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Original Article

Comparison of Serum Prolactin Levels Between the Acute Phase of Heart Failure and After Guideline-Directed Medical Therapy

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ABSTRACT

Background: Prolactin (PRL) has increasingly been recognized to play a stimulatory role in inflammatory response. Recently, studies have reported an increase in the PRL level among patients with chronic heart failure (HF); however, there are conflicting data about its role as a prognostic factor in these patients. We aimed to measure the PRL level in the acute phase of HF and the post guideline-directed medical therapy (GDMT) of HF to clarify whether PRL is an acute-phase reactant or more than an acute phase-reactant in patients with HF.

Methods: The serum PRL level was assessed in 94 patients with HF in the acute phase of HF decompensation and post-GDMT of HF. Serum N-terminal pro-brain natriuretic peptide, high-sensitive C-reactive protein, 6-minute walk test, erythrocyte sedimentation rate, CRP, blood urea nitrogen, creatinine, serum sodium, and white blood cell count were also measured. Our secondary end points were mortality, transplantation, and hospitalization due to acute HF. All the patients were followed up for 6 months.

Results: The mean serum PRL level in the acute phase was 31.3 ng/mL, which was significantly higher than the normal reference values (4.04–15 ng/mL) ($P < 0.001$). The mean serum PRL level before discharge was 34.84 ng/mL, which was significantly higher than the normal reference values and similar to the acute phase values. The mean PRL level in the patients with dilated cardiomyopathy was 33.61 ng/mL in the acute phase and 43.15 ng/mL after the GDMT of HF. The mean PRL level in the patients without dilated cardiomyopathy was 33.42 ng/mL in the acute phase and 29.92 ng/mL before discharge. The mean PRL level in the patients with re-admission was higher (27.7 ng/mL in the acute phase and 29.7 ng/mL before discharge in the patients with no re-admission and 37.4 ng/mL in the acute phase and 42.5 ng/mL before discharge in the patients with re-admission).

Conclusions: In 57% of the patients, the mean level of PRL increased after treatment. The level remained unchanged in 3.5% of the patients and had a drop in 39.2%. Our findings suggest that PRL may be more than an acute-phase reactant alone. Larger studies are needed to further elucidate the role of PRL in patients with HF. Research regarding the treatment of patients suffering from HF with high levels of PRL post-GDMT of HF with bromocriptine may have consequences like those in peripartum cardiomyopathy. ***(Iranian Heart Journal 2017; 18(1):20-24)***

Keywords: Hyperprolactinemia, Cardiomyopathy, Peripartum

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Heart failure (HF), a major cause of morbidity and mortality throughout the world, is responsible for a high rate of hospitalization and is a principal complication of all forms of heart diseases. Although the results of extensive investigations in this field have a great role in understanding THE HF pathophysiology and better management of patients, the prognosis of this disorder remains poor. [1, 2]

The pathophysiology of HF is closely associated with neuroendocrine changes. The activation of neuroendocrine systems contributes to the progression of HF. Many neuroendocrine factors are changed in congestive HF. Not only are the neuroendocrine changes a marker of the severity of cardiac dysfunction, but also they directly worsen it. The cornerstone of HF therapy is modulating these neuroendocrine changes and decreasing their adverse effects.[4-6]

Prolactin (PRL), mainly its 16-kDa angiostatic and proapoptotic form, is a key factor in the pathophysiology of peripartum cardiomyopathy (PPCMP). Previous reports have suggested that bromocriptine may have beneficial effects in women with the acute onset of PPCMP. [3]

Serum PRL is associated with neuro-hormonal/immune activation and depressive symptoms and is an independent predictor of prognosis in advanced congestive HF.

The aim of this study was to assess the PRL level in patients admitted with acute HF and post guideline-directed medical therapy (GDMT) with a view to assessing whether or not PRL has an acute-phase reactant role.

METHODS

Study Participants

A total of 94 patients with the diagnosis of HF according to the European Society of Cardiology's Guidelines [1] admitted to our Heart Failure Clinic between June and March 2014 were enrolled. The inclusion criteria were ischemic cardiomyopathy and dilated cardiomyopathy (DCM) in patients with a left ventricular ejection fraction (LVEF) < 50% and New York Heart Association (NYHA) functional classes II–IV.

