Endocrine effects on heart function

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Abstract

Among the factors associated with thalassemic heart disease, endocrine disturbance is also a contributing factor. We present a retrospective, cross sectional study, which aims to establish the prevalence of cardiac complications in thalassaemia major (TM) patients with endocrine complications and to evaluate the influence of endocrine disease on cardiac complications. Endocrinological and cardiological parameters were considered on 957 TM patients who are enrolled in the Myocardial Iron Overload in Thalassemia (MIOT) network in 68 sites in Italy. Patients with pubertal hypogonadism (163 males and 175 females), hypothyroidism (192), diabetes mellitus (87) and hypoparathyroidism (61), were compared according to cardiac complications: global heart T2*, cardiac dysfunction, heart failure, arrhythmias, pulmonary hypertension and myocardial fibrosis. Control groups were made up according to the age range of patients with the corresponding endocrinopathy. The prevalence of cardiac dysfunction, arrhythmias and heart failure was significantly increased in patients with endocrinopathies. Cardiac complications tended to increase according to the number of endocrinologies affecting the patient.

Introduction

In thalassemia heart diseases are associated with many factors. Iron overload and chronic anemia are the leading causes but a role is also played by other elements such as myocarditis, pulmonary hyper-

tension, cirrhosis, defect in antioxidant mechanisms, nutritional deficiencies, genetic factors, premature vascular aging, endocrine diseases.^{1, 2} Endocrine diseases and cardiac complications share the same etiologic factors that are chronic anemia and iron overload,^{3, 4} but the relationship between endocrine diseases and cardiac complications is not well established. In fact, in the literature only case reports regarding cardiac failure secondary to decompensated hypothyroidism and hypoparathyroidism or heart failure associated with growth hormone deficiency are present.^{5, 6}

Aim of our retrospective and cross sectional study was to establish the prevalence of cardiac complications in thalassemia major (TM) patients with endocrine diseases and to evaluate the influence of endocrine diseases on cardiac complications.

Patients and Methods

We considered the data of TM patients enrolled in the Myocardial Iron Overload in Thalassemia (MIOT) network, involving 8 cardiac Magnetic Resonance Imaging (MRI) Centres and 68 thalassemia sites in Italy. The MIOT Centres are linked by an online database designed to collect and share patient history, clinical and diagnostic data. The magnetic resonance protocol includes the evaluation of liver and myocardial iron content, heart function and myocardial fibrosis. In all Centres MRI examinations are performed in a standardized fashion by using 1.5T scanners (GE Medical Systems, Milwaukee, WI, USA).^{7, 8}

A multislice multiecho T2* approach was used to measure myocardial iron overload.^{9, 10} Three short-axis views of the left ventricle (LV) were acquired and the myocardium was divided into 16 segments, according to the American Heart Association (AHA) standardized LV model.¹¹ The T2* value on each segment was calculated as well as the global value. Morphological and functional biventricular parameters were quantitatively evaluated in a standard way by SSFP cine images using MASS® software. In order to detect myocardial fibrosis, contrast delayed enhanced images were acquired after 10-18 minutes from the intravenous administration of a gadolinium-based contrast medium. Short, vertical, horizontal, and oblique long-axis views were acquired. Delayed enhancement (DE) extent was evaluated visually using a two-point scale (enhancement absent or present) and considered present when visualized in two different views.¹²

A T2* value of 20 ms¹³ was used as the normal cut-off for all segments. The normal values of ejection fraction (EF) normalized by sex and age, previously obtained in a cohort of 142 TM patients without cardiac disease and iron overload,^{14, 15} were used to define left and right heart dysfunction (EF < mean - 2 standard deviation). Heart failure was diagnosed by MRI in presence of a LV or right ventricular (RV) EF lower than 4 standard deviations from the normalized mean value and by a positive

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history (clinical symptoms, confirmation by physical examination and treatment). A pulmonary hypertension was diagnosed if the trans-tricuspidal velocity jet was greater than 3.2 m/s or the gradient values were greater than 40mmHg.¹⁶ The diagnosis of arrhythmias, such as atrial fibrillation, atrial flutter, ventricular or supraventricular tachycardia, and ventricular fibrillation, was demonstrated by the ECG.

