

Rapid Iron Loading in Heart and Liver in a Patient with Transfusion Dependent Thalassaemia after Brief Poor Compliance with Iron Chelation Therapy

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تحميل سريع للحديد في القلب والكبد عند مريض مصاب بمرض الثلاسيميا عند عدم تناوله دواء خلاصة الحديد

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المخلص: يعتقد أن تحميل الحديد عند المرضى المصابين بالثلاسيميا المعتمدين على نقل الدم يحدث بشكل أولي في الكبد ثم في بقية أعضاء الجسم عند تشبع الكبد بالحديد. ندرج في هذا التقرير حالة مريض ذكر أزيل طحاله وهو أيضا يعالج من مرض الكبد الوبائي ج قبل تناوله الأدوية المضادة للفيروس، وحافظنا على معدل الفيريتين أقل من 500 نانوجرام/مليتر باستعمال دواء الديفيريبرون لوحده، وسجلت صور الرنين المغناطيسي للقلب 48.8 ملي ثانية وللکبد 19.5 ملي ثانية. بعد إثنا عشر شهرا من تناول الدواء المضاد للفيروس والتي كان المريض أثناءها لا يلتزم بتاتا بأخذ العلاج (ديفيروكسامين) ارتفع مستوى الفيريتين الى 3820 نانوجرام/مليتر وكذلك كانت النتائج في القلب والكبد 12.7 ملي ثانية و 14.5 ملي ثانية على التوالي والذي يؤشر الى زيادة تحميل الحديد فيهما خاصة في القلب. وبعد خمسة عشر شهرا من بدء العلاج المشترك (خلب) انخفض الفيريتين الى 95 نانوجرام/ملي ثانية ومستواه في القلب والكبد الى 27.5 و 28.5 ملي ثانية على التوالي والذي يعكس نهاية تامة لتحميل الحديد في العضوين. تبين هذه الحالة أن حالة تحميل الحديد يمكن أن تحصل سريعا وفي بعض الحالات يكون تحميل الحديد أسرع نسبيا في القلب عنه في الكبد.

مفتاح الكلمات: ثلاسيميا كبرى، تحميل الحديد، ديفيريرون، ديفيروكسامين، خلاصة الحديد، التصوير بالرنين المغناطيسي، تقرير حالة، عمان.

ABSTRACT: Iron loading in patients with transfusion dependent thalassaemia is considered to occur primarily in the liver and, once the liver becomes saturated, other organs begin loading. We report here a splenectomised male patient who was treated for hepatitis C virus infection. Prior to starting antiviral therapy, his serum ferritin was maintained below 500 ng/ml with deferiprone monotherapy; cardiac T2* by magnetic resonance imaging was 48.8ms and hepatic T2* was 19.5ms. After twelve months of antiviral treatment during which time he was very poorly compliant with his deferoxamine chelation therapy, his ferritin had risen to 3820 ng/ml and cardiac and hepatic T2* findings were 12.7 ms and 14.5 ms respectively, indicating increased iron loading in both organs, but particularly in the heart. Fifteen months after recommencing combination chelation, his ferritin was 95 ng/ml and cardiac and hepatic T2* were 27.5 and 28.4ms respectively, indicating complete clearance of iron load in both organs. This case demonstrates that iron overload can develop rapidly and in some cases there is relatively rapid iron loading in the heart as compared to the liver.

Keywords: Thalassaemia Major; Iron overload; Deferiprone; Deferoxamine; Chelation therapy; Magnetic resonance imaging; Case report; Oman

IN THE PAST, THE IMPACT OF CESSATION OR poor compliance with chelation therapy was not easily assessable except by serum ferritin levels. These have ultimately been found to be relatively unreliable with respect to demonstrating the degree of iron load in the heart and liver.^{1,2}

Liver biopsies, though valuable, were traumatic and had low patient acceptance. With the advent of magnetic resonance imaging (MRI) techniques (T2*), such assessments are more easily accessible although expensive.³ The patient described here was followed prospectively before and after the

