A cross-sectional magnetic resonance imaging assessment of organ specific hemosiderosis in 180 thalassemia major patients in Hong Kong

The advent of magnetic resonance imaging (MRI) organ-specific iron assessment and oral chelators has improved survival in European thalassemia major patients.[1] It is uncertain whether this experience is reproducible in Asia, with our inherent differences in genetic and co-morbid factors, as well as clinical transfusion and chelation practices. In this context, a cross-sectional MRI study was performed on 180 consecutive thalassemia major patients in Hong Kong (91 male, 89 female, median age 26 years, range 12-48). Subcutaneous deferoxamine (35-60 mg/kg 3-6 times per week) was used for life-long chelation (except deferiprone 75 mg/kg/d) in 24 cases commenced for 1-8 months). Their mean monthly transfusion was 3.5 units of red cells (range 1-5), while the mean monthly ferritin level for the last 12 months was 2,898 ng/mL (range 135-18,933). Hormonal replacement was used to define hypogonadism (n=84, 47%), diabetes mellitus (n=44, 25%), hypoparathyroidism (n=16, 9%) and hypothyroidism (n=36, 20%). All MRI examinations were performed with a 1.5T scanner (Sonata, Siemens Medical, Erlanger, Germany). Heart failure was defined by MRI ejection fraction (EF) below 55%. Reproducibility of the liver and cardiac scans between the Hong Kong and London scanners were verified in 10 cases.[2] The normal MRI values of pancreas and pituitary glands were determined from local controls as reported.[3,4] Data was analyzed by SPSS 11.0 software (Chicago IL, USA). The study was approved by the ethics review boards of all participating hospitals.

There was a high incidence of cardiac hemosiderosis (severe T2*<10 ms: 26% of cases; mild-moderate 10ms-20 ms, 24%). In comparison, most patients had mild to moderate liver iron overload (severe T2*<1.4 ms: 14%; mild-moderate T2* <6.3 ms: 63%). Iron deposition was also commonly found in the pancreas (T2*<23 ms, 84%) and pituitary gland (T2*<5.9 ms, 24%). The correlations between the various iron assessments are shown in Table 1. MRI measurements between the organs showed significant correlation, and all T2* values fall significantly with high ferritin levels (Table 1). Logarithmic transformation of pancreatic T2* reading increased the R-values for all correlations. The three pituitary assessments (T2*, T2 and SIR) showed significant but not perfect correlation. Paradoxically, liver and pancreas T2* values both increase (improve) with age, and the EF was also higher in older patients. Functionally, the EF falls significantly with an increase in iron content in the heart and endocrine organs. A history of heart failure, defined clinically or by an imaging result, was documented in 62 cases (34%). However, at the time of assessment, only 34 patients (19%) had EF<55%, with 14 cases being asymptomatic. Current heart failure was predicted by abnormal MRI values in all organs, with the strongest relation with cardiac T2* (Table 1B, Figure 1A-B). All four endocrine failures were significantly predicted by low cardiac T2* (all p<0.001, Table 1B, Figure 1C) on both univariate and

Table 1. (A) Pearson correlation (R-values in numbers and level of significance in asterisks) between radiological and clinical variables. (B) Wilcoxon analysis (p values , signficant p values on multivariate analysis value in brackets) of predictors of organ failure.

A	*Age*	*Ferritin*	*Heart T2**	*Liver T2**	*Pan T2** *(Log-Pan T2*)*	*Pit T2*	*Pit SIR*	*Pit T2**
Ferritin	NS	-	-	-	-	-	-	-
Heart T2*	NS	-0.29***	-	-	-	-	-	-
Liver T2*	0.24***	-0.44***	0.18*	-	-	-	-	-
Pan T2* (Log-Pan T2*)	0.16*	-0.22** (-0.35)**	0.33*** (0.54)***	0.35*** (0.54)***	-	-	-	-
Pit T2	-0.17*	-0.43***	0.66***	0.21**	0.33*** (0.52)***	-	-	-
Pit SIR	-0.26***	-0.41***	0.63***	0.63***	0.29*** (0.44)***	0.89***	-	-
Pit T2*	NS	NS	0.37***	0.17*	0.21**	0.35***	0.31***	-
EF	0.20**	NS	0.24**	NS	0.18*	0.16*	NS	0.22**
B	*Age*	*Ferritin*	*Heart T2**	*Liver T2**	*Pan T2**	*Pit T2*	*Pit SIR*	*Pit T2**
Heart failure n=34	NS	NS	<0.001	NS	0.001	0.013	0.017	0.009
Diabetes n=44	<0.001 (0.001)	NS	<0.001 (0.004)	NS	NS	0.015	0.001	0.055
Hypogonadism n=84	<0.001 (0.001)	NS	<0.001 (0.049)	NS	0.057	<0.001	<0.001 (0.05)	NS
Hypothyroid n=36	0.061	<0.001	<0.001	NS	NS	<0.001	<0.001 (0.023)	NS
Hypoparathyroid n=16	0.004 (0.008)	NS	<0.001 (0.006)	NS	NS	0.062	0.003	0.058

