Early cardiac iron overload in children with transfusion-dependent anemias

Quantitative magnetic resonance imaging (MRI) heart iron assessment has been an important advance in the follow-up of patients with transfusion-dependent anemias.[1] Few longitudinal data are available on the natural history of cardiac iron overload.[2] We refer this letter to the manuscript by Wood *et al.*[3] in which they recently reported that in pediatric patients with thalassemia major (TM) no detectable cardiac iron overload was observed in children under the age of 9.5 years. Another study showed that cardiac iron loading in patients with increased transfusion requirements occurred only after at least 13 years of chronic transfusion therapy.[4] These facts are important in determining the appropriate age at which to start screening for increased iron in the heart with an expensive technique such as MRI. However, as published in recent guidelines,[5] it has been hypothesized that these observations should only be true if chelation therapy has started early and been received regularly as well as there having been no increases in transfusion needs. To evaluate if cardiac iron overload might occur in younger children who do not satisfy these requirements, we assessed pediatric patients from 7-18 years of age with chronic transfusion therapy undergoing MRI to detect cardiac iron loading. Cardiac T2* assessment was performed on a 1.5T Siemens Symphony scanner using previously described validated techniques.[6]

A total of 23 patients were scanned (61% male, mean age 12.6±3.1 years) with thalassemia major being the most frequent diagnosis (78%), followed by thalassemia intermedia (13%), sideroblastic anemia (4%), and sickle cell disease (4%). In this cohort, there were 4 patients diagnosed with cardiac iron overload, 3 of them males under the age of ten (Table 1). The fourth patient was 17 years of age (older than the age reported for the first findings of cardiac iron overload in previous studies) and was not included in the analysis (heart T2* of 17.2msec). All other patients had normal heart T2* with no other cardiac findings (27.3±6.5msec).

In common, the 3 patients under the age of ten with cardiac iron overload reported suboptimal chelation therapy prior to the MRI scans, either due to irregular use of the prescribed chelator or late access to chelation early in the course of the disease. Chelation history for these patients included late start for patients 1 and 2 (17 and 28 months gap between transfusions and desferrioxamine use, respectively) and irregular use for patient 3. All patients had adequate prescriptions for subcutaneous desferrioxamine at the time of cardiac iron overload diagnosis, with deferiprone added after heart involvement diagnosis. It is interesting to note that the mean transfused iron input for these patients was 189.1±98.5 mg/kg/y, a total iron dose similar to that previously reported.[3] Moreover, in all these patients the degree of cardiac iron overload was always severe with only one patient already showing symptoms of heart failure (patient 3). This patient in particular already showed signs of heart failure (shortness of breath while playing with other children and premature ventricular complexes in the ECG) at the age of three with no other etiologies besides cardiac siderosis being found.

Regarding the other 20 patients in the cohort, chelation therapy included subcutaneous desferrioxamine only in 15 patients, desferrioxamine plus deferiprone in one patient and deferasirox in the remaining 4. Compared to the 3 patients described, all these patients reported good adherence to chelation therapy, defined as correct intake of the prescribed medication more than 90% of the time.

Table 1. Characteristics of study patients.

Characteristics	Patient 1	Patient 2	Patient 3	All other patients
Age (years)	9.7	7.4	9.8	12.6±3.1
Diagnosis (see text)	TM	TM	Sideroblastic anemia	Varied
Age at start of transfusion therapy (mo)	6	12	1	9.4 (1-18)
Age of initial chelation therapy (years)	1.9	3.3	0.7	1.4 (0.6-3.3)
Serum ferritin range (ng/dL)	2008-2568	1313-2316	1299-3076	957 (340-4211)
Transfusional iron input (mg/kg/y)	143.6	121.5	302.1	133.7 (76-403)
Cardiac T2* (ms)	8.1	6.9	3.2	27.3±6.5
Liver iron concentration (mg/g)	8.4	16.7	12.7	6.4 (1.2-18.9)

Data for all group reported as means±SD or (range).

In this letter, we showed that increased cardiac iron deposition can occur even at a younger age then predicted by previous studies. The main reason for this occurrence seems to be inadequate compliance with chelation therapy as has been reported in unchelated adult patients with myelodysplastic syndromes.[7] Other reasons for the results observed, such as anemia as a potential factor for iron overload, were not assessed in this study. Although chelation therapy is mentioned in previous reports with young patients, the compliance status of the population described was not portrayed,[3] leaving the possibility that all patients were well chelated or that poorly compliant subjects were not included. Nevertheless, it seems prudent to recommend starting MRI screening as early as 7-years of age if poor chelation is assumed, even in the absence of symptoms of heart disease. Cardiac MRI can be performed with no need for sedation in children at this age and normal reference ranges have been extensively studied for comparisons of heart function.[8] While cost and availability should be considered, especially if one assumes that patients with difficult access to chelation will also have the same problems with MRI, these are the patients that should benefit most from precocious screening.

