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Migraine chronification is associated with higher body mass index and elevated serum interleukin-6 levels

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Abstract

Aim: Chronification of migraine is a serious health problem with difficulties in management and is related to increased disability. Inflammation is suggested to have a role in migraine and its chronification. We aimed to determine whether systemic inflammatory response tested by serum interleukin-6 (IL-6) levels and obesity were related to migraine attack frequency.

Materials and Methods: A total of 40 female participants (20 chronic migraine patients, 10 episodic migraine patients, 10 healthy controls without headache) were included in the study. None of the migraine patients were on migraine prophylaxis. Episodic migraine patients were evaluated interictally with a 72 hour headache free period before and after blood collection. Migraine headache frequency, body mass index (BMI) and age of the patients were recorded. Serum IL-6 levels were measured by ELISA method.

Results: Serum IL-6 levels were significantly elevated in chronic migraine patients compared to episodic migraine patients and healthy controls. Chronic migraine patients were overweight with a BMI greater than 25 kg/m^2. BMI was higher in chronic migraine patients compared to episodic migraine patients and healthy subjects even though it did not reach statistical significance. Serum IL-6 levels and BMI were positively correlated with migraine headache frequency.

Conclusion: Elevated systemic circulating IL-6 levels and BMI were related to an increase in migraine headache frequency. BMI and serum IL-6 levels seem to be risk factors for chronic migraine in women. Strategies to reduce inflammation and obesity must be integrated to the treatment of chronic migraine. Identification of modifiable risk factors for chronification of migraine is crucial for sustainable treatment of migraine.

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Introduction

Migraine chronification is an important problem in current neurology practice. It is harder to treat chronic migraine patients and new options for the management and modification of the course of the disease are required. Neurogenic inflammation is suggested to have a pivotal role in migraine pathophysiology and migraine chronification. In various neurological diseases, systemic inflammation has been shown to effect neurogenic inflammation. However, studies on the role of systemic inflammation in migraine pathophysiology and migraine chronification are still inadequate. Interleukin-6 (IL-6) is a pro-inflammatory cytokine that has an essential role in immune response and is targeted in various inflammatory disorders [1]. IL-6 has been also implicated to have a role in migraine, especially in migraine animal models. IL-6 has been shown to stimulate and sensitize meningeal nociceptors. Dural application of IL-6 has been shown to lead to facial and hindpaw allodynia in rodents [2-5]. Moreover, following the application of IL-6 to the dura mater, the rats even responded to subthreshold triggers including CGRP and decreased pH suggesting a heightened susceptibility to triggers [4, 5]. Decreased nociceptive responses such as decreased mechanical allodynia have been shown in IL-6 knock-out mice [6, 7]. IL-6 was also demonstrated to be elevated in the internal jugular blood of migraine without aura patients during a migraine attack [8].

Obesity is suggested to be a risk factor for chronic migraine. Even overweighted patients (body mass index greater than 25 kg/m^2) were reported to have increased risk of chronic headaches compared to normal weighted subjects [9].

In this preliminary study, we aimed to test the hypothesis

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that higher body mass index (BMI) and elevated IL-6 levels have a role in increased migraine attack frequency. We evaluated serum IL-6 levels and BMI in woman migraneurs (both episodic and chronic migraine patients) and healthy controls without headache. Also, we assessed possible correlations between IL-6 levels, BMI, migraine headache frequency (migraine days/month) and age of the patients.

Materials and Methods

Episodic and chronic migraine patients were recruited from Gazi University Faculty of Medicine, Department of Neurology and Algology, Headache Unit. The episodic and chronic migraine patients were included if 1) they were aged between 18-65 years and 2) they were diagnosed with episodic or chronic migraine according to International Classification of Headache Disorders 3rd Edition and 3) they were not using any prophylactic migraine treatment. The healthy subjects were included if 1) they were aged between 18-65 years and 2) they had no history of headache. Exclusion criteria for were all subjects were 1) having any other neurological disease or chronic disease 2) regular use of any medications, 3) use of alcohol or any other drugs and 4) presence of any major psychiatric disorder.

Serum IL-6 was assessed using enzyme-linked immunosorbent assay (ELISA) following blood sample collection from both the patients and healthy controls and after centrifugation of the blood samples. The blood samples were collected in the interictal period (headache free 72 hours before and after the blood collection) in episodic migraine patients. Serum samples were kept at -80°C until testing. The study was performed according to the standards set by Declaration of Helsinki and it was approved by the local ethics committee (Gazi University Clinical Research Ethical Committee, E-22-143).

Enzyme-Linked Immuno Sorbent Assay (ELISA)

Serum IL-6 levels were measured using high-sensitivity ELISA kit from Elabscience Biotechnology Inc., Houston, TX, USA. On the of day of testing, all of the reagents were brought to room temperature. Reference standards were diluted according to the instructions of the manufacturer. Wash buffers were prepared by adding distilled water to the concentrated wash buffers. Serum IL-6 was measured according to the kit procedure. Combiwash Human ELISA plate washer was used for washing operations. Enzyme substrate reaction was terminated by adding stop solution and the color turned yellow. Optical densities of the wells were measured with Chromate reader at 450 nm.

Statistical analysis

The data were analysed using SPSS 22.0 for Windows software. Descriptive statistics were reported as mean ± standard deviation and the categorical variables were shown as frequencies and percentages (%). Normalisation of data was assessed by Kolmogrov-Smirnov test. Analysis of continuous variables was performed with one-way ANOVA when there were three independent groups and with independent samples T test when there were two independent groups. Post-hoc multiple comparisons were carried out with Šidák's multiple comparisons test. Possible correlations between serum IL-6 levels, migraine frequency, age and BMI were evaluated with Pearson's correlation analysis. A p value of less than 0.05 was considered statistically significant.