All data were analyzed using SPSS v. 13.0 (Chicago, IL) statistical package. All continuous variables were expressed as the mean and standard deviation. The Wilcoxon's signed rank test was applied for the comparison of global heart T2* values. χ^2 testing was performed for non-continuous variables. The univariate logistic regression analysis was used to evaluate the odds ratio (OR) with 95% CI. Adjustment for age or/and co-morbidity was applied. In all tests, a 2-tailed probability value of 0.05 was considered statistically significant.

Results and Discussion

Data on 957 TM patients at the first cardiac MRI examination (466 M and 491 F, mean age 30.8 ± 8.7 years) were analyzed.

Pubertal hypogonadism was present in 163 males (age 15-59 years) and in 175 females (age 14-51 years), hypothyroidism in 192 patients (age 14-50 years; 80% under l-thyroxine treatment), diabetes mellitus in 87 cases (age 19-51 years; 97% under insulin treatment), hypoparathyroidism in 61 patients (age 19-51 years; all under Vitamin D treatment).

The prevalence of endocrine complications is shown in Figure 1. No difference between males and females was found.

Control groups were made up according to the range of age found in patients with the corresponding endocrinopathy. For each endocrinopathy, the age and the presence of other associated endocrine diseases were significantly higher in patients having the related endocrinopathy.

The global heart T2* values, the prevalence of cardiac complications and myocardial fibrosis according to endocrine diseases are reported in Table 1. Global heart T2* values were significantly lower in all groups of patients with a specific endocrinopathy, with the exception of hypoparathyroidism. The prevalence of cardiac dysfunction was not significantly different in patients with and without a specific endocrinopathy, but it was near to the statistical significance in males with hypogonadism, in patients with hypothyroidism and diabetes. The overall prevalence of heart failure (by MRI and by patient history) ranged between 14% in females with hypogonadism and 30% in diabetic patients, and it was significantly more frequent in patients with than without every considered endocrinopathy. Hyperkinetic arrhythmias,

mainly supraventricular, were found most frequently than the hypokinetic types. Only hyperkinetic arrhythmias were significantly more prevalent in patients with than without an endocrinopathy. The highest prevalence (18%) was found in males with hypogonadism and diabetic patients. As for pulmonary hypertension, no significant difference in prevalence between groups was revealed. Cardiac complications, including heart failure, arrhythmias and pulmonary hypertension, were significantly more frequent in patients with than without a specific endocrinopathy (Figure 2). The highest rate of cardiac complications (46%) was detected in patients with diabetes and the lowest one (21%) in females with hypogonadism. The prevalence of myocardial fibrosis, ranging from 19 to 30%, was significant higher only in patients with diabetes. Logistic regression analysis relative to the risk of cardiac diseases and co-morbidity, showed that the presence of one, two and more than two versus no endocrine diseases increased the risk for cardiac complications, such as arrhythmias and heart failure. The number of endocrine diseases didn't influence the presence of cardiac dysfunction and myocardial fibrosis. Data are reported in Figure 3. The fact that the patients with a specific endocrinopathy had more cardiac iron content and complications, in particular heart failure and hyperkinetic arrhythmias, than patients without the endocrinopathy confirmed the causative role of iron overload in both endocrine and cardiac complications.