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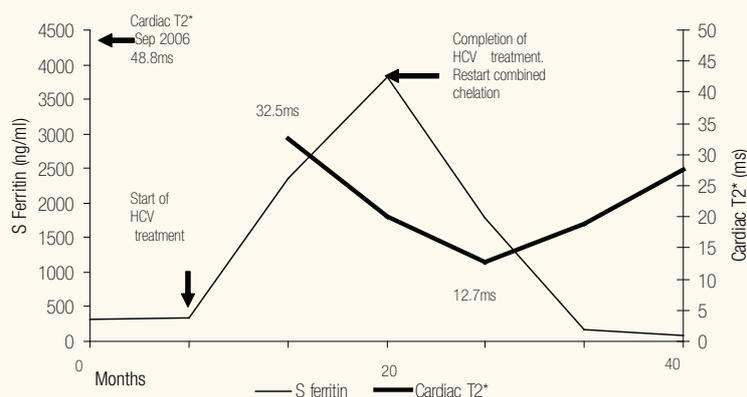


Figure 1: Changes in serum ferritin and cardiac T2* before starting interferon therapy and the subsequent course

period during which he was on interferon therapy which precluded the use of deferasiprone. This demonstrates the impact of poor compliance with chelation therapy for a relatively short period of 12 months.

Case Report

This patient, with transfusion dependent thalassaemia, was born in 1974. He commenced regular blood transfusion at 22 months of age and regular deferoxamine iron chelation therapy at the late age of 19 years, when his ferritin was 4869 ng/ml. By 2001, aged 27, his ferritin was 3755 ng/ml. With the availability of the oral chelator deferasiprone, and information that combination therapy with deferasiprone and deferoxamine was resulting in at least an additive effect with respect to iron excretion,⁴ he commenced combination therapy in August 2001. The regime was as follows: deferasiprone orally at 75 mg/kg/day in three doses and deferoxamine at 40 mg/kg infusion for 5 days of the week. He was always very compliant with his oral chelator and was able to manage 2 days per week of Desferoxamine infusions. He did not show any cardiac complications and glucose and thyroid metabolism were normal. Gonadal function was normal until the age of 30, at which time he required testosterone replacement. By May 2005, his ferritin was 540 ng/ml, the deferoxamine was stopped and he continued on deferasiprone monotherapy.

On the basis of being hepatitis C virus (HCV) polymerase chain reaction (PCR) positive with persistently elevated hepatic enzymes

(alanine aminotransferase 50-85 IU/l, aspartate aminotransferase 80-115 U/l) and his liver biopsy showing chronic hepatitis with moderate activity and stage 5 fibrosis, he commenced interferon and ribavirin treatment in September 2007. He had an excellent response with viral load falling from >500,000 IU/ml to below detectable limits within 9 weeks of commencing treatment. At the start of HCV therapy his ferritin level was 335 ng/ml. As interferon can cause neutropaenia, and as deferasiprone can also cause both neutropaenia and agranulocytosis, the deferasiprone was stopped, and he continued on deferoxamine treatment alone. He was poorly compliant with this treatment and his ferritin gradually rose to a peak of 3820 ng/ml at the end of his HCV therapy. The effect of his poor compliance was compounded by increased transfusion requirements over the period of HCV therapy (increase of 40 mls/kg/year packed red cells). Table 1 shows the liver and cardiac T2* before starting interferon, during the treatment, soon after ceasing combination therapy and after recommencing it, the last reading being 15 months after completing HCV therapy.

