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Letter to the Editor

Brain natriuretic peptide as marker of myocardial iron load in β-thalassemia

Savvas Nikolidakis [a], Constantina Flessa [a], Nikolaos Nikolaou [b], Efstathios D. Gotsis [c], Michael Koutouzis [a], Eleni Polyhronaki [d], Eleni Vrettou [d], Zenon S. Kyriakides [a,*]

[a] *Red Cross General Hospital, Athens, Greece*
[b] *Agia Olga General Hospital, Athens, Greece*
[c] *Euromedica-Encephalos Institute, Athens, Greece*
[d] *Red Cross Thalassemia Unit, Athens Greece*

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Abstract

Cardiomyopathy due to iron overload represents a frequent life-limiting complication in patients with β-thalassemia major. We have conducted a study which proved that brain natriuretic peptide plasma levels have high sensitivity and negative predictive value in detecting cardiac hemosiderosis.

Keywords: Magnetic resonance imaging; β-Thalassemia major; Myocardial hemosiderosis; Brain natriuretic peptide

The implementation of a vigorous transfusion regimen to maintain adequate hemoglobin level in β-thalassemia major patients has improved survival and quality of life. Repeated blood transfusions, though, result in iron accumulation in the reticuloendothelial system and parenchymal cells. The principal damage occurs in the heart, liver and endocrine organs, making cardiomyopathy the major cause of death from iron overload in this setting [1,2]. Quantifying myocardial iron is important in making therapeutic decisions regarding chelation treatment and in determining prognosis [3].

Magnetic resonance imaging represents the only imaging method in clinical use with the potential to detect iron within the heart [4]. It is, however, a relatively expensive technique.

Brain natriuretic peptide is a cardiac-derived natriuretic peptide. Its levels increase in myocardial dysfunction even before symptoms appear [5,6], and can be used in the detection of myocardial involvement with preserved left ventricular ejection fraction such as sarcoid and myocardial ischemia without ST elevation [7,8]. We therefore undertook this study to investigate whether brain natriuretic peptide could be used to estimate functional consequences of

Table 1
Comparison of the patient characteristics between the group with severe myocardial iron deposition and the rest of the patients

	$T_2 \geq 24$ ms ($n=59$)	$T_2 < 24$ ms ($n=17$)	p
Age	35 (30, 38)	35 (29, 37)	NS [a]
Male sex, *n* (%)	26 (44)	4 (24)	NS
Spleenectomy, *n* (%)	39 (66)	15 (88)	0.07
Left ventricular ejection fraction (%)	69 (63, 75)	66 (58, 73)	NS
Blood units, *n*	988 (780, 1113)	1059 (748, 1164)	NS
Ferritin (μg/l)	2436 (1220, 3685)	2922 (2170, 4359)	NS
BNP [b] (pg/ml)	23 (14, 47)	45 (32, 78)	0.008

Data are summarized as median (25th, 75th centiles), unless otherwise stated.
[a] NS: not statistically significant.
[b] BNP: brain natriuretic peptide.

* Corresponding author. B Cardiology Department, Red Cross Hospital, 1 Erythrou Stavrou str. Athens 115 26, Greece. Tel.: +30 210 6414 705, +30 210 6414 587, +30 210 8104 554; fax: +30 210 6414 587.
E-mail address: zskyr@otenet.gr (Z.S. Kyriakides).

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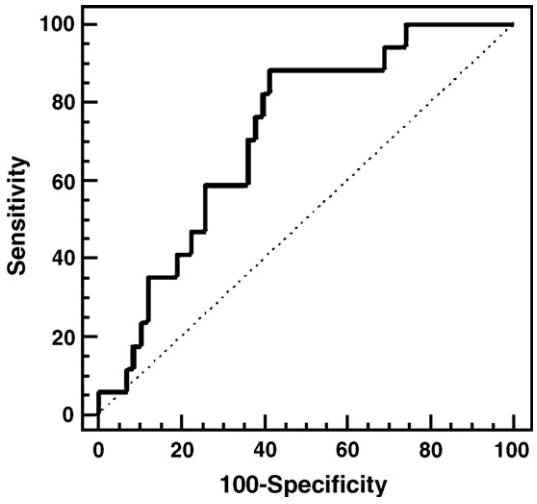

Fig. 1. Receiver–operator characteristic curve of brain natriuretic peptide values for the identification of patients with severe myocardial hemosiderosis.

magnetic resonance imaging documented myocardial iron overload in patients with thalassemia.

For that purpose, 76 regularly transfused, adult, β-thalassemia major patients were recruited (30 males, median age 35 years). All had been on iron chelation therapy for several years, with no one having overt heart failure.

All subjects underwent quantitative cardiac magnetic resonance imaging and T_2 relaxation times were determined for the estimation of myocardial iron deposition. All magnetic resonance imaging studies were conducted at 1.5 T (GE, SIGNA CVI with 40 mT/m gradients and complete cardiac package), with an electrocardiograph-gated multi-echo spin echo sequence. The entire myocardium was imaged with 6–8 slices (slice thickness 8 mm, interslice gap of 2 mm) and the mean T_2 value from all slices was recorded as the final T_2 relaxation time of the myocardium.

Subsequently, patients were divided in two groups, according to their T_2 levels. Those with severe hemosiderosis ($T_2 < 24$ ms) and those with lesser myocardial iron burden.

Peripheral brain natriuretic peptide plasma levels were estimated before transfusion in whole blood samples using Triage® System for Brain Natriuretic Peptide (Biosite Diagnostics, La Jolla, CA, USA).

For the statistical analysis, all continuous variables were summarized using the median and the interquartile range (25th and 75th percentiles). The Mann–Whitney *U*-test was used for comparisons between groups. Differences in proportions were judged by chi-square analysis. Associations between variables were tested using Spearman's rank *R*. Diagnostic performance of BNP levels was tested using receiver–operator characteristic curve analysis. Brain natriuretic peptide plasma levels were statistically higher in the severely hemosiderotic group (Table 1). They correlated inversely with myocardial T_2 relaxation time values (Spearman's $R = -0.26$, $p = 0.03$). The area under the receiver–operator characteristic curve was 0.71 (95% CI = 0.59–0.81), (Fig. 1). Using magnetic resonance imaging as the comparative "gold" standard, a brain natriuretic peptide value of 29 pg/ml had a sensitivity of 88% and a specificity of 58%. Negative predictive value was 94% while positive predictive value was 37%.

Therefore, it seems that brain natriuretic peptide measurement offers the opportunity to detect myocardial hemosiderosis before conventional indices of systolic function such as the ejection fraction are affected. This is of utmost importance as it is well known that iron-induced cardiomyopathy is reversible if chelation treatment is instituted in time. By using this cut-off value of 29 pg/ml, 46% of our patients could be spared from undergoing further unnecessary testing, as they are highly unlikely to have severe myocardial hemosiderosis.

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