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References

1. Modell B, Khan M, Darlison M, Westwood MA, Ingram D, Pennell DJ. Improved survival of thalassaemia major in the UK and relation to T2* cardiovascular magnetic resonance. J Cardiovasc Magn Reson 2008;10:42.
2. Aessopos A, Berdoukas V, Tsironi M. The heart in transfusion dependent homozygous thalassaemia today--prediction, prevention and management. Eur J Haematol 2008;80:93-106.
3. Wood JC, Origa R, Agus A, Matta G, Coates TD, Galanello R. Onset of cardiac iron loading in pediatric patients with thalassemia major. Haematologica 2008; 93:917-20.
4. Wood JC, Tyszka JM, Carson S, Nelson MD, Coates TD. Myocardial iron loading in transfusion-dependent thalassemia and sickle cell disease. Blood 2004;103:1934-6.
5. Angelucci E, Barosi G, Camaschella C, Cappellini MD, Cazzola M, Galanello R, et al. Italian Society of Hematology practice guidelines for the management of iron overload in thalassemia major and related disorders. Haematologica 2008;93:741-52.
6. Anderson LJ, Holden S, Davis B, Prescott E, Charrier CC, Bunce NH, et al. Cardiovascular T2-star (T2*) magnetic resonance for the early diagnosis of myocardial iron overload. Eur Heart J 2001;22:2171-9.
7. Di Tucci AA, Matta G, Deplano S, Gabbas A, Depau C, Derudas D, et al. Myocardial iron overload assessment by T2* magnetic resonance imaging in adult transfusion dependent patients with acquired anemias. Haematologica 2008;93:1385-8.
8. Robbers-Visser D, Boersma E, Helbing WA. Normal biventricular function, volumes, and mass in children aged 8 to 17 years. J Magn Reson Imaging 2009;29:552-9.

Improved survival in thalassemia major patients on switching from desferrioxamine to combined chelation therapy with desferrioxamine and deferiprone

Life expectancy in thalassemia major (TM) is reduced, mainly as a result of deaths from transfusion iron-overload and cardiac dysfunction. Early deaths are preventable by effective long-term iron chelation therapy, but 50% are unable to adhere adequately to standard treatment consisting of sub-cutaneous desferrioxamine (DFO) infusions administered at least five times per week.[1,2] In a previous report on a cohort of TM patients treated in Cyprus, we noted a significantly lower incidence of fatal events co-inciding with follow-up and treatment after 1999,[3] an observation also made in the UK.[4] The oral chelating agent deferiprone (DFP) was licensed in the European Union in 1999. Since effectiveness of DFP as monotherapy was thought to be insufficient, and there had been reports of more efficient chelation when DFP was used in combination with DFO,[5] a protocol of combination chelation therapy (CCT) was introduced in Cyprus to optimize the benefit from DFP. In the previous study, we suggested that use of CCT was the explanation for the decrease in mortality, but could not show this statistically due to insufficient data. With a further two years of follow-up, we have readdressed this question.

Indications for CCT were: moderate or high iron stores (ferritin <1500 µg/L), cardiac dysfunction (symptomatically or on echocardiography) or decreased myocardial T2* (<20 milliseconds). The protocol for CCT was similar to that described by Origa *et al.*:[6] DFP 75-100 mg/kg per day seven days per week, and DFO 30-50 mg/kg over 12-24 hours 2-5 infusions per week depending on ferritin levels. DFO was generally stopped if ferritin was consistently <500 µg/L, but DFP continued.

The patient cohorts and methods of follow-up were described in the original publication.[3] The cohort born after 1973 has undergone an additional analysis as a birth cohort (these patients were prospectively registered at diagnosis and consist of all new diagnoses in Cyprus). Cox Proportional Hazards was used to assess factors impacting on survival with CCT modelled using time of starting as a time-dependent covariate. We exclude those treated for less than six months.

Demographic data are shown in Table 1. The full cohort includes 5 more than in the previous publication: these had been erroneously omitted. Sixty-five patients died between 1/1/80 and 31/12/06. Thirty-two (49% of

Table 1. Demographic data for Cyprus patients.

	Full cohort n=544		Birth cohort n=286	
	Number	%	Number	%
Sex				
Male	284	52.2	148	51.7
Female	260	47.8	138	48.3
Decade of birth				
1960-9	134	24.6	0	0.0
1970-9	327	60.1	203	71.0
1980-9	59	10.8	59	20.6
1990-	24	4.4	24	8.4
Clinic				
Larnaca	121	22.2	54	18.9
Limassol	136	25.0	71	24.8
Nicosia	232	42.6	125	43.7
Paphos	51	9.4	34	11.9
Other	4	0.7	2	0.7
Thal mutation[1]				
Severe/severe	392	72.1	220	76.9
Severe/mild	85	15.6	40	14.0
Not known	67	12.3	26	9.1
Bone marrow transplant	7	1.3	5	1.7

[1]*Severe: IVS 1-110, IVS 1-1, IVS 2-745, codon 39; mild: IVS 1-6,-87, Hb Knossos, Hb Lepore.*

Table 2. Hazard ratios for prediction of survival in multivariate analysis.

	Hazard ratio	95% CI	*p* value
Full cohort: all cause mortality			
Female sex	0.43	0.25-0.73	0.002
Born >1973	0.30	0.17-0.51	<0.001
Combination therapy (per year of therapy)	0.14	0.04-0.41	<0.001
Birth cohort: all cause mortality			
Female sex	0.57	0.20-1.64	0.300
Combination therapy (per year of therapy)	0.38	0.16-0.91	0.029
Full cohort: cardiac mortality			
Female sex	0.39	0.18-0.84	0.016
Born >1973	0.24	0.11-0.56	0.001
Combination therapy (per year of therapy)	Unable to calculate		

(Clinic and β thalassemia mutation are not included as they were not associated with mortality in univariate analysis).