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Serum cytokine and pro-brain natriuretic peptide (BNP) levels in patients with migraine

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Abstract. – *Objective:* **Although migraine has been related with an increased risk for ischemic stroke and cardiovascular events, there is insufficient data for role of pro-brain natriuretic peptide (pro-BNP) in migraine. In present case-control study, serum levels of pro-inflammatory (TNF-α, IL-1β and IL-6) and anti-inflammatory cytokines (IL-2, and IL-10) of migraine patients were investigated to determine the role of cytokines and pro-BNP in migraine.**

Patients and Methods: **Sixty-four consecutive newly diagnosed migraine patients and 34 healthy controls were enrolled. Serum TNF-α, IL-1β, IL-2, IL-6, IL-10 and pro-BNP levels were measured by using a chemiluminescence assay.**

Results: **Migraine patients had significantly higher concentrations of IL-1β and IL-6 compared with the healthy controls (for IL-1β; 5.73 ± 1.44 vs. 4.90±1.40 pg/mL, respectively, p =0.006; for IL-6; 3.1±1.44 vs. 2.40±0.22 pg/mL, respectively, p =0.007). The mean IL-10 levels were found to be significantly lower in migraine patients (3.38±2.93 pg/mL) than controls (6.76 ± 1.48 pg/mL) (p =0.007). There were no differences in TNF-α (27.2±48.1 vs. 15.4±0.7) and IL-2 (1017±661 vs. 1153±228) levels between patients with migraine and healthy controls. Migraine patients had higher concentrations of pro-BNP compared with healthy controls (27.0 ± 28.0 versus 13.2±8.6, p =0.006).**

Conclusions: **Migraine patients have higher serum IL-1β and IL-6 levels, and lower IL-10 levels than healthy subjects. These findings support that cytokines may be related to neurogenic inflammation in the pathogenesis of migraine. Also, increased pro-BNP may indicate to preclinical cardiac involvement in patients with migraine.**

Key Words:

Migraine, Pro-BNP, Cytokine, Pathogenesis, Biomarker.

Introduction

Migraine is a chronic neurovascular disorder, characterized by episodic and disabling headaches with autonomic symptoms. There is a growing body of evidence to suggest that migraine and inflammation are linked, and often the term neurogenic inflammation is used[1,2]. Epidemiological evidence suggests that migraine affects the cerebral and systemic circulation. There is evidence that the vascular nature of migraine is not only affected to neurovascular involvement but also other vascular involvement[3]. The physiologic profile of migraine involves the neurovascular system, and population-based studies have related migraine with a higher prevalence of cardiovascular risk factors, such as an elevated Framingham risk score for coronary heart disease. In recent studies, migraine has been associated with increased risk of ischemic stroke, and ischemic heart disease[3-5]. The pro-brain natriuretic peptide (pro-BNP) reflects an integral of risk factors resulting in the current functional cardiovascular status of individual patients. Pro-BNP is a cardiac neurohormone specifically secreted from the ventricles in response to volume expansion and pressure overload. Also, pro-BNP inhibits the sympathetic nervous system and the activities of several other hormone systems, including the renin-angiotensin-aldosterone system. Measurement of pro-BNP has recently become valuable in the rapid diagnosis of heart failure, has been used for risk stratification, and is predictive of short-term mortality[6]. There is insufficient evidence for role of pro-BNP in migraine, but migraine has been related with an increased risk for ischemic stroke and adverse cardiovascular events, including aortic stifness, angina, myocardial infarction, and cardiovascular death[7,8].

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Cytokines are small proteins produced by most cells in the body, which lead to multiple biologic activities that promote cell-cell interaction. Cytokines play an important role in several physiological and pathological settings, such as immunology, inflammation, and pain[9,10]. Cytokines are now considered the pain mediators in neurovascular inflammation[11]. Cytokines have been shown to induce headache, but few studies have studied cytokine levels in migraine patients[2,11,12]. Following injury, the initial inflammatory response requires increased localized production of pro-inflammatory cytokines, such as tumor necrosis factor-alpha (TNF-α), interleukin-1β (IL-1β), and IL-6, and decreased production of antiinflammatory cytokines, such as IL-10. Interleukin-10 inhibits the production of proinflammatory cytokines by monocytes and enhances the production of IL-1[13,14].

Because of different responses of cytokines, we investigated the levels of pro- and anti-inflammatory cytokines (TNF-α, IL-1β, IL-2, IL-6, and IL-10) in the serum of the migraine patients to understand the role of cytokines in migraine. Also, second our aim are to determine relation between pro-BNP and migraine to estimate the cardiac damage.

