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The N-terminal pro-brain natriuretic peptide as a marker of mitoxantrone-induced cardiotoxicity in multiple sclerosis patients

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ABSTRACT

Background and purpose: Mitoxantrone (MTX) has been shown to reduce progression of disability and number of clinical exacerbations in patients with progressive multiple sclerosis (MS). Prolonged administration of MTX, however, is limited by the risk of cardiotoxicity. Cardiac monitoring in MTX-treated patients includes usually measurement of left ventricular ejection fraction (LVEF) by means of echocardiography. The N-terminal pro-brain natriuretic peptide (NT-proBNP) represents a novel diagnostic tool in the assessment of heart failure. This study was aimed to evaluate the usefulness of NT-proBNP for early detection of MTX-induced cardiotoxicity in MS patients.

Materials and methods: We measured the NT-proBNP plasma levels in 45 MS patients who completed 24-month MTX therapy and in 37 MS patients of control group.

Results: The median NT-proBNP plasma value was 15.12 pg/mL. In 12 MTX-treated patients (27%), NT-proBNP plasma values were elevated, though this subgroup of patients neither clinical showed evidence of myocardial damage nor had the LVEF value <50%. In five patients with normal NT-proBNP, we observed LVEF decline >10%. We did not observe correlations between the NT-proBNP levels and patient age, MS duration, relapses index, Extended Disability Status Scale (EDSS), MTX single dose and the total cumulative dose of MTX. In 8 patients (22%) from control group, NT-proBNP plasma levels were also elevated.

Conclusions: The results of our study confirm that MTX therapy is safe for carefully selected and closely monitored MS patients. We believe that serial evaluation of NT-proBNP levels (before, during and after MTX therapy) can identify MS patients at high risk for MTX-induced cardiotoxicity.

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1. Introduction

Mitoxantrone (MTX) has been shown to reduce progression of disability and clinical exacerbations in patients with progressive multiple sclerosis (MS) [1]. Mitoxantrone is approved by the European Medicines Agency (EMEA) and Food and Drug Administration (FDA) for the treatment of patients with worsening relapsing-remitting MS (RRMS), progressive-relapsing MS (PRMS) and secondary progressive MS (SPMS). Although MTX is generally well tolerated, it is associated with a variety of potential toxic effects. One of the more serious adverse events associated with MTX treatment is cardiotoxicity [2–4]. Cardiac monitoring in MTX-treated patients includes usually the evaluation of left ventricular ejection fraction (LVEF) by means of echocardiography. This technique, however, did not exhibit the expected sensitivity for detection of early cardiac dysfunction.

Natriuretic peptides have recently emerged as biomarkers potentially useful in the diagnosis and prognosis stratification of patients with heart diseases [5,6]. The evaluation of N-terminal pro-brain natriuretic peptide (NT-proBNP) provides information independent from the traditional diagnostic measures [7]. NT-proBNP was found to be an independent predictor of mortality or cardiac events [8,9]. Some studies showed that in patients after high-dose chemotherapy persistently increased NT-proBNP is strongly associated with development of cardiac dysfunction [10]. These findings have important practical implications for identifying patients at risk of developing MTX-induced cardiotoxicity.

2. Materials and methods

We examined 82 patients with clinically defined MS, according to the McDonald criteria, revision 2010 [11]. Examined patients were divided into two groups, A and B: the group A consisted of 45 patients who completed 24 months of MTX therapy, and the group B consisted of 37 MS patients who were not treated with MTX (Table 1). There were 24 females and 21 males in group A; their mean age was 43 ± 9 years, mean disease duration was 16 ± 9 years, and mean Expanded Disability Status Scale (EDSS) score was 3.6 ± 1.8. In 17 patients, MS course was relapsing-remitting (RRMS), in 16 – progressive-relapsing (PRMS) and in 12 patients – secondary progressive (SPMS). The total cumulative dose of MTX was 86.8 ± 20.6 mg/m^2. Mitoxantrone was administered every 3 months with mean MTX single dose of 9.2 ± 1.8 mg/m^2. In group B, there were 25 females and 12 males, their mean age was 37 ± 11 years, mean disease duration was 11 ± 8 years, and mean EDSS was 3.6 ± 1.7. Relapsing-remitting MS was diagnosed in 25 patients, PRMS – in 7 patients and SPMS – in 5 patients. Eleven patients previously underwent therapy with interferon beta-1b and three with glatiramer acetate.