Patients had to be on standard HF therapy with diuretics and neurohormonal blockers according to the latest guidelines on HF management. [1] The study population was subsequently followed up for 6 months. Hospitalization due to acute HF, transplantation, and death were also registered. No patient was lost during the follow-up, and HF medications were not changed unless an expected event occurred.

Data acquisition and laboratory measurements

Primary evaluation, clinical history, and physical examination were obtained from all the patients, and the demographic data and the NYHA classifications were recorded. The NYHA class was evaluated, whereby class I indicated no limitations of physical activity, class II indicated slight limitation of physical activity, class III indicated limitation of physical activity, and finally class IV indicated symptoms of dyspnea at rest. [1] The exercise tolerance and functional performance of the patients were assessed via the 6-minute walk test (6MWT) according to the protocol of Guyatt and colleagues. [8]

The levels of N-terminal pro-brain natriuretic peptide (NT-proBNP) for neurohormonal status [9-11] and high-sensitive C-reactive protein (hs-CRP) as a pro-inflammatory marker [7,10] have been recognized as important quantitative plasma biomarkers for the development of prognostic tools for idiopathic dilated cardiomyopathy. Peripheral blood samples were collected for NT-proBNP analysis using the ELISA method (BioMedia Corp, Bratislava, Slovakia). Serum hs-CRP levels were measured via the slide agglutination method and immunoturbidimetry using an hs-CRP latex kit (Bionic, USA) for each sample. Serum PRL was measured via the 2-site immunoradiometric assay (IRMA) (Pathan, Iran). The reference range was 4.04–15.2 ng/mL. Thyroid-stimulating hormone (TSH) was also measured through radioimmunoassay (Autobio, China) in all the patients with a reference range of 0.27–4.2 mU/mL. All the blood samples were collected from the patients in a fasting state and sitting position, an hour after awakening from an overnight sleep.

After GDMT and before discharge, the aforementioned biomarkers (especially PRL) were checked again to compare their pre- and post-treatment levels.

Statistical Analysis

IBM SPSS Statistics 19.0 for Windows (IBM Corp. Armonk, NY, USA) was used for the statistical analysis. The data are expressed as mean ± standard deviation (SD) for the interval and count (percent) for the categorical variables. The one-Sample Kolmogorov–Smirnov test was used to test the normal distribution of the interval variables. The one-sample *t*-test was employed to analyze differences in the mean values of hormonal concentrations between the patients and the normal reference values and between the pre- and post-treatment values. The interval variables were compared between the 2 groups using the Student *t*-test (for the normally distributed data) or its non-parametric equivalent, the Mann–Whitney *U*-test (for the non-normally distributed data). The Pearson correlation coefficient (*r*) was also utilized to show linear correlations between the interval variables. A *P* value < 0.05 was considered significant. A logistic regression model was applied for multivariable analysis.

RESULTS

Baseline Characteristics

There were 94 patients, comprised of 30 (31.9%) female and 64 (68.1%) male patients, at a mean age of 48.8 years old (range =14–89 y). The mean LVEF was 19.4%. Concerning the NYHA functional class, 2 (2.1%) patients were in class II, 71 (75.5%) in class III, and 21(22.3%) in class IV. Twenty-nine (30.9%) patients had DCM. All the patients were on standard recommended medical treatment for HF, including angiotensin-converting enzyme (ACE) inhibitors/angiotensin receptor blocker (ARB), beta-blockers, spironolactone, diuretics, and digoxin. The mean number of admission days was 13.3 days (3–42 d). Thirty-eight(40.4%)patients had re-admission.