Patients and Methods

The 64 consecutive newly diagnosed migraine patients who did not receive any prophylactic migraine medication were enrolled into the study. The study group consisted of 64 patients, suffering from migraine with aura (n = 25) and migraine without aura (n = 39), admitted in the Department of Neurology. Diagnosis was made using the criteria of the second edition of the International Headache Classification[15]. The patients in the migraine group were divided into subgroups as migraine in the attack period (with and without aura) (n = 25) and migraine in the interictal period (with and without aura) (n = 39). Patients who had hypertension, diabetes mellitus, stroke, renal disease, a medical history including the intake of prophylactic medication for migraine, and a history of cardiovascular disease, inflammatory, infectious, or autoimmune diseases were excluded from this study. The control group included 34 healthy participants without the history of headache, with a negative history of vascular diseases, hypertension, diabetes mellitus, and renal, infectious, autoimmune and/or cardiac diseases. Informed consent was obtained from all patients and controls and the study protocol was approved by the local Ethics Committee. Blood sampling was performed within 2-5 h from the onset of migraine headache or headache-free period in patients with migraine. Blood samples were also obtained from healthy individuals. Each collected blood sample was immediately centrifuged at 4000 rpm +4°C for 10 min and then transferred into an Eppendorf tube. Serum was stocked at –80°C for not more than 15 days. TNF-α, IL-1β, IL-2 IL-6, IL-10, and pro-BNP levels were measured using a chemiluminescent enzyme-immunometric assay (IMMULITE Automated immunoassay system; Immulite DPC, Los Angeles, CA, USA).

Statistical Analysis

All statistical analyses were performed using SPSS, version 11.5, for Windows (SPSS Inc., Chicago, IL, USA). Data were expressed as mean ± standard deviation. The normality of the distribution for all variables was assessed by the Kolmogorov–Smirnov test. Student's t-test was used for normally distributed variables. Mann-Whitney U-test was used for non-parametric variables. A p value of less than 0.05 was considered statistically significant.

Results

Mean age of the migraine patients was 35.4 ± 11.5 years (17-56 years). Study group consisted of 45 women and 19 men. The control group comprised of 24 women and 10 men. Mean age of the control group was 34.7 ± 11.7 years (17-55 years). No differences were found in mean age and gender distribution between the study and the control groups (p>0.05). The demographical and biochemical variables of the study and control groups are shown in Table I.

Serum concentrations of TNF-α, IL-1β, IL-2, IL-6, IL-10, and pro-BNP of the patients are shown in Table II. Migraine patients had significantly higher concentrations of IL-1β and IL-6 compared with the healthy controls (p=0.006 and p=0.007, respectively). IL-10 levels were found significantly lower in migraineurs than controls (p=0.007). There were no differences in TNF-α and IL-2 levels between patients with migraine and healthy controls (p>0.05). Migraine patients had higher concentrations of pro-BNP compared with healthy controls (27.0 ± 28.0 vs 13.2 ± 8.6

Table I. The demographical and biochemical variables of the study and control groups.

	Migraine patients (n = 64)	Controls (n = 34)	p values
Age	35.4 ± 11.5	34.7 ± 11.7	N.S.
Sex (F/M)	45/19	24/10	N.S.
HDL-C	48.4 ± 13.6	50.2 ± 8.9	N.S.
LDL-C	102.1 ± 23.8	95.7 ± 34.2	N.S.
Cholesterol	174.6 ± 32.4	176.8 ± 31.2	N.S.
Fasting glucose	93.0 ± 6.3	92.1 ± 5.2	N.S.
Systolic blood pressure	106.2 ± 10.8	108.4 ± 12.3	N.S.
BMI	25.4 ± 1.7	25.6 ± 2.1	N.S.

F/M: female/male, N.S: statistically not significant (p>0.05), BMI: Body mass index.

p=0.006, Table II). In patients with migraine, pro-BNP concentrations were correlated with IL 10 (r=0.43, p=0.001); IL-2 (r=0.34, p =0.006), and IL-6 (r=0.30, p =0.018), but not IL-1β and TNF-α (p>0.05).