Table 1 – Characteristics of patients in groups A and B.

	Group A (patients after MTX therapy)	Group B (control group)
Number of patients	45	37
Age [years]; mean ± SD	43 ± 9	37 ± 11
MS duration [years]; mean ± SD	16 ± 9	11 ± 8
EDSS score; mean ± SD	3.6 ± 1.8	3.6 ± 1.7
Patients with RRMS (*n*)	17	25
Patients with PRMS (*n*)	16	7
Patients with SPMS (*n*)	12	5

MTX, mitoxantrone; MS, multiple sclerosis; SD, standard deviation; EDSS, Expanded Disability Status Scale; RRMS, relapsing-remitting MS; PRMS, progressive-relapsing MS; SPMS, secondary progressive MS.

All patients underwent extensive neurologic evaluation; impairment and disability were measured using EDSS.

In all patients, we evaluated basic laboratory tests during MTX treatment and follow-up phase. Troponin serum concentration was measured in all patients.

2.1. NT-proBNP evaluation

Blood samples were taken after 24 months of MTX treatment. They were collected into tubes containing sodium citrate solution. The samples were then centrifuged and plasma was stored at −70 °C until analysis was performed. NT-proBNP plasma concentration was measured using immunoassay based on double-antibody sandwich technique (Biomedica). As the cutoff, we used the value approved by FDA: <125 pg/mL.

2.2. Echocardiographic analyses

All patients underwent cardiologic evaluation including transthoracic echocardiography. Clinical examination was performed at each visit in order to exclude the presence of overt heart disease. Serial transthoracic two-dimensional echocardiograms were obtained from each patient before starting therapy for MS, 12 months after the treatment initiation and after the end of treatment. All examinations were performed by an experienced sonographer with the patient in left lateral decubitus position using Hewlett-Packard Sonos 2500 (Hewlett-Packard, Andover, USA) and Philips iE33 (Philips, Eindhoven, Netherlands). Left ventricle end-systolic and end-diastolic volumes as well as the ejection fraction were calculated on the basis of the biplane Simpson's rule.

2.3. Statistical analysis

Patient characteristics by type of NT-proBNP response pattern were compared by the Fisher exact test for categorical variables and Wilcoxon two-sample test for continuous variables. All analyses were conducted with SAS [12]. A two-sided P-value < 0.05 was considered statistically significant.

3. Results

The median NT-proBNP plasma level in group A (after MTX treatment) was 15.12 pg/mL (range: 0–739.2 pg/mL, mean 85.1 ± 157.5 pg/mL). NT-proBNP plasma concentration was increased in 12 patients (7 females and 5 males, 27% of examined patients). In group of patients with elevated NT-proBNP

Table 2 – The N-terminal pro-brain natriuretic peptide (NT-proBNP) plasma concentrations in patients treated with mitoxantrone.

Variables	NT-proBNP > 125 pg/mL	NT-proBNP < 125 pg/mL
NT-proBNP [pg/mL]; mean ± SD	291.6 ± 188.0	10.2 ± 15.9
Number of patients	12	33
Age [years]; mean ± SD	39.5 ± 9.9	44.1 ± 8.7
MS duration [years]; mean ± SD (years)	14.7 ± 7.5	16.5 ± 9.8
EDSS score before treatment; mean ± SD	4.5 ± 1.5	4.3 ± 1.6
EDSS score after the end of treatment; mean ± SD	3.9 ± 2.0	3.5 ± 1.8
Number of relapses in 2 years before treatment; mean ± SD	3.8 ± 3.4	3.6 ± 3.8
Number of relapses during treatment; mean ± SD	1.7 ± 2.1	1.2 ± 1.8
MTX – single dose [mg/m^2]; mean ± SD	9.1 ± 1.4	9.3 ± 1.8
MTX – total cumulative dose [mg/m^2]; mean ± SD	84.0 ± 20.4	87.9 ± 21.0