In order to define the impact of the considered endocrinopathies on the development of cardiac diseases, we selected cases without myocardial iron overload (all normal segmental T2* values) (Figure 4). The prevalence of myocardial fibrosis and cardiac complications which were current at the time of the study according to the endocrinopathies is reported in Table 2. Cardiac dysfunction ranged between 12% in patients with hypoparathyroidism and 43% in males with hypogonadism. A borderline significance was found when comparing patients with diabetes or hypoparathyroidism versus patients without the specific endocrinopathy. The prevalence of heart failure varied from 7% in females with hypogonadism to 24% in patients with diabetes and it was significantly higher only in patients with versus no diabetes. The prevalence of hyperkinetic arrhythmias speckled from the 10% in females with hypogonadism to the 35% in patients with diabetes and it was significantly more frequent in all groups having versus not having a specific endocrinopathy. Myocardial fibrosis was more prevalent in patients with than without a specific endocrinopathy, but the difference was significant only considering the diabetes. The probability of arrhythmias increased significantly in presence of two or more associated endocrine diseases (Figure 3). No effect of endocrine co-morbidity was found on heart failure, fibrosis and cardiac dysfunction. Data regarding the OR corrected for age and co-morbidity are showed in

Figure 1. Prevalence of endocrine complications in 957 patients with thalassemia major .

(Hyp M= pubertal hypogonadism in males; Hyp F=pubertal hypogonadism in females; Hypothy=hypothyroidism; DM=diabetes mellitus; Hypopara=hypoparathyroidism).

Figure 2. Prevalence of cardiac complications (heart failure, cardiac dysfunction, arrhythmias) in patients with thalassemia major according to endocrinopathy.

Table 3. The males with hypogonadism were significantly more likely to have arrhythmias even after adjustment for a single or for both factors (OR 17.21). In females having hypogonadism odds ratio for arrhythmias lose significance after the adjustment for age and co-morbidity. Patients with hypothyroidism were significantly more likely to have arrhythmias after the correction for age, but not for co-morbidity and for both variables. Comparing patients with and without diabetes, the odds ratio remained significant for arrhythmias after the adjustment for age and co-morbidity, for heart failure only after the adjustment for the presence of another endocrinopathy and for myocardial fibrosis after the correction for both variables. Comparing patients with and without hypoparathyroidism, the odds ratio for arrhythmias lose significance after the correction for both factors. It is important to note that hypoparathyroidism appeared to reduce significantly the risk of cardiac dysfunction. The odds ratio after correction for age and co-morbidity was, in fact, 0.24. Globally, the analysis performed in patients without cardiac iron overload displayed some impact of the considered endocrinopathy on cardiac complications. Hypogonadism in females

Table 1. Global Heart T2* values, prevalence of cardiac complications and myocardial fibrosis according to endocrine diseases in patients with thalassemia major.

	Pubertal hypogonadism in males		Pubertal hypogonadism in females		Hypothyroidism		Diabetes mellitus		Hypoparathyroidism	
	with	without	with	without	with	without	with	without	with	without
Number of patients	163	272	175	290	192	727	87	708	61	798
Global Heart T2* (ms)	27.0 ± 13.3	30.9 ± 11.2	25.9 ± 12.5	29.1 ± 11.7	26.4 ± 12.9	29.2 ± 11.9	25.5 ± 12.6	29.2 ± 11.9	26.9 ± 12.9	28.6 ± 12.1
p	0.008		0.005		0.007		0.017		ns	
Cardiac dysfunction (%)	51	43	25	29	41	34	45	35	33	37
p	ns		ns		ns		*0.064		ns	
Heart failure (by MRI and by patient history) (%)	27	13	14	7	21	11	30	12	28	13
p	<0.0001		0.010		<0.0001		<0.0001		<0.0001	
Hyperkinetic arrhythmias (%)	18	4	8	1.4	14	4	18	6	13	6
p	<0.0001		0.001		<0.0001		<0.0001		0.04	
Hypokinetic arrhythmias (%)	0.6	0.4	0.6	0	0.5	0.3	0	0.3	1.6	0.1
p	ns		ns		ns		ns		ns	
Pulmonary hypertension (%)	0.6	2.6	1.7	1.7	0.5	1.9	1.1	2.1	1.6	1.8
p	ns		ns		ns		ns		ns	
Myocardial fibrosis (%)	19 (29/152)	17 (38/228)	24 (37/154)	19 (48/250)	19 (33/171)	19 (121/630)	31 (24/78)	19 (114/610)	22 (12/54)	20 (136/697)
p	ns		ns		ns		0.012		ns	