There were no significant differences between migraineurs during headache attacks and migraineurs during interictal period in the serum levels of TNF-α (30.0 ± 49.6 vs 22.8 ± 46.2 pg/mL, p>0.05), IL-1β (6.03 ± 1.3 vs 5.5 ± 1.5 pg/mL, p>0.05), IL-2 (823 ± 673 vs 1140 ± 613 pg/mL, p>0.05), IL-6 (3.2 ± 1.6 vs 3.05 ± 1.4 pg/mL, p>0.05), IL-10 (3.19 ± 3.05 vs 3.5 ± 2.9 pg/mL, p>0.05), and pro-BNP (20.5 ± 24.9 vs 31.1 ± 29.4). Likewise, no statistically significant difference was determined in the levels of TNF-α, IL-1β, IL-2, IL-6, IL-10, and pro-BNP, the patients with migraine with aura compared to the patients with migraine without aura in migraine group (p>0.05).

Discussion

Our findings demonstrated that, serum levels of IL-1β, IL-6, and pro-BNP in migraine patients were higher compared to healthy subjects. However, serum IL-10 levels in migraine patients were lower than healthy individuals. Proinflammatory cytokines, such as TNF-α, IL-1β, IL-6, and anti-inflammatory cytokines, such as IL-10 have been reported to play a significant role in the modulation of pain threshold and they could contribute to trigeminal nerve fibers sensitization[9-14]. Microbial antigens, cell degradation products, complement components and neuropeptides involved in migraine can stimulate the release of proinflammatory cytokines. In addition, cytokines have been found to have pain-mediating functions as well as immunological functions. For example, when TNF-α and IL-6 are administered centrally or peripherally, they cause hyperalgesia. All those findings of our study supported that cytokines might be considered in inflammation and hyperalgesia in migraine[11,16,17].

Pro-inflammatory cytokines are primarily produced by activated immune cells and are involved in the regulation of the inflammatory response. Human IL-1β and IL-6 is produced by various cells. IL-6 is a major inducer of the acute phase reaction in response to inflammation or tissue damage. IL-6 regulates the growth and differ-

Table II. Comparison of levels tumor necrosis factor-alpha (TNF-α), interleukin-1β (IL-1β), IL-2, IL-6, IL-10, and pro-BNP between the migraine patients and the control group.

	Migraine patients (n = 64)	Controls (n = 34)	p
IL-1β (pg/ml)	5.73 ± 1.44	4.90 ± 1.30	0.006
IL-6 (pg/ml)	3.1 ± 1.44	2.40 ± 0.22	0.007
IL-10 (pg/ml)	3.38 ± 2.93	6.76 ± 1.48	0.007
IL-2 (pg/ml)	1017 ± 661	1153 ± 228	N.S.
TNF-α (pg/ml)	27.2 ± 48.1	15.4 ± 0.7	N.S.
Pro-BNP (pg/ml)	27.0 ± 28.0	13.2 ± 8.6	0.006

N.S: statistically not significant (p>0.05).

entiation of several cell types, with significant effects in inflammation. Healthy individuals may have undetectable levels of IL-6 in their serum, but high levels are detected in inflammatory situations[18]. We found a significantly higher serum IL-6 and IL-1β level in migraine patients compared with controls. Similar to the earlier studies, migraine patients had a higher IL-6 and IL-1β level than healthy controls, but we did not find a significant difference between migraine with aura and migraine without aura. The increasing IL-6 and IL-1β level support that cytokines may be related with the pathogenesis of migraine[19].

Previous studies have also investigated TNF-α level during and outside migraine attacks with contradictory results. While some studies found no difference in TNF-α serum levels, others described increased levels of TNF-Symbol during migraine attack[12,20-22]. The fact that TNF-α is an unstable molecule with a reduced half-life, similar to TNF-α levels between control group and the migraine group, does not mean that TNF-α does not have a role in the mechanism of immune pathogenesis of migraine.

Currently, there is little information about the role of IL-10 and IL-2, which are anti-inflammatory cytokines, in migraine. Originally described as a cytokine synthesis inhibitory factor, IL-10 has major down-regulatory influences on inflammation[14]. It has been indicated that IL-10 is a very potent anti-inflammatory cytokine as demonstrated in experimental models of chronic pain. The expression of IL-10 by antigen-presenting cells may have a role in attenuating inflammation through this ability to inhibit synthesis of nonspecific proinflammatory cytokines, such as IL-1, IL-6, and TNF-α[23,24]. We found a significantly lower serum IL-10 level in migraine patients compared with healthy controls. In contrary to the earlier studies[12,14,25], migraine patients had a lower IL-10 level than healthy controls in the present study. Unlike our study, Munno et al.[14] reported that the patients during attacks had higher levels IL-10 compared to the healthy group. In another investigation, IL-10 levels of cerebrospinal fluid were not different in patients with migraine compared to controls[26]. Based on the changes in IL-10 levels, which is known to be cytokine synthesis inhibitory factor, IL-10 can inhibit the production of proinflammatory cytokines. Decreased level of IL-10 results in loss of inhibition in the production of proinflammatory cytokines and, as shown in our study, proinflammatory cytokines can increase. Therefore, our findings of decreased IL-10 level and increased pro-inflammatory IL-1β and IL-6, support the existence of an inflammatory condition in the pathogenesis of migraine.

