Pancreatic Exocrine Function and Cardiac Iron in Patients with Iron Overload and with Thalassemia

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Introduction

Regular transfusion and chelation treatment in ß-thalassemia major (TM) is improving patients' quality of live, but creates a state of iron overload with the consequence of iron deposition in parenchymal tissues. Especially, elevated cardiac iron concentration is an early marker for the risk of cardiomyopathy and arrhythmia. In patients with iron overload, assessment of cardiac iron by fast MRI-R2/R2* methods has become a standard of care. A significant but loose correlation was found between cardiac T2* and logarithmically transformed pancreatic T2* relaxation times. Earlier studies have already documented an involvement of the endocrine pancreas in TM patients, but little has been published about iron deposition and alterations of the exocrine pancreas. However, in thalassemia patients with impaired function the association with endocrine function tests is spoiled by fatty infiltration of the pancreas, which can cause water-fat shift artifacts in MRI-R2/R2* methods. We measured R2* relaxation rates in the myocardium by MRI in comparison with the exocrine pancreatic function by means of serum pancreatic enzyme determination in patients with ß-thalassemia.

Material and Methods

Twenty-seven transfusion dependent TM patients (age 11 – 47 years, 9 females), had measurements of heart iron by ECG gated single breathhold multi-echo MRI-R2*, liver iron by SQUID biomagnetic liver susceptometry, and pancreatic exocrine function by serum amylase (PAM) and lipase (LIP). All patients gave their written informed consent. Seventeen other patients with iron overload due to blood transfusion or iron loading (MDS, AML, SCD, DBA, CDA: n = 12, or HFE-associated hereditary hemochromatosis, non-transfused thalassemia intermedia: n = 5, respectively) were also investigated. Most patients (91 %) were on long-term chelation or phlebotomy treatment. The selection of patients for cardiac MRI was based on elevated LIC with actual LIC > 700 µg/gliver (about 4.2 mg/g dry wgt) for 90 % of patients.In MRI, the nuclear proton resonance signal decays at a faster rate in the microscopic vicinity of magnetic centers as generated by hemosiderin and ferritin storage iron molecules exhibiting a high paramagnetic susceptibility in an external magnetic field. Heart iron can be assessed as transverse relaxation rate R2* by a mono-exponential fit to the averaged signal amplitudes in the septum with constant signal level offset (TE = 1.3 – 25.5 ms, Δt = 2.8 ms, TR = 244 ms, FA = 20°). In principle, the atomic magnetic susceptibility, which is strongly related to tissue iron concentration, can be directly measured by means of standard physical methods. Thus, in-vivo liver iron concentration (LIC) was measured by SQUID biomagnetic liver susceptometry as described elsewhere (11). Pancreatic serum amylase and lipase were measured in blood samples taken at the day of blood transfusion with a detection threshold of < 13 U/L (i.e. 12.9; normal range: 13 – 53 and 13 - 60 U/L, respectively).

Results

The relationship between cardiac R2* and pancreatic lipase for patients with ß-thalassemia major (LIC = 597 – 9454 µg/gliver) and other patients with iron overload (LIC = 200 – 7681 µg/gliver) is shown in Fig. 1. For receiver operated characteristic (ROC) analysis, patients were divided in two groups with cardiac R2* < 50 s-1 or T2* > 20 ms (range 23 – 49 s-1) and R2* > 50 s-1 (range 51 – 387 s-1) (see Table 1).

There was a highly significant correlation between LIP and PAM (spearman rank correlation RS = 0.70, p < 10-4). Lipase significantly correlated with cardiac R2* (RS = -0.45, p = 0.0023), while amylase only showed a negative trend (RS = -0.29, p = 0.057). No significant correlation (p > 0.2) was observed with any other parameter (age, LIC, ferritin).

ROC analysis for correctly classifying patients with and without cardiac iron by pancreatic amylase revealed a significant discriminatory power (ROC curve area = 0.80, p < 10-4) and equal true positive (sensitivity) and negative (specificity) rates of 75 % at a cut-off level of 19 U/L. An even better discrimination was found for the pancreatic LIP (ROC curve area = 0.88, p < 10-4, sensitivity = specificity = 82% at a cut-off level of 18 U/L). A similar discrimination was achieved in patients with thalassemia major (ROC curve area = 0.89). In contrast, LIC could not predict cardiac iron (ROC curve area = 0.60, p = 0.13).

Parameter	R2* < 50 s^{-1}	R2* > 50 s^{-1}	p (U-test)
n	28	16	
Diabetes (m/n)	3 / 28	8 / 16	0.009 #
Splenectomy (m/n)	6 / 28	6 / 16	0.3 #
Age (y)	28.5 (9-67)	33.3 (14-79)	0.25
LIC (µg/g_{liver})	2191 (200-9454)	3360 (683-8293)	0.25
Ferritin (µg/l)	2195 (62-10529)	4484 (455-16391)	0.10
Amylase (U/L)	26.4 (12.9-51.0)	16.8 (12.9-32.9)	0.0011
Lipase (U/L)	32.6 (12.9-64.0)	16.3 (12.9-31.0)	< 10-4

Distinct cardiac siderosis in hypertrophic myocytes had been demonstrated by myocardial biopsy in the past. On the other hand, the 3 patients with R2* > 50 s-1 but LIP > 19 U/L, had PAM levels < 23 U/L. With the addition of pancreatic amylase in patients with LIP ≥ 19 U/L, cardiac iron (R2* > 50 s-1) could be predicted to 67% also in these patients at a cut-off level of PAM < 23 U/L (ROC curve area = 0.83, p < 10-3).

Conclusion

Patients at risk of elevated cardiac iron levels could be identified by the exocrine pancreatic lipase and amylase function parameters.

Key words:
iron, myocardium, relaxation rate, R2*, boundary effect