* near to the statistical significance

Figure 3. Risk of cardiac diseases in presence of one, two, three or more versus no endocrine diseases in patients with thalassemia major.

and hypothyroidism didn't seem to play any role on the development of cardiac complications. Hypoparathyroidism appeared to be associated with a significant reduction of the risk of cardiac dysfunction. In this case, a role of vitamin D therapy can be supposed. Hypogonadism in males strongly increased the risk of arrhythmias. Males were expected to be more sensitive than females to iron damage¹⁷ and arrhythmias might be the consequence of a previous but resolved cardiac iron overload. However, the link between pubertal hypogonadism and arrhythmias has to be clarified. Diabetes increased the risk of arrhythmias as well as myocardial fibrosis, with a borderline effect on heart failure: a cardiomyopathy secondary to diabetes could be assumed.

This study presents some limitations. Secondary hypogonadism, subclinical hypothyroidism, hormone replacement therapy in hypogonadism, effects of sex on endocrinopathies out of hypogonadism were not taken into account. Besides this, growth hormone deficiency, reported prevalent up to the 40 % of adult patients with TM, was not expected¹⁸

Table 2. Prevalence of cardiac complications and myocardial fibrosis in patients with thalassemia major without myocardial iron overload (T2* >20 ms in all segment) according to endocrinopathies.

	Pubertal hypogonadism in males		Pubertal hypogonadism in females		Hypothyroidism		Diabetes mellitus		Hypoparathyroidism	
	with	without	with	without	with	without	with	without	with	without
Number of patients	70	137	62	130	75	333	29	329	24	353
Cardiac dysfunction (%)	43	37	18	20	33	28	45	28	13	32
p	ns		ns		ns		*0.061		*0.065	
Heart failure (by MRI and by patient history present at the time of the study) (%)	17	11	7	4	13	8	24	8	13	9
p	ns		ns		ns		0.004		ns	
Hyperkinetic arrhythmias (%)	24	1.5	10	2	16	5	35	5	21	6
p	<0.0001		0.015		<0.0001		<0.0001		0.021	
Myocardial fibrosis (%)	19 (12/65)	17 (19/111)	30 (17/56)	19 (21/113)	23 (14/61)	19 (56/293)	38 (9/24)	20 (56/287)	29 (6/21)	20 (136/697)
p	ns		ns		ns		0.037		ns	

* near to the statistical significance

Figure 4. Risk of cardiac diseases in presence of one, two, three or more versus no endocrine diseases in patients with thalassemia major without myocardial iron overload.

Table 3. OR for cardiac complications and myocardial fibrosis in patients with thalassemia major without myocardial iron overload according to endocrinopathies.

	OR	p	Adjusted for					
			age		Endocrinopathy		Both	
			OR	p	OR	p	OR	p
Hypogonadism in males								
Arrhythmias	21.65	<0.0001	17.25	<0.0001	17.16	<0.0001	17.21	0.0001
Hypogonadism in females								
Arrhythmias	6.86	0.021	3.72	ns	8.09	*0.070	2.24	ns
Hypothyroidism								
Arrhythmias	4.04	0.001	2.86	0.018	2.14	ns	1.36	ns
Diabetes mellitus								
Arrhythmias	9.66	<0.0001	3.75	<0.0001	7.28	<0.0001	3.5	0.015
Heart failure	3.78	0.006	2.02	ns	3.21	0.017	1.94	ns
Fibrosis	2.46	0.043	2.31	ns	2.14	ns	2.12	0.017
Hypoparathyroidism								
Arrhythmias	3.96	0.012	2.52	ns	1.99	ns	1.59	ns
LV/LR dysfunction	0.31	*0.060	0.24	0.025	0.28	0.043	0.24	0.027

* near to the statistical significance

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