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Case Report

Triple Drug Iron Chelation Therapy in Thalassemia Major; A Case Report

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ABSTRACT

Regular packed cell transfusion in patients with thalassemia major leads to iron overload. Chelation therapy is one of the important aspects of thalassemia care as iron overload causes significant cardiac, hepatic, and endocrine dysfunction. We report a case of thalassemia major with severe iron overload causing cardiac and liver dysfunction who benefitted from triple drug chelation therapy. Triple iron chelation therapy in thalassemia major could be suggested in severe iron overload patients.

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Introduction

Beta thalassemia major is a hereditary disorder due to impaired beta chain synthesis. Although bone marrow transplantation is a definitive cure for the disease, the availability of an HLA-matched donor and the cost of the procedure limits the applicability of this treatment.[1] As a result, regular blood transfusions are the only option for long-term survival of the patients. Iron deposition in major organs such as heart, liver and endocrine organs leads to cardiac, hepatic and endocrine dysfunction. Hence, growth retardation, diabetes mellitus and cardiomyopathy are well-known complications in patients with thalassemia.[2] Measurement of liver iron by biopsy is the most reliable method to detect the state of iron overload, but is an invasive procedure.[3] Dynamic MRI (T2* and R2) is a noninvasive method for quantifying cardiac and hepatic iron overload.[4] Iron chelating drugs such as deferoxamine, deferasirox and deferiprone are widely used to reduce iron overload in thalassemia patients. There are various studies that have determined the efficacy of each drug when given alone or in combination.[5] We report a case of beta-thalassemia major who presented with high cardiac and hepatic iron overload who improved in terms of iron status with triple iron chelation therapy.

Case Presentation

A thirteen-year-old girl with beta-thalassemia major diagnosed at the age of six months and on regular transfusion since then, started chelation therapy from two years of age. She was receiving deferasirox with a dose of 25 mg/kg/day with a poor compliance to the therapy when she referred to our center. In view of the persistently high serum ferritin values (serum ferritin: 11,477 µg/L with a

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mean ferritin of 7,759 µg/L), she was planned to receive combination of deferoxamine at a dose of 35 mg/kg/day, subcutaneously, 5 days per week and 40 mg/kg/day of deferasirox daily, respectively. Echocardiography showed a left ventricular ejection fraction of 66%. Cardiac and liver MRI, three months later showed severe iron overload with T2* value of 8.2 ms for heart (normal>20 ms) and 1.2 ms for liver (normal>15.4 ms). Iron concentration in the liver and heart were equivalent of 26.7 mg/g and 3.2 mg/g of dry weight of liver and heart, respectively.

She was then scheduled to receive triple chelation therapy with: deferasirox (40 mg/kg/day) once daily, deferoxamine (35 mg/kg/day, 5 days per week) and deferiprone (75 mg/kg/day). Serum ferritin showed significant improvement after one year. The mean ferritin was 4,126 ng/ml after one year of triple chelation (last ferritin level: 1,271 ng/ml). T2* MRI repeated after a year of triple chelation therapy showed improvement in liver iron concentration (value of 3.2 ms), but not in cardiac iron overload (T2* value of 6.5 ms). Currently, she is taking deferasirox at 40 mg/kg/day, deferiprone at 50 mg/kg/day and deferoxamine at 35 mg/kg/day with no significant side effects. We did not interrupt the chelation therapy for the past 18 months. Informed consent was obtained form the parents to report the case.

Discussion

Iron overload in patients with thalassemia is related to blood transfusion as well as increased absorption of iron from the gut.[1] Monitoring for iron overload and chelation therapy is extremely important to avoid morbidity and mortality in these patients. Serum ferritin measurement, liver and myocardial T2* MRI, and liver biopsy are the main available methods used to monitor iron overload. Myocardial and liver MRI T2* is a reliable, non-invasive method that can be used for this purpose.[4] The risk of developing cardiac disease is low, if the cardiac T2* value is above 20 ms. Values of 10-20 ms are of intermediate risk requiring effective iron chelation therapy, whereas cardiac T2* below 10 ms necessitates prompt adjustment in chelation owing to the high risk of developing arrhythmias and congestive heart failure.[6]

Combination chelation therapy is increasingly being used especially in cases where liver iron is unacceptably high and/or in the presence of iron related cardiac disease. Combination chelation therapy has an advantage of enhancing iron removal secondary to synergistic effect of the drugs and improve organ-specific iron removal by combining the differential abilities of the drugs to chelate cardiac and liver iron. Adverse effects of the chelators may be minimized by reducing the dose of the individual chelator drug.[5] Combination of deferiprone with deferoxamine is the most common studied among combined iron chelators. These two drugs act by a mechanism called "shuttle hypothesis".[7] Combined therapy with deferasirox and deferoxamine is particularly effective at rapidly reducing high liver iron concentration and also removes cardiac iron, though at a slower rate.[5] Combination of deferasirox and deferiprone has the benefit of being an only oral regimen. Karami *et al.* observed some improvement in cardiac and liver MRI values in 6 patients with beta-thalassemia, although the difference between the cardiac MRI T2* values before and after treatment was not statistically significant.[8] Comparison of combination of deferasirox/deferoxamine and deferiprone/deferasirox showed that both regimens were equally effective in decreasing iron concentration and serum ferritin with no increased toxicity, and also increase in cardiac T2* was significantly observed in patients who received combination of deferipron/deferasirox.[9] However, combined therapy with deferiprone and deferoxamine is the standard of care to clear cardiac iron and stabilize ventricular function,[10] but combination of two oral chelators also results in improved cardiac T2*.

In our case, a very high serum ferritin level and significantly high cardiac and liver T2* values and non-improvement with dual chelation therapy mandated us to treat the patient with three iron chelators. The child is receiving three chelating drugs for 18 months with no significant adverse effects. Liver MRI values and serum ferritin has significantly improved after one year of treatment, although cardiac iron concentration has not improved yet, knowing that it takes time and needs a more prolonged course of intensive iron chelation.

Conclusion

We suggested triple iron chelation therapy in beta-thalassemia major patients with severe iron overload to enable better control of iron burden and improve patient outcome. Further studies and trials are required to evaluate the safety and efficacy of triple iron chelation in thalassemic patients.

Statement of ethics: Written informed consent was taken from the parents to publish this case.

Conflict of Interest: None declared

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