Studies have shown that patients who have a cardiac T2* result of <10 ms are at high risk for cardiac disease due to iron overload, and that those whose T2* is above 20 ms are in the 'normal' range.^{3,5} Our patient's cardiac T2* fell from well within the normal range to just above the high risk cut-off in a relatively short period of time [Table 1 and Figure 1]. He had no cardiac symptoms and his echocardiogram was normal. His liver iron load, as assessed by MRI, also increased during this period

Table 1: Serum ferritin and T2* readings before, during, and after interferon therapy

Date	Serum Ferritin ng/ml	T2* Heart (ms)	T2* Liver (ms)	LIC mg/gdw
Sept 2006	309	48.8	19.5	1.5
Aug 2007	335			
Nov 2007	2,366	32.5	8.6	3.2
Jul 2008	3,820			
Nov 2008	1,792	12.7	4.5	6.8
Jul 2009	162	18.8	16.5	1.4
Oct 2009	95	27.5	28.4	0.4

Legend: LIC = Liver iron concentration

from completely normal to the upper limit of mild iron loading after 12 months. His most recent study 2 years after recommencing combination therapy shows complete removal of iron in the liver and normalisation of cardiac T2* at 27.5ms. Figure 1 shows serial values of cardiac T2* and ferritin levels over the period before, during, and after HCV therapy,

It is important to note that the T2* of both the liver and heart started reducing within two months of ceasing chelation therapy. The most striking feature of his results was that the cardiac T2* fell from absolutely normal to a level that was a cause for concern. This was associated with his hepatic iron load reaching the upper limit of mild iron loading. In the past, such levels of iron loading in the liver were considered safe, but it has now been shown that in many patients liver iron does not correlate to cardiac iron.^{3,6}

Discussion

This case report demonstrates the rapid iron loading that occurred in one patient after the cessation of effective iron chelation therapy and failure to comply with deferoxamine infusion. A case of a pregnant woman showing increased rapid loading after completely ceased chelation therapy for 12 months has been reported.⁷ However, unlike that patient, whose cardiac iron status remained the same, our patient had a greater rate of iron loading in his heart than in his liver. Noetzli *et al.* have shown that in many patients cardiac iron loading and unloading lags behind liver iron.⁸ Our patient, however, is similar to the small number of patients in that study who loaded more rapidly in their

hearts than in their livers. He also demonstrated a rapid reversal of cardiac iron which is also different to the results of the above study. It would seem that differential iron loading may be very different from one patient to another, hence the need for MRI monitoring, particularly during phases of inadequate iron chelation. The differences in relative rate of uptake of iron in various organs in different patients have not yet been adequately explained. It may be that viral infections such as hepatitis play a role, but larger studies are needed to evaluate this. Patients should be properly counselled prior to any therapy that may compromise their chelation even though this may be short term. The use of deferoxamine is standard therapy, but compliance is a problem. As the oral chelator deferasirox rarely causes neutropaenia, it may be the chelator of choice in these patients, provided there is no contraindication to its use. As in the case with rapid loading during pregnancy,⁷ it is also likely that the free iron that results from the iron overload may be very avidly taken up in the liver and may be taken up even more quickly in the heart.

Another interesting point in this patient is that he has recently reversed his hypogonadism. In April 2009, eight months after restarting combination chelation, he was azoospermic. However, he was able to cease hormone replacement therapy in June 2009, and in October 2009 his sperm count was 76 million/ml, with 10% abnormal forms and 90% motility. These encouraging outcomes are similar to those recently published in which a reversal of hypogonadism was associated with very low ferritin levels.⁹ Our patient had very low ferritin levels from July 2009 to March 2010 and this was associated with the marked improvement in the sperm count.

It is very likely that such low ferritin levels are essential to achieve such improvements.

Conclusion

In all transfusion dependent patients, cessation or change to possibly less acceptable chelation therapy may result in rapid iron overload of the heart over a relatively short period of time. Patients and physicians should be aware of this risk in order to encourage patients to maintain consistent chelation therapy.

CONFLICT OF INTEREST

Shahina Daar has received funding for clinical studies from Novartis Inc. and been a speaker for ApoPharma Inc. as well as attending key opinion leader meetings sponsored by ApoPharma Inc. Vasili Berdoukas is a consultant for ApoPharma Inc. and has a confidentiality agreement with Novartis Inc. with respect to the development of deferasirox. Saaed Ahmed has no conflicts of interest to declare.

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