Legend: p value: n: number of cases; NS: not significant; Pan: pancreas; Pit: pituitary; T2 ms: value in milliseconds; SIR: signal intensity ratio of pituitary to muscle. *p<0.05 /**p<0.01/*** p<0.001; -: not analyzed; NS: not significant*

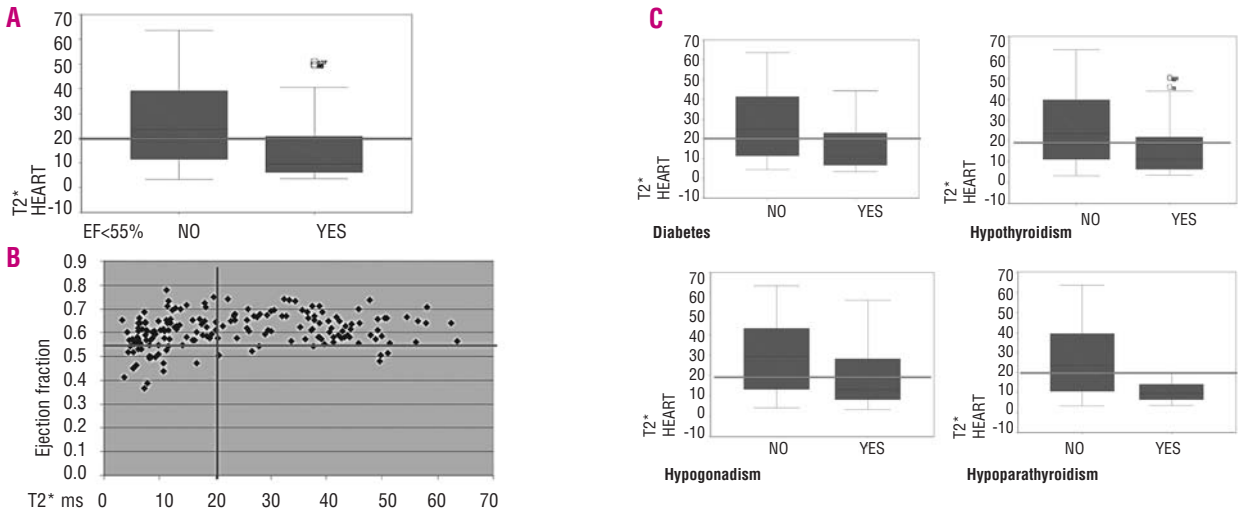

Figure 1. A and B: Relationship between T2* MRI heart with ejection fraction and MRI documented heart failure (ejection fraction <55%). (A) p<0.001 comparing T2* for patients with and without heart failure. (B) T2* <20 ms predicts normal EF except for 8 borderline patients. (C) Cardiac T2* <20 ms as a cut-off for clinically defined endocrine failures. p<0.001 comparing T2* for patients with and without organ failure for all endocrine organs.

multivariate analyses. Endocrine failure also increased with age (p value from 0.06 to <0.001), but were not statistically related to liver or pancreatic T2* results. Among the three pituitary MRI parameters, pituitary SIR appeared to be superior in predicting all forms of endocrine failures. Interestingly, ferritin levels were highly significant in predicting clinical hypothyroidism on univariate analysis.

This study investigates the usefulness and clinical correlation of comprehensive MRI scanning at a central calibrated facility. Similar to other countries, the incidence of iron loading and organ damage was high, reflecting deferoxamine incompliance and its relative inefficiency in chelating the heart and endocrine organs.[5,6] The paradoxical decrease in heart failure and iron overload with age is explained by the longer survival of better-chelated patients without (or who had recovered from) heart failure. Poor chelators who died early will not appear in a cross-sectional survey.[7] On the other hand, endocrine failures increase with age since they were neither immediately fatal nor reversible.[7] Our data confirmed that liver MRI is not useful to predict heart failure,[5,8] and further showed that it cannot predict endocrine failures. Cardiac MRI T2*, however, was useful in predicting both heart and endocrine failures. A normal T2* MRI heart (>20 ms) is only rarely associated with mildly abnormal EF (Figure 1A, n=8, T2*=20.6-50.9 ms, EF=48-55%). However, patients with currently normal MRI cardiac T2* can still have established diabetes (n=13), hypothyroidism (n=9) and hypogonadism (n=32). This may be due to previous iron load, non-iron related organ insults[9] and individual differences in organ reserves.

This is the first extensive study of the usefulness of MRI of the pancreas and pituitary gland in thalassemia major. The ideal assessment algorithm is uncertain and histological or biochemical tissue iron assessments were not available for correlation. Nonetheless, the T2* MRI results of the two endocrine glands showed good correlation, and also with T2* readings of the heart and liver. It appeared that log-pancreatic T2* and pituitary SIR showed the best clinical correlation. However, cardiac MRI T2* (using the standardized CMR tools algorthim) appeared to be a better predictor of endocrine failure than direct endocrine MRI measurements.[10] Therefore, MRI T2* heart measurement may provide a valuable and affordable screening test in Asia. A value above 20 ms would indicate a reduced risk of most organ failure. It would also be imperative to compare our results with other large cohorts of Oriental patients with access to standardized scanners. Since both T2* and EF measurements improve with treatment,[11,12] especially with novel iron chelators, urgent studies are also needed to determine the optimal time for repeat scanning in Oriental cohorts.

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