Available online at www.sciencedirect.com
ScienceDirect
Neuroscience Letters 417 (2007) 322–325
Neuroscience Letters
www.elsevier.com/locate/neulet

Elevated plasma N-terminal ProBNP levels in unmedicated patients with major depressive disorder

Pierluigi Politi [a], Piercarlo Minoretti [b], Noemi Piaggi [a], Natascia Brondino [a], Enzo Emanuele [b,*]

[a] *Department of Applied Health and Behavioural Sciences, Section of Psychiatry, University of Pavia, Pavia, Italy*
[b] *Interdepartmental Center for Research in Molecular Medicine (CIRMC), University of Pavia, Viale Taramelli 24, I-27100 Pavia, Italy*

Received 18 January 2007; received in revised form 22 February 2007; accepted 22 February 2007

Abstract

There is considerable evidence that cardiovascular diseases are more prevalent in patients with major depressive disorder (MDD). Secretion of N-terminal pro-B-type natriuretic peptide (NT-proBNP) increases in several cardiac illnesses, making this neurohormone a reliable diagnostic and prognostic biomarker of cardiovascular risk. We measured plasma NT-proBNP levels in the following three groups of subjects free of overt cardiovascular disease: unmedicated patients with MDD ($n = 40$), unmedicated patients with schizophrenia ($n = 44$), and normal control subjects ($n = 42$). The severity of depressive symptoms was rated using the Hamilton Depression Rating Scale (HAMD). Plasma NT-proBNP levels were assayed by ELISA. Plasma NT-proBNP levels were significantly higher in the MDD group (median: 217.1 pmol/L; interquartile range: 179.4–277.1 pmol/L) than in patients with schizophrenia (175.7 pmol/L [139.0–218.9]; $P < 0.05$) or in the control group (158.9 pmol/L [98.3–212.1]; $P < 0.001$). Among patients with MDD, there was a significant positive correlation (Spearman's rank correlation = 0.422, $P = 0.008$) between plasma NT-proBNP and HAMD scores. Altogether, our results indicate that elevated NT-proBNP levels may play a role in linking MDD with increased cardiovascular risk.

Keywords: Major depressive disorder; Schizophrenia; Cardiovascular risk; Natriuretic peptides; ELISA

A growing body of evidence has now accrued that major depressive disorder (MDD) and cardiovascular disease may be closely interrelated. Accordingly, a number of epidemiological studies have repeatedly demonstrated an increased risk of adverse cardiac events in individuals with MDD or other chronic negative mood states [7,16,17]. Hence, it has been posited that MDD could share common risk factors with cardiac illnesses [12]. Although several pathobiological mechanisms – including abnormal platelet reactivity, hypercoagulability, endocrine alterations and abnormal lipid profile – have been advocated to explain such relationship [4], the exact biochemical pathways underlying the increased risk for cardiac events in depressed individuals remain largely elusive.

The N-terminal fragment of B-type natriuretic peptide (NT-proBNP) is primarily secreted from cardiomyocytes in response to left ventricular stretching or wall tension [25]. A bulky of published data have clearly indicated that elevated NT-proBNP could serve as a reliable biochemical marker in diverse cardiac conditions such as heart failure, cardiac hypertrophy, acute coronary syndromes, arrhythmias, fibrosis, and coronary endothelial dysfunction [14,18,23]. Notably, it has been also shown that increased NT-proBNP concentrations may predict future adverse cardiac outcome and death from cardiovascular causes in initially healthy individuals [11]. Intriguingly, a report by Bunevicius et al. [2] has recently demonstrated that depressed patients with coronary artery disease may display significantly higher NT-proBNP concentrations compared to their nondepressed counterparts. To date, however, no data is available regarding circulating levels of NT-proBNP in patients with MDD without overt cardiovascular disease. To address this issue, we examined plasma NT-proBNP levels in unmedicated patients with MDD. Additionally, we carried out the same measurement in unmedicated patients with schizophrenia. As is the case with depressed patients, patients with schizophrenia are at increased risk for cardiovascular disease [9,20]; hence, the results obtained with a sample with schizophrenia may be useful to identify a specific neurohormonal response among patients with MDD.

* Corresponding author. Tel.: +39 0382 528 341; fax: +39 0382 526 259.
E-mail address: enzo.em@libero.it (E. Emanuele).

0304-3940/$ – see front matter © 2007 Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/j.neulet.2007.02.056

Table 1
General characteristics and plasma NT-proBNP values of the study participants