Serum prolactin changes between the acute phase of heart failure and after guideline-directed medical therapy and before discharge and its associations with the NYHA function class and other prognostic factors

The mean serum PRL level in the acute phase was 31.3 ng/mL, which was significantly higher than the normal reference values (4.04–15 ng/mL) (*P* < 0.001). The mean serum PRL level before discharge was 34.84 ng/mL, which was significantly higher than the normal reference values and similar to the values in the acute phase. The mean PRL level in the patients with DCM was 33.61 ng/mL in the acute phase and 43.15 ng/mL after the GDMT of HF. The mean PRL level in the non-DCM patients was 33.42 ng/mL in

the acute phase and 29.92 ng/mL before discharge. The mean PRL level in the patients with re-admission was higher (27.7 ng/mL in the acute phase and 29.7 ng/mL before discharge in the patients with no re-admission and 37.4 ng/mL in the acute phase and 42.5 ng/mL before discharge in the patients with re-admission). The mean PRL level in the female patients, pre and post treatment, was higher than that in the male patients. Vis-à-vis the TSH level, none of the patients had hypothyroidism. As an important prognostic factor in these patients, the associations between the NYHA function class, serum PRL pre and post treatment, and the other prognostic factors were assessed specifically.

The mean PRL level in the patients with DCM after treatment and before discharge was higher than that in the non-DCM patients (43.15 ng/mL vs 29.92 ng/mL), but there was no significant correlation. The mean PRL level in the patients with re-admission was higher, but the difference did not constitute statistical significance. The relationships between the serum PRL level and the other prognostic factors were also investigated. No significant correlations were seen between PRL and age (r = 0.05 ; P = 0.64), erythrocyte sedimentation rate (r = 0.05; P = 0.59), hs-CRP (r = -0.06 ; P = 0.67), serum sodium (r = -0.04 ; P = 0.69), serum uric acid (r = 0.10 ; P = 0.39), serum creatinine (r = 0.04; P = 0.66), NT-proBNP (r = 0.07; P = 0.51), and duration of hospitalization (r = -0.014 ; P = 0.89).

Findings in the patients' follow-up

All the patients were followed up for 6 months for events such as mortality due to HF, hospitalization for acute HF, and transplantation. During this follow-up period, 20 (21.2%) patients died (all of them with LVEF < 20% and NYHA class IV). Additionally, 7 (7.4%) patients underwent transplantation and 38 (40.4%) were hospitalized at least once with a diagnosis of acute HF. The patients with events had higher NT-proBNP, hs-CRP, and TSH levels and lower LVEF and 6MWT. Nevertheless, except for NT-proBNP, none of the differences was statistically significant. Despite the higher mean level of PRL in the patients with re-admission and in those with DCM, this correlation was not significant.

DISCUSSION

In the present study, we found a higher-than-normal serum PRL concentration among our 94 patients. There are several reports on the measurement of the serum PRL level in patients with HF. Opalinska et al [3] measured the levels of several hormones, including PRL, in 27 male patients suffering from HF with an LVEF < 35% and found hyperprolactinemia. Limas et al [4] reported that hyperprolactinemia was present in 25% of their patients with HF. In 2 recent studies, Landberg et al [5] and Parissis et al [6] showed elevated levels of serum PRL in different groups of patients with HF.

The aim of the current study was to assess the PRL level in patients admitted with acute HF and post GDMT with a view to assessing whether or not PRL has an acute-phase reactant role. We presumed that PRL might be an acute-phase reactant and elevated levels of PRL in the acute phase might decrease following the GDMT and stabilization of patients. In this study, the mean level of PRL was significantly different from its normal value, especially in the patients with DCM.

In 57% of our patients, the mean level of PRL increased after treatment. The mean level remained unchanged in 3.5% of the patients and decreased in the remaining 39.2%. In light of this finding, it can be posited that PRL may play a role more than that of an acute-phase reactant alone. Be that as it may, larger studies are required to shed sufficient light on the role of PRL in patients with HF. Research into the treatment of patients suffering from HF with high levels of PRL following the GDMT of HF with bromocriptine may have consequences like those in PPCMP.

One of the strengths of this study is its utilization of a new design to clarify the role of PRL in patients with HF.

CONCLUSIONS

PRL, as a multifunctional hormone, plays an important role in immune-regulation, osmoregulation, metabolism, and angiogenesis [3-7] and there is substantial evidence in favor of its involvement in the pathogenesis of PPCMP. [10] However, given the results of the current and other studies regarding the role of PRL in patients with HF, this role cannot simply be considered as a prognostic factor in HF and further investigations are needed to shed more light on the role of PRL in the pathophysiology of HF.

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