Results

Forty female subjects (20 chronic migraine patients, 10 episodic migraine patients and 10 healthy volunteers) who met the inclusion critera and agreed to participate were included in the study. Mean age was 39.4 ± 7.5 in chronic migraine patients, 37.8 ± 8.2 in episodic migraine patients and 37.6 ± 10.0 in healthy controls ($p = 0.83$). Migraine frequency was 21.5 ± 6.1 days/month in chronic migraine patients and 3.4 ± 2.5 days/month in episodic migraine patients ($p < 0.001$). Mean BMI values were 26.5 ± 3.0 kg/m^2 in chronic migraine patients, 24.8 ± 2.8 kg/m^2 in episodic migraine patients and 24.8 ± 2.7 kg/m^2 in healthy subjects ($p = 0.2$) (Figure 1). Mean serum IL-6 levels were 6.3 ± 3.0 pg/ml in chronic migraine patients, 2.6 ± 1.3 pg/ml in episodic migraine patients and 3.2 ± 1.8 pg/ml in healthy controls (Figure 2). Serum IL-6 levels were significantly higher in the chronic migraine patients compared

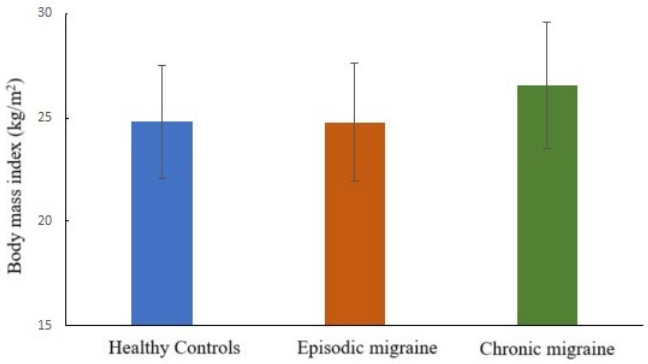

Figure 1. Mean BMI values were 24.8 ± 2.7 kg/m2 in healthy controls, 24.8 ± 2.8 kg/m^2 in episodic migraine patients and 26.5 ± 3.0 kg/m2 in chronic migraine patients ($p = 0.2$).

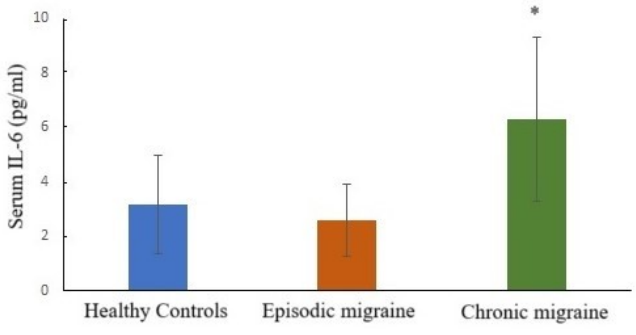

Figure 2. Serum IL-6 levels were significantly higher in chronic migraine patients compared to episodic migraine patients ($p = 0.001$) and healthy controls ($p = 0.006$) and similar between episodic migraine patients and healthy controls ($p = 0.095$). * $p<0.05$.

to episodic migraine patients and healthy controls ($p = 0.001$ and $p = 0.006$, respectively) (Figure 2). Serum IL-6 levels were comparable between episodic migraine patients and healthy controls ($p = 0.95$). There was a positive correlation between IL-6 levels and migraine frequency ($r = 0.65$). BMI was also positively correlated with migraine frequency ($r = 0.42$). There were no correlations between IL-6 levels, BMI and age of the patients.

Discussion

Elevated serum IL-6 levels were shown in chronic migraine patients compared to episodic migraine patients and healthy subjects. BMI was higher in chronic migraine patients even though it did not reach statistical significance. Notably, chronic migraine patients had a mean BMI of >25 kg/m^2 compatible with overweight definition. Serum IL-6 levels were positively correlated with migraine frequency, as migraine headache days/month increased, serum IL-6 levels increased. We also showed that there was a moderately positive correlation between BMI and migraine frequency.

There are conflicting results in the literature regarding serum IL-6 levels in episodic migraine patients during the attacks and interictally. In one study, serum IL-6 levels were similar between episodic migraine patients and healthy controls and there was no difference between ictal and interictal serum IL-6 levels in episodic migraine patients [10]. In a study where blood samples were taken from internal jugular vein via a catheter, augmented IL-6 levels were shown during a migraine attack compared to interictal period however, there were no healthy controls in this study due to ethical reasons [8]. In another previous study, serum IL-6 levels were reported to be significantly higher in chronic migraine patients compared to episodic migraine patients and healthy subjects. In the same study, higher serum IL-6 levels were shown in episodic migraine patients compared to healthy controls [11], however, in that study, presence of a headache-free period 72 hours before and after the blood sample collection in episodic migraine patients was not provided. We detected comparable serum IL-6 levels in episodic migraine patients and healthy subjects. This could be due to the fact that we defined interictal period by questioning the presence of a 72 hour headache free period, since serum IL-6 levels could be also affected during pre-ictal and post-ictal phases.

Similar to our study, a preceding study showed that total body obesity and abdominal obesity were associated with higher prevalence of migraine and increased migraine frequency [12]. Total body obesity was associated with migraine independent of abdominal obesity however not vice-versa [12]. In another study, patients with BMI > 25 kg/m^2 had an enhanced relative risk of having chronic headache compared to subjects with normal weight [9]. Suggested mechanisms that underly obesity