	MDD ($n=40$)	Schizophrenia ($n=44$)	Healthy controls ($n=42$)	P-value
Age (years)	35.4 ± 10.1	33.9 ± 9.6	35.6 ± 10.2	0.21
Age at onset (years)	34.1 ± 9.6	26.4 ± 9.6	–	–
HAM-D scores	23.7 ± 5.2	–	–	–
BPRS scores	–	45.1 ± 15.9	–	–
Gender, male/female	18/22	23/21	20/22	0.46
BMI (kg/m^2)	24.7 ± 3.3	25.0 ± 2.9	24.8 ± 3.6	0.87
Erythrocytes sedimentation rate (mm/h)	14 (10–26)	13 (9–23)	13 (10–22)	0.42
White blood cells (10^3 per μl)	7.7 ± 2.1	7.5 ± 2.2	7.5 ± 1.9	0.64
Creatinine (mg/dL)	0.8 ± 0.2	0.8 ± 0.1	0.8 ± 0.1	0.47
Plasma glucose (mg/dL)	85.8 ± 20.4	87.6 ± 24.9	84.4 ± 12.6	0.87
Total cholesterol (mg/dL)	197 ± 37	211 ± 39	201 ± 34	0.13
Triglycerides (md/dL)	99 (77–131)	112 (81–139)	105 (70–124)	0.20
NT-proBNP (pmol/L)	217.1 (179.4–277.1)	175.7 (139.0–218.9)	158.9 (98.3–212.1)	<0.001

Three groups of subjects were investigated in the current study: 40 individuals with MDD (18 males and 22 females, mean age: 35.4 ± 10.1 years), 44 patients with schizophrenia (23 males and 21 females, mean age: 33.9 ± 9.6 years), and 42 healthy comparison subjects (20 males and 22 females, mean age: 35.6 ± 10.2 years). Psychiatric patients were recruited from the Department of Psychiatry at the Pavia University School of Medicine and from Outpatients Departments from which we receive referrals. Each patient was given a diagnostic assessment by an experienced psychiatrist based on the Structured Clinical Interview for DSM-IV. All patients had active or psychotic symptoms at the time of recruitment. All psychiatric patients were either medication-naive (first-onset) or medication-free for at least four months. The psychopathological status of the patients at the time of blood sampling was assessed using the Hamilton Rating Scale for Depression (17-item HAMD) [8] for patients with MDD and the Brief Psychiatric Rating Scale (BPRS) [19] for patients with schizophrenia. Psychiatric exclusion criteria were: eating disorders, addiction, anxiety disorders and mental retardation. Psychiatric patients were required to be medically healthy. All participants underwent a comprehensive clinical examination including heart and lung auscultation. Body mass index (BMI) was calculated as an indicator of nutritional status. Subjects with known ischemic heart disease, hypertension, chronic lung disease, liver disease, and diabetes were excluded. All psychiatric patients had a normal ECG, as well as a normal left ventricular function as assessed by echocardiography.

A total of 42 healthy volunteers of similar age and sex distribution were selected as a control group. All of them were interviewed using the Mini-International Neuropsychiatric Interview [22] and none had a personal or family history of psychiatric disorders. All controls were free of chronic and acute physical illness. They showed normal findings in routine blood chemistry, ECG, and echocardiography. The study was approved by the local ethics committee in accordance to the Helsinki Declaration and written informed consent was obtained from each participant.

Blood samples were collected in vacuum tubes containing EDTA (Becton-Dickinson, Oxford, UK) in the morning after an overnight fast and a resting period of 20 min to minimize possible circadian effects on plasma NT-proBNP values. Inflammatory profile (erythrocyte sedimentation rate and leukocyte count) was measured using standard methodology. Serum creatinine was determined as an index of renal function. Plasma glucose, total cholesterol and triglycerides were assessed using enzymatic procedures (Boehringer, Mannheim, Germany). For NT-proBNP measurements, samples were centrifuged at 1500 × g for 20 min at room temperature. Plasma was separated, stored in aliquots, and kept frozen at −70 °C until analysis. Plasma NT-proBNP was measured using a competitive enzyme immunosorbent assay (Biomedica Laboratories, Vienna, Austria) according to the manufacturer's protocol [1,13]. The assay has no cross-reactivity with other hormones or pharmaceutical drugs. All measurements were performed in duplicate and in random order.

Continuous variables were tested for normal distribution with the Kolmogorov–Smirnov statistics and are expressed as mean ± S.D. or as medians with interquartile ranges. Comparison of categorical variables was generated by the Pearson χ^2-test. For three group comparisons of quantitative variables, a one-way analysis of variance (ANOVA) or Kruskall–Wallis analysis, with post-hoc Dunn's testing, was performed. Correlations among variables were computed with the use of Spearman's rank-correlation coefficients. Not normally distributed variables were log transformed. Multivariable linear regression was performed to determine the independent predictors of plasma NT-proBNP after adjustment for potential confounders. All statistical analyses were carried out using SPSS, version 11.0 (SPSS Inc., Chicago, IL, USA). Two-tailed P-values < 0.05 were considered to be significant.

The clinical and biochemical characteristics of the study participants are shown in Table 1. The three groups were well balanced with regard to age, gender, and BMI. No differences in erythrocyte sedimentation rate or white blood cells count were evident. In addition, serum creatinine, plasma glucose, total cholesterol and triglycerides concentrations were similar among the three groups. Levels of NT-proBNP in plasma were significantly different across the three groups (Kruskall–Wallis non-parametric test, $P < 0.001$, Fig. 1). Subsequent post-hoc analyses using the Dunn's test revealed that the median [interquartile range] NT-proBNP concentration was