EDITORIAL

Iron Overload and Myocardial Restriction

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ABSTRACT

Heart failure still remains the main cause of death in β-thalassemia, despite the progress, which was made by intensification of iron chelation therapy. Iron myocardial deposition, due to regular blood transfusions, can cause congestive heart failure as a result of left- or right-sided heart failure combined with left ventricular myocardial restriction. Regular and intense chelation therapy has improved quality of life and survival by decreasing secondary hemochromatosis. However, heart failure has not been prevented despite the intensification of iron chelation therapy.

Acute myocarditis in β-thalassemia major has been reported to contribute to heart failure in addition to iron overloading. However, apart from myocarditis which may lead to immune mediated chronic left ventricular dysfunction and failure, other factors acting through immunologic or genetically defined mechanisms might also affect the development of left sided heart failure. Multiple transfusions represent a repetitive antigenic stimulus together with iron chelation therapy itself. In this brief overview, the pathogenetic mechanisms of myocardial involvement and heart failure in β-thalassemia major are discussed.

KEY WORDS: *anemia, thalassemia, heart failure, iron toxicity, chelation therapy, cardiomyopathy, myocarditis*

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β-THALASSEMIA, MYOCARDIAL IRON AND CONGESTIVE HEART FAILURE

Iron myocardial deposition can cause congestive heart failure as a result of left- or right-sided heart failure combined with left ventricular myocardial restriction. Heart failure still remains the main cause of death in β-thalassemia, despite the progress, which was made by intensification of iron chelation therapy.[1,2] It is traditionally considered the result of iron overload due to regular blood transfusions, iron intestinal hyperabsorption and ineffective erythropoiesis during the life span of the patients.[3,4] Regular and intense chelation therapy has improved quality of life and survival by decreasing the patients' secondary hemochromatosis. However, heart failure has not been prevented despite the intensification of iron chelation therapy.[5,6] It can thus be hypothesized that either deferoxamine is less effective than it is believed or other factors might be involved in the pathogenesis of heart failure.

β-thalassemia is not a pure iron storage disease and the pathophysiology of cardiac dysfunction is poorly understood and multifactorial in etiology.[7,8] Left-sided and subsequently biventricular heart failure appears early in the patients' life. This is the commonest mode of heart failure in this disease characterized at diagnosis by left ventricular systolic dysfunction, dilatation and failure.[3,9-11]

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MYOCARDIAL RESTRICTION

Chronic iron myocardial deposition does not affect left ventricular relaxation but causes left ventricular myocardial restriction with highly elevated pulmonary arteriolar resistance and pressure. It appears in the elderly β-thalassemia major population with the highest serum ferritin levels. The patients eventually develop right ventricular dilatation while left ventricular dimensions and systolic function remain within normal range. This is the pre-stage of heart failure with predominant symptoms and signs of right-sided heart failure.[12]

MYOCARDITIS

Engle et al in 1964 first reported the co-existence of pericarditis and fatal arrhythmias with heart failure in β-thalassemia major. Of note, pericarditis usually coincides to some degree with myocarditis being a part of inflammatory heart disease which has usually an immunological background.[3,13,14] Years later we proved[15] that acute infectious myocarditis in β-thalassemia major apart from acute can also cause a chronic left-sided heart failure in 27.6% of myocarditis patients within 3.5 years approximately, compared to β-thalassemic population aged and sex-matched with no difference in iron loading. The estimated prevalence of overt myocarditis in β-thalassemia was 4.5% in a population with clinical evidence of myopericarditis documented mainly by myocardial biopsy. However, the exact significance of acute myocarditis as a contributing factor for heart failure development is not easy to be defined since there is a possibility of existence of latent undiagnosed myocarditis in unknown percentage of β-thalassemia major population. Myocarditis can cause acute or chronic left ventricular systolic dysfunction and dilatation analogous to dilated cardiomyopathy which appear to be mediated by predominantly immunologic mechanisms rather than viral infection and replication.[16,17] The increased frequency of infections associated with β -thalassemia seems to be related to abnormalities of the immune system.[18,19] The predisposition to autoimmune diseases is under the control of immune response genes, which play a central role in the presentation of antigens to the immune system.[20] In dilated cardiomyopathy, immune related disorders show preferential associations with HLA genes.[21] In β-thalassemia major left ventricular dysfunction attributed to myocarditis seems to be related to immune system dysregulation being under immunogenetic control. HLA-DRB1* 1401 allele frequency was found significantly increased in patients with β-thalassemia major without left sided heart failure compared with those with heart failure and healthy controls. HLA-DQA1*0501 allele frequency was also significantly increased in β-thalassemic patients with heart failure compared with patients without heart failure and healthy controls. HLA-DRB1*1401 allele might have a protective effect in the pathogenesis of heart failure, while HLA-DQA1*0501 allele is possibly related to an increased risk for heart failure development.[22]

IMMUNOGENETIC RISK FACTORS

Apart from myocarditis which may lead to immune mediated chronic left ventricular dysfunction and failure, other factors acting through immunologic or genetically defined mechanisms might also affect the development of left sided heart failure. Multiple transfusions represent a repetitive antigenic stimulus together with iron chelation therapy itself. This is supported by the increased IgA neutral antibody activity found in the sera of patients with homozygous β-thalassemia major.[23] Iron loading apart from its toxic effect might contribute to heart failure development through immune mediated mechanisms.[24] The exact mechanism of iron overload toxicity has been uncertain for many years. Via the iron-driven Fenton and Haber-Weiss reactions, the nontransferrin plasma iron in its bivalent or trivalent form has a high toxicity through the formation of hydroxy radicals (OH).[25] Imbalance between production of oxygen free radicals and antioxidant defense mechanisms can result in oxidative stress and human disease.[26] In the heart, the imbalance between free radicals and antioxidant mechanisms is manifested as impaired function of the mitochondrial inner membrane respiratory chain, resulting in abnormal energy metabolism expressed clinically with dilated cardiomyopathy, which is also observed in patients with acute myocarditis in the acute or chronic phase. As shown in animal models, oxygen free radicals may also contribute to the pathogenesis of infectious myocarditis.[27,28]

In homozygous β-thalassemia, organ damage is mainly attributed to excessive iron deposition through the formation of free radicals. β-thalassemia major patients without left sided heart failure have an apolipoprotein Eε4 allele frequency similar to that of healthy controls, while patients with left sided heart failure have a higher frequency of this allele relative to controls.[29] The apolipoprotein Eε4 allele may represent a genetic risk factor for the development of heart failure through the mechanisms of free radicals, which are related either with iron toxicity or acute infectious myocarditis. Thus, despite that it is conventionally believed that cardiac involvement leads to a mixed dilated/restrictive cardiomyopathy with both systolic and diastolic dysfunction,[30] recent studies showed that left ventricular dysfunction and failure is related to a multifactorial etiology.[7] It seems that apart from iron loading, immunogenetic risk factors trigger the mechanisms of left sided heart failure development, on the basis of dilated type cardiomyopathy.

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