Early Detection of Cardiac Iron Overload in Thalassemia Major Patients

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Thalassemia Major is an inherited transfusion dependent anaemia. Repeated transfusions lead to iron overloading of body tissues. Iron overload cardiomyopathy is the major cause of death in these patients. Early detection of iron overloading is the solution to managing these patients by iron chelation therapy. Once iron overload cardiomyopathy develops, it becomes extremely difficult to treat or reverse this condition. Different direct and indirect methods have been put forth to assess iron overload. These methods are summarized in this manuscript along with the advantages and disadvantages regarding their use. It is required to establish methods which can be used readily and with sufficient accuracy and at the same time be non-invasive and cost effective.

Key Words: Thalassemia Major, Iron overload, cardiomyopathy, Serum Ferritin, MRI, NTBI, ECG, echocardiography.

Introduction

Thalassemia is the most common hereditary disease in the world, which has an autosomal recessive inheritance.13 In this condition, since the globin chain synthesis is affected, the result is anaemia.4,5 Beta-Thalassemia is the most common type of Thalassemia.6 The estimated prevalence of Beta Thalassemia is 16% in Cyprus, 3-14% in Thailand and 3-8% in India, Pakistan, Bangladesh and China. However, prevalence is low in African black people (0.9%) and in Northern Europe (0.1%).7 Thalassemia is known to occur in three forms (Table 1).

In order to improve the condition of the patient, regular blood transfusions are given but these, unfortunately, cause iron overload.2 A unit of red blood cells contains approximately 250 mg of iron, and only about 1 mg per day can be excreted.9 After about a year of receiving blood transfusions, iron starts to be deposited in various body tissues.9 Iron overload damages many organs, but it is the increase in cardiac iron that is the main cause of death in Thalassemia major (TM) patients.10,11

The cardiac complications seen most often are bradycardia, conduction defects, serious cardiac tachyarrhythmias leading to sudden cardiac death, and heart failure.12 Studies have been conducted in different countries all over the world to determine the frequency of cardiac complications in patients of TM (Table 2).

Table 1 : Forms of Beta Thalassaemia

<table>
<thead>
<tr>
<th>Type</th>
<th>Symptoms</th>
<th>Hemoglobin level</th>
<th>Requirement of blood transfusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beta Thalassemia trait</td>
<td>Symptomless</td>
<td>10-12 gm/dl</td>
<td>Not required</td>
</tr>
<tr>
<td>Thalassemia Intermedia (TI)</td>
<td>Clinically moderately anaemic</td>
<td>7-10 gm/dl</td>
<td>Usually not required</td>
</tr>
<tr>
<td>Thalassemia Major (TM)</td>
<td>Severe anaemia, clinical symptoms appear at about 3-6 months of age</td>
<td>Very low</td>
<td>Cannot survive more than a few months without transfusions</td>
</tr>
</tbody>
</table>

Table 2 : Frequency of cardiac complications in patients of Thalassemia Major.

<table>
<thead>
<tr>
<th>Country of study</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>USA</td>
<td>22%35</td>
</tr>
<tr>
<td>Canada</td>
<td>37%15</td>
</tr>
<tr>
<td>UK</td>
<td>11-15%8</td>
</tr>
<tr>
<td>France</td>
<td>10%36</td>
</tr>
<tr>
<td>Cyprus</td>
<td>53.4%3</td>
</tr>
<tr>
<td>Greece</td>
<td>71%38</td>
</tr>
<tr>
<td>Italy</td>
<td>13%13</td>
</tr>
<tr>
<td>Netherlands</td>
<td>5.23%3</td>
</tr>
<tr>
<td>Iran</td>
<td>16-19%40,41</td>
</tr>
<tr>
<td>India</td>
<td>31.5%3</td>
</tr>
<tr>
<td>Pakistan</td>
<td>40-41%6,42</td>
</tr>
</tbody>
</table>

Iron toxicity is believed to be due to the presence of free iron non transfusion bonded iron (NTBI) which is its most harmful form.9,11,12 Iron catalyzes the production of free oxygen radicals, by the Haber Weiss and Fenton reactions.12 It cause per-oxidation of lipids, proteins, and nucleic acids, and eventually lead...
to apoptosis and fibrosis.\textsuperscript{8,10} Studies have shown that high intracellular iron causes selective interference in the function of the sodium channels, and the delayed rectifier potassium channels, and in so doing affects repolarization.\textsuperscript{1,8}

Iron chelation therapy helps to deal with the iron overload seen in such patients. This therapy needs to be started as soon as possible, and a rigorous regime undertaken to prevent the development of iron induced cardiomyopathy, and if already present, to reverse it. However, once clinical symptoms of cardiomyopathy appear, reversal becomes increasingly difficult to achieve. Early detection of cardiac involvement in these patients by a non invasive, readily available and cost effective method, can circumvent many deleterious effects of iron overload. Various methods, direct and indirect, that are used for early recognition of involvement of the heart in iron overload conditions, along with the controversy regarding their use, are reviewed here.

**Evaluation of Cardiac Iron in Thalassaemia**

As cardiomyopathy, due to iron overload, becomes clinically apparent when damage to the heart has already taken place, so a clinical assessment of such patients is not helpful to detect this pathology in its initial stages. Instead, various other means have been put forth to be used for this purpose. The indirect methods are preferred as the direct ones are invasive and, cannot be used most of the time.

**Indirect Methods**

**Serum Ferritin:** This is most commonly used as it is a simple, low cost and non invasive test that is readily available, and has been used for a long time for determining iron status of individuals in cases of iron deficiency as well as excess.\textsuperscript{13} Studies have shown that there is a direct correlation between the amount of blood given and the level of serum ferritin in TM patients.\textsuperscript{14} It has been shown that maintaining a Serum Ferritin level below 2,500 ng /ml is associated with low risk of cardiac disease in TM patients.\textsuperscript{15} In addition, a level of Serum Ferritin > 5000 ng/ml has been found to be associated with abnormal findings on Electrocardiography and echocardiography.\textsuperscript{16} The drawback of using serum ferritin for assessment of cardiac iron load is that as, ferritin is an acute phase reactant protein, it is found to be raised in various other conditions as well e.g. inflammation, collagen disease, malignancy and liver disease, and decreased when the level of ascorbic acid is low, a situation which is common in TM patients.\textsuperscript{10,12,14} L J Anderson et al. in their study demonstrated that myocardial iron load could not be predicted from Serum Ferritin levels.\textsuperscript{11} In another study, Serum Ferritin was also not found to be directly correlated to the iron stores of the body or the cardiac iron load.\textsuperscript{17}

**Non Transferrin Bound Iron (NTBI):** NTBI is the free form of iron which appears in the plasma when saturation of iron binding capacity of Transferrin occurs. It is thought to be a good measure of iron overload, however it is mainly used only for research purposes, as no agreement, so far, has been reached regarding the method for its measurement and a threshold value.\textsuperscript{18}

**Echocardiography:** Clinically, echocardiography is a useful means for the appraisal of cardiac function. It can also detect dysfunction of the heart due to iron loading, but by the time it does so, extensive and irreparable cardiac damage has already taken place.\textsuperscript{21}

**Magnetic Resonance Imaging (MRI):** MRI detects increased iron load in the heart of patients who have an, otherwise, normal cardiac function, and so is considered to be the gold standard for this purpose.\textsuperscript{20} MRI T2\textsuperscript{*} assessments are done for this and all organs should be monitored for iron overload in TM patients.\textsuperscript{17} There is an inverse relationship between the T2\textsuperscript{*} values and the level of cardiac iron. L J Anderson et al. in their study reported that below a myocardial T2\textsuperscript{*} of 20 ms, there was a progressive and significant decline in LVEF and an increase in LVESV index and LV mass index.\textsuperscript{13} Early detection of cardiac iron overload by this method is possible which allows for early initiation of chelation therapy.\textsuperscript{21} Cassinerio et al. performed a study to evaluate the changes in cardiac function, following iron chelation therapy, by measurement of MRI T2\textsuperscript{*}. It was seen that when chelation therapy was administered at appropriate doses, a marked improvement in the Myocardial T 2\textsuperscript{*} was observed.\textsuperscript{22} P Kirk et al. in their study made an effort to find the predictive value of cardiac T2\textsuperscript{*} MRI for heart failure and arrhythmias in TM patients. They found that cardiac T 2\textsuperscript{*} MRI identifies such patients who are at a high risk of developing the aforementioned conditions due to cardiac iron overloading in TM and is superior to Serum Ferritin and liver iron measurements for this purpose.\textsuperscript{23} However, many countries including Pakistan do not have easy availability of cardiac MRI T2\textsuperscript{*} facilities and when available, are extremely costly, time consuming and performed in a closed setting which may not be acceptable to many patients. Moreover, it cannot be used in patients who have artificial pacemakers.\textsuperscript{24}
Electrocardiography: Electrocardiography has the benefit of being non-invasive and cost effective. Some studies have been conducted to determine the usefulness of ECG in detecting cardiac iron overload. Jon Detterich et al. in their study on asymptomatic but, iron overloaded TM patients, observed alterations in ECG, like bradycardia and repolarization changes. According to them, a criterion of QT >407ms, prolonged QTc, non specific ST –T wave abnormalities, and bradycardia had a sensitivity of 89% and a specificity of 70% in detecting cardiac iron.\(^1\) Quraishi et al. in their study concluded that if out of the three abnormalities of tachycardia, wide QRS complexes and inverted T waves, if any two were present, then these had a sensitivity of 81% and a specificity of 91% in predicting the development of heart failure in TM patients.\(^20\) Beta Thalassemia major was found to be associated with significant changes in heterogeneity of ventricular repolarization and corrected QT (QTc) was demonstrated to be a useful marker of risk of sudden cardiac death in such patients.\(^25\) Another study concluded that young asymptomatic patients of TM have increased cardiac repolarization variability, as assessed by QT variability indices.\(^26\) Separately, it was observed that patients of beta TM have higher mean QT, QTc and QTd values as compared to a control group. However no significant correlation was found between QTd and Serum Ferritin.\(^27\) Pepe et al. in their study observed a strong correlation between MRI and ECG recorded changes in TM patients, and they concluded that ECG changes showed a good accuracy in predicting scarring of the myocardium.\(^28\) Krzysztof et al. studied acutely ill patients and found that elevated Serum Ferritin level and Serum Iron level led to QT prolongation and QT dispersion.\(^29\) Two studies on gerbil models of iron overload cardiomyopathy showed PR prolongation, increase in QRS interval duration and arrhythmias which were concluded to be because of the reduction in the inward sodium current caused by iron overloading of the heart.\(^30\) Garadah et al., found that when TM patients were compared with controls, they had differences of QT dispersion and QTc but these were of no statistical significance.\(^32\)

Direct Methods

Liver and Myocardial biopsy: The liver is the major site of iron storage and overload. Liver iron concentration (LIC) is closely related to total body iron, when iron overload is due to transfusions. So, evaluation of liver iron concentration gives an accurate estimate of iron overload, but this procedure is invasive and so cannot be used normally to observe iron levels.\(^9\) Several studies have not found any relationship between LIC and cardiac iron status or cardiac dysfunction.\(^12\),\(^17\) It has also been demonstrated that the rates of iron accumulation and clearance are different in the liver and the heart, and MRI studies have shown that when chelating therapy is stepped up, iron clears faster from the liver, as a result of which liver iron reaches normal levels while, myocardial iron is still high.\(^12\),\(^24\),\(^33\) Myocardial biopsy, again, is an invasive procedure and is not a good option to be used for determining the extent of iron deposition in the heart as the deposition takes place in a non homogenous manner. Studies have been conducted to observe the distribution of iron in the myocardium of patients of secondary haemochromatosis. It was observed that deposition of iron in the samples of the subendocardial and the subepicardial layer showed substantial inconsistency, leading to the conclusion that endomyocardial biopsy was not a very precise method to be used for this purpose.\(^34\)

Conclusion

1. In order to prevent the development of cardiac complications in beta thalassaemia major patients, early detection of cardiac iron overloading is essential so as to start chelating therapy as soon as possible.
2. A non-invasive, cost effective and readily available method is needed for detection of cardiac involvement due to iron overloading, before the emergence of clinical manifestations of cardiomyopathy, an irreversible state once it is established.
3. ECG is a cost effective and sensitive method to detect early cardiac abnormalities.

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