IL-2 is normally produced in the body during an immune response. IL-2 drives the proliferation and differentiation of T cells, which have a central role in the adaptive immune system. IL-2 is related to lymphocyte activation and usually involved in inflammation due to viral etiology[25,27,28]. In addition, Steinberg at al.[27] found an increase of IL-2 was during cluster headache. Shimomura et al.[28] reported decreased serum IL-2 level in patients with migraine. However, we found no significant difference in the serum IL-2 level of migraine patients compared with controls. Furthermore, we did not find a significant difference in serum IL-2 level between migraine with aura and migraine without aura. Unlike the previous study, this finding suggests that IL-2 may not be related to the pathogenesis of migraine[27]. In addition, this finding suggested that neuroinflammation in migraine pathogenesis may be related to cytokines other than IL-2.

Interest in the role of the vasculature in patients with migraine is increasing because of growing evidence that migraine is a risk factor for clinical and subclinical brain ischaemia, as well as for more widespread vascular changes. The vasculopathy of migraine is associated with endothelial dysfunction, a disorder of endothelial activation and impaired vascular reactivity, which is a risk factor for all vascular events[29]. People with migraine (especially in migraine with aura) have at increased risk of death from coronary heart disease, stroke and increased a prevalence of mitral valv prolapsus[30]. In two large-scale prospective cohort studies, it is found associations between migraine and ischemic heart disease[4,31]. The ischemic heart disease is the most important cause of heart failure[32]. Pro-BNP levels in the blood used in the diagnosis of heart failure. Measurement of BNP or its N-terminal pro-BNP has recently become valuable in the rapid and early diagnosis of heart failure, has been used for risk stratification, and is predictive of short and long term mortality[33-35]. It is also found that pro-BNP is raised in nearly two thirds of acute stroke patients, whereas elevated cardiac troponins are found only in a small number of acute ischemic stroke patients[6]. Despite the known risk factors for ischemic heart failure in patients with migraine, there is insufficient evidence about relation between pro-BNP and mi-

graine. In this study, due to increased risk of ischemic cardiovascular events and stroke in with migraine, we suggested that can be cause to subclinical cardiac dysfunction in patients with migraine. The early recognition of cardiac disease and initiation of treatment might influence clinical outcome with migraine patients. Therefore, pro-BNP levels were investigated in patients with migraine. In patients with migraine, we found higher serum levels of molecular marker of cardiac damage (pro-BNP) in comparison to the healthy control. The increased pro-BNP might be related to a higher prevalence of cardiovascular risk factors in patients with migraine. However, in this study we excluded all subjects with major vascular risk factors, and patients and controls were accurately matched by age, sex, and blood pressure. As a result, cardiovascular risk profile was similar in patients with migraine and in control subjects. It has been suggested that subclinical left ventricular dysfunction during the phenylephrine test may be in patients with migraine[8]. Also, it has been found that migraine is independently associated with increased aortic stiffness and enhanced pressure wave reflection[36]. Therefore, the left ventricular dysfunction, and/or aortic stiffness may be increased BNP in patient with migraine[37]. Also, endothelial dysfunction may cause increased BNP in patients with migraine[6]. The inflammatory cytokines increase the production and secretion of BNP in cultured cardiac myocytes[38]. In addition, it has been shown that serum concentrations of proBNP are correlated with levels of pro-inflammatory cytokines in rheumatoid arthritis without clinical heart failure[39]. Untill now, relationship between pro-inflammatory cytokines and pro-BNP have been not studied in patients with migraine. In this study, pro-BNP concentrations were correlated with IL-2, and IL-6 in patients with migraine, but not IL-1β and TNF-α. It may indicate subclinical cardiovascular dysfunction and a inflammatory state in migraine.

In conclusion, migraine patients had higher IL-1β, IL-6 levels, and pro-BNP and lower IL-10 levels than healthy individuals. These findings supported that cytokines may be related to the pathogenesis of migraine. Also, we indicated that pro-BNP may be marker a subclinical cardiac dysfunction in patients with migraine. The importance of these findings on the pathogenesis, clinical characteristics, and treatment of migraine needs to be investigated in further detailed studies.

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