MTX, mitoxantrone; MS, multiple sclerosis; SD, standard deviation; EDSS, Expanded Disability Status Scale.

concentration, the median NT-proBNP plasma level was 249.5 pg/mL (range: 125.8–739.2 pg/mL, mean 291.1 ± 188.0 pg/mL). All of them neither showed clinical evidence of myocardial damage nor had the LVEF value < 50%. Table 2 shows the characteristics of patients (group A) with normal and increased NT-proBNP plasma concentration.

In group A, no correlation was observed between the NT-proBNP levels and the following parameters: patients age, MS duration, relapses number during two years before treatment, relapses number during MTX treatment, EDSS before treatment, EDSS after the end of treatment, MS course: RRMS, PRMS, or SPMS, total cumulative dose of MTX and MTX single dose. In cardiologic evaluation, none of these patients showed clinical evidence of cardiac dysfunction. None of patients experienced reduction in LVEF to <50% in echocardiography. Mean LVEF was 60 ± 2%. The LVEF decrease of more than 10% of the baseline value was found in five patients (11.1%) but the mean LVEF remained within normal limits (64.8 ± 5%). The NT-proBNP plasma level in these patients was normal.

In group B (not treated with mitoxantrone), the median NT-proBNP plasma level was 3.4 pg/mL (range: 0–588 pg/mL, mean 85.9 ± 155.8 pg/mL). NT-proBNP plasma concentration was elevated in 8 patients (4 females and 4 males, 22% of examined patients). In the group with elevated NT-proBNP concentration, the median NT-proBNP plasma value was 357 pg/mL (range: 132.7–588 pg/mL, mean 352 ± 137.8 pg/mL). Table 3 shows the characteristics of patients (group B) with normal and increased NT-proBNP plasma concentration. We did not observe clinical evidence of myocardial damage in patients with increased NT-proBNP plasma level. Left ventricular ejection fraction below 50% (47%) was found in one patient with normal NT-proBNP plasma concentration. This patient had benign relapsing-remitting MS, and he did not undergo any disease modifying therapy. In this group, as for group A, there was no correlation between the NT-proBNP levels and the following parameters: patients age, MS duration, EDSS, and MS course: RRMS, PRMS, SPMS.

Elevated NT-proBNP plasma concentration was found both in group A – treated with MTX (12 patients, 27%) and in group B – control group (8 patients, 22%). No difference was found between the NT-proBNP levels in both groups ($P = 0.794$; Wilcoxon two-sample test; $P = 0.6176$; Fisher exact test).

Troponin serum concentration was normal in all patients.

Table 3 – The N-terminal pro-brain natriuretic peptide (NT-proBNP) plasma concentrations in the control group.

Variables	NT-proBNP > 125 pg/mL	NT-proBNP < 125 pg/mL
Number of patients	8	29
Age [years]; mean ± SD	35.2 ± 15.1	38.2 ± 10.0
MS duration [years]; mean ± SD	11.7 ± 13.2	10.1 ± 5.7
EDSS score; mean ± SD	3.2 ± 1.1	3.7 ± 1.8

MS, multiple sclerosis; SD, standard deviation; EDSS, Expanded Disability Status Scale.

4. Discussion

Treatment of MS patients with MTX requires careful monitoring for its possible cardiac toxicity. Although currently available noninvasive diagnostic techniques such as echocardiography may reveal cardiac dysfunction before it becomes clinically overt, they lack adequate sensitivity to detect early cardiac damage and to identify individuals at increased risk of subsequent heart failure. However, there is the need to find easy, sensitive, moderate-cost methods, such as serum tests, to predict MTX-induced cardiotoxicity. NT-proBNP has been demonstrated to be a useful marker of left ventricular damage in both symptomatic and asymptomatic patients [5,6,8]. Elevated NT-proBNP plasma levels have been found not only in patients with acute myocardial infarction or advanced congestive heart failure but also in patients with asymptomatic or minimally symptomatic left ventricular dysfunction [9]. Several studies have suggested that the assessment of NT-proBNP plasma concentration might be useful in the detection of clinical or subclinical left ventricular dysfunction in patients receiving chemotherapy (anthracyclines) [10,13,14]. Horacek et al. [13] examined 26 patients treated for acute leukemia with 2–6 cycles of chemotherapy containing anthracyclines. Measurement of NT-proBNP concentration and echocardiography were made before chemotherapy, after the first and last cycles and 6 months after treatment. Marked NT-proBNP elevation correlated with left ventricle dysfunction on echocardiography. In the study of 2005 [10], NT-proBNP level was measured

in 52 patients with aggressive malignancies treated with high-dose chemotherapy. Blood samples were taken before treatment and 12, 24, 36 and 72 h after the end of each course of chemotherapy. Cardiac function was assessed by echocardiography at baseline and at 4 and 12 months after the end of treatment. Persistently increased concentration of NT-proBNP was associated with the development of subsequent cardiac dysfunction. One published report showed that high NT-proBNP level in MS patients treated with MTX preceded echocardiographic and clinical signs of congestive heart failure. Bertora et al. [15] evaluated five SPMS patients treated with mitoxantrone. NT-proBNP was checked at baseline and at each MTX administration. Echocardiography was performed before treatment as well as before the fourth and eighth MTX treatment. In one patient, increased NT-proBNP was followed by LVEF decrease to 30%. The limitation of this study was small sample (5 patients) and lack of control group. Luchowski et al. [16] measured brain natriuretic peptide (BNP) concentration in 22 MS patients during MTX treatment (at baseline, after 9 and 15 months of mitoxantrone therapy). In that study, BNP level slightly increased during MTX treatment, exceeding normal values in only one patient. In two other cases, about threefold increase in BNP concentration was observed with no detectable changes in echocardiographic parameters. The authors suggest that these results indicate subclinical myocardial dysfunction in mitoxantrone-treated group.

Our study was aimed to evaluate the usefulness of NT-proBNP for early detection of MTX-induced cardiotoxicity in MS patients. In our group, none of the patients experienced congestive heart failure. Mild subclinical deterioration of cardiac function (LVEF decline of more than 10% from the baseline value) was found in five patients (11% patients), but still LVEF value was normal in all these patients. Elevated NT-proBNP plasma concentrations were observed both in MS patients treated with MTX and in MS patients who did not undergo therapy with potentially cardiotoxic drugs. This is of special interest, because it indicates a possibility of mild cardiac dysfunction existing in non-treated MS patients. In fact, significant decrease in right and left ventricular ejection fraction and asymptomatic ventricular dysfunction were already shown in active MS patients without any disease modifying therapy [17]. This may be related to the impairment of cardiovascular autonomic function or may result from immunological myocarditis. The possibility of cardiac dysfunction in MS makes very careful selection of patients for MTX treatment necessary. It seems that NT-proBNP is a good candidate for an early marker predictive of cardiac dysfunction before and during MTX therapy in MS patients. It seams that the normal values of LVEF and NT-proBNP should rule out the possibility of heart failure during MTX therapy. On the contrary, the increased NT-proBNP level can indicate patients at risk of cardiac disorders. These patients need thorough and frequent echocardiographic evaluation.

The main limitation of our study was that the NT-proBNP plasma concentration was measured only once after the end of MTX treatment. We believe that serial evaluation of NT-proBNP levels (before, during and after MTX therapy) could significantly increase the detection of early cardiac dysfunction in such patients.

5. Conclusions

Mitoxantrone therapy is safe for carefully selected and closely monitored MS patients. Whether or not the elevated NT-proBNP level can identify MS patients at highest risk for MTX-induced cardiotoxicity requires further study.

Conflict of interest

None declared.

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None declared.

Ethics

The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; Uniform Requirements for manuscripts submitted to Biomedical journals.

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