardium with severe ventricular restriction (C) (arrows).

DISCUSSION

Current available considerations of HF in ß-TM

In the current era, where ß-TM patients have improved longevity, there is an unmet clinical need to define various subsets of HF in ß-TM, which forms the basis for the current study. In a study by Ladis, et al.[4] 14.71% of all deaths in ß-TM were due to cardiomyopathy. Various studies have also shown that global and segmental LV function remains within normal range until late stages of the disease. Occasionally, 2D-ECHO and haemodynamic investigations may reveal a severe RV cardiomyopathy in the absence of pre-capillary pulmonary hypertension. This kind of "primary" RV involvement usually develops in thalassaemic cardiomyopathy, and is potentially reversible and is associated with a haemodynamic pattern resembling that of restrictive cardiomyopathy.[5]

Diagnostic assessment of ß-TM

Early diagnosis of myocardial involvement in ß-TM is crucial for initiating therapeutic interventions in a timely manner. ECG is the earliest and the most cost-effective investigation for the detection of cardiac involvement in ß-TM. Abnormal ECG was found in 46% of ß-TM patients without HF (T wave abnormalities in 34% and right bundle branch block in 12%).[6] Common findings include P wave prolongation, decreased in QRS amplitude or increased QRS duration and T wave inversion beyond lead V1.

Serum ferritin (SF) levels correlate with body iron stores, and is often used to monitor progression of disease in response to chelating agents. SF level greater than 2 500ng/mL is considered as a strong risk factor for developing iron-induced cardiac complications. Persistent low SF levels (<500ng/mL) during chelation should be avoided to prevent toxic effects of over chelation.

LV diastolic dysfunction usually precedes systolic dysfunction. It is likely that ß-TM patients would present with restrictive haemodynamics in early stages, specifically those receiving multiple transfusions without iron chelating agents.[7] 2D-ECHO may be normal until extensive myocyte iron deposition has occurred. Chronic hypoxia from anaemia in ß-TM affects sub-endocardium and global longitudinal strain (GLS), while iron deposition occurs predominantly in sub-epicardial tissue affecting global circumferential strain (GCS). Since first alteration caused by iron overload is a decline in GCS, followed by GLS at a later stage, strain imaging echocardiography is more sensitive for early detection of cardiac dysfunction than routine 2D-ECHO.

Myocardial iron deposition, stored as ferritin or hemosiderin, can be quantified with CMR myocardial T2* relaxometry. The T2* sequence on CMR can detect increased iron overload in the myocardium, which appears darker on grey-scale imaging. In patients with moderate-to-severe iron deposition, T2* values are substantially reduced from the normal value of ~50ms or greater to <20ms. When T2* is <20ms, LV systolic function progressively declines, accompanied by an increase in LV end-systolic volume index and LV mass. The CMR T2* may have predictive value in identifying risk of developing iron overload cardiomyopathy (IOC), thus allowing targeted intensification of treatment before symptoms of HF develop.

The measurement of LIC by CMR, or superconducting quantum interference device, is another method to assess iron overload in the body. LIC should always be maintained below 7 000µg/g dry weight or 1 100µg/g wet weight to avoid iron-induced organ damage. Though liver biopsy is considered as a "gold standard" for assessing iron levels, it has been largely superseded by non-invasive methods.

Pathogenesis of HF in ß-TM

The primary cause of cardiac damage in ß-TM is iron overload. In ß-TM patients, iron deposition in parenchymal tissues begins

within 1 year of starting regular transfusions. When the iron transfer capacity of transferrin is exceeded, as in the case of iron overload, a non transferrin-bound form of iron appears in the blood. This non transferrin-bound free iron is capable of generating oxygen free radicals, is usually buffered by the cytosolic ferritin, and converted to hemosiderin, and stored in the lysosomes. When this buffering mechanism fails, iron levels rise in the cardiomyocytes, resulting in oxidative damage to cell membranes and ionic channels. Cardiac complications in well-chelated and well-monitored ß-TM patients are significantly lower than in inadequately treated patients.

Cardiac complications manifest as various clinical subsets, namely: (i) high output HF, (ii) iron overload cardiomyopathy, (iii) non-iron overload dilated cardiomyopathy and (iv) overlap syndrome.[8]

(i) High output HF

In ß-TM patients, impaired LV contractility is defined as ejection fraction <55%, considering the high output state due to chronic anaemia.[9] Additionally, increased LV diastolic dimensions and LV mass, LV diastolic dysfunction, pulmonary hypertension with evidence of RV systolic overload are echocardiographic manifestations of high output failure in ß-TM. A recent analysis has shown that LVEF values of 60% - 65% were associated with the lowest mortality while values lower or higher had increased mortality. The group of patients with LVEF >65% may be classified as HF with supra-normal ejection fraction (HFsnEF).[10]

Treatment is aimed at correcting the underlying cause of anaemia. Blood transfusion may be necessary, rapid blood volume expansion may worsen pulmonary oedema. Vasodilators and afterload reducing agents (e.g. ACE inhibitors, ARBs) have little role to play in this cohort of patients. ß-blockers in small doses can counteract the sympathetic and renin-angiotensin-aldosterone system (RAAS) overdrive, and reduce arrhythmias.[11] Our first patient presented with high output cardiac failure. Removal of trigger (anaemia) and management with anti-failure medications and chelation therapy reversed the deteriorating cardiac functions.

(ii) Iron overload cardiomyopathy (IOC)

The IOC is a secondary form of cardiomyopathy resulting from the accumulation of iron in the myocardium. Iron overload occurs when iron intake is increased over a sustained period of time, either as a result of chronic blood transfusions or increased absorption of iron through the gastrointestinal tract. Since ß-TM patients receive regular blood transfusions, iron overload is inevitable as the human body lacks the mechanism to excrete excess iron. Iron accumulation, due to uptake of non-transferrin bound iron, is toxic to many tissues and can lead to HF, cirrhosis, liver cancer, pituitary dysfunction, growth retardation and other multiple endocrine abnormalities.

IOC can occur in patients who are not on chelation therapy, as early as the second decade of life. IOC has been defined as the presence of systolic or diastolic cardiac dysfunction secondary to increased deposition of iron in the heart.

Management involves judicious use of diuretics, reduce sympathetic over-activity with ß-blockers, correction of anaemia and iron overload prevention with chelating agents. Chelation therapy should be started early (at 1 year of chronic transfusions) with LIC of least 3 000µg/g dry weight.

In high risk cases with decreased LVEF, 2 chelating agents can be given simultaneously (as in our case study 2). Though aggressive therapy may be more effective in preventing iron-induced organ injury, this strategy needs to be balanced to prevent drug toxicity.

(iii) Non-iron overload dilated cardiomyopathy

Iron-negative cardiac dysfunction is usually encountered in older thalassaemia patients. Patchy and delayed hyper-enhancement, consistent with fibrosis, may be due to longstanding cardiotropic hepatitis-C infection producing smouldering myocarditis and myocardial dysfunction. It is not uncommon to have both hepatitis-C and HIV co-infection in patients on long term blood transfusions. These infections may induce myocarditis and dilated cardiomyopathy.

(iv) Overlap syndromes

It is not unusual to get patients with overlap of various aetiopathological patterns described above. Patients may present with heart or liver failure due to combination of various factors like anaemia, iron overload, hepatitis-C infection or passive congestion. Endocrine dysfunction and metabolic deficiencies can also mimic or exacerbate HF. Overlap syndromes are usually associated with rapid deterioration and poor clinical outcomes.

In our second patient, anaemia with restrictive phenotype of IOC and possible viral myocarditis due to hepatitis-C infection leading to intractable HF, was probably due to overlap syndrome.

Pathogenesis of arrhythmias in ß-TM

Rhythm disturbances can result due to myocardial iron overload, secondary to LV dysfunction or due to viral myocarditis. Arrhythmias in ß-TM are a mixture of triggered and re-entrant type. Atrial fibrillation (AF) is the most common atrial rhythm

disturbance observed. AF can be secondary to atrial iron deposits causing atrial cardiomyopathy. Atrial iron cannot be measured by CMR, but atrial arrhythmia risk can be correlated with ventricular T2* iron estimates.

Ventricular arrhythmias are more specific for iron cardiotoxicity. Frequent premature ventricular contractions, by themselves, are not specific, but couplets, non-sustained ventricular tachycardia, or mixtures of frequent atrial and ventricular premature contractions should raise clinical suspicion.

Sudden cardiac death (SCD) accounts for about 5% of deaths in ß-TM. Severe iron overload can cause increased QT dispersion, revealing iron-mediated repolarization abnormalities and torsade de pointes as a causative mechanism for SCD.[12] Atrio-ventricular (AV) conduction defects and high-grade AV blocks were common before use of chelating agents. Serial ECG monitoring from childhood is advisable to detect iron cardio-toxicity, to initiate chelation therapy, to reduce life-threatening arrhythmias.

It is important to differentiate various phenotypes of cardiomyopathy in ß-TM, since the management of each varies. 2D-ECHO and CMR are invaluable tools in diagnosis and management of cardiac failure in ß-TM. Arrhythmias and PH should not be overlooked and promptly treated. A well-targeted approach can improve longevity, reduce risk of hospitalisation and improve quality of life. Chelation therapy removes myocardial storage iron very slowly (months to years). Chelation can reverse iron mediated heart dysfunction more rapidly (weeks) by chelating labile iron, if prolonged (24 hours a day and 7 days a week) chelation cover is achieved. The primary emphasis in ß-TM must be to prevent iron overload by encouraging regular chelation therapy and maintaining CMR T2* >20ms. Judicious use of safe blood transfusions and regular monitoring of cardiac function and rhythm can significantly improve patient outcomes. Optimal adherence is key to maximize benefit from chelation and to avoid toxic effects of over-chelation.

CONCLUSION

HF is a predominant cause of morbidity and mortality in ß-TM. Iron alone can result in diastolic dysfunction and myocardial restriction. Whereas iron overload in combination with other factors (e.g. inflammatory and immunogenetic) can cause LV systolic dysfunction, dilatation, and HF. Management of ß-TM patients requires multi-disciplinary approach that include HF specialists, haematologist, hepatologist, endocrinologist, psychologist, transfusion experts and nursing personnel, to maximise benefits from the application of the modern HF therapeutic strategies, in evaluation, monitoring, and treatment. Intensification of blood transfusions and the iron-chelation therapy in addition to the conventional HF treatment can improve clinical outcomes.

Ethical declaration and consent to participate

Ethical approval was not required since it is an accepted procedure. Both the patients gave consent to participate

Consent for publication

Both the subjects gave written informed consent to publish the case report.

Availability of data and material

Not applicable.

Competing interests

The authors declare that they have no conflict of interest to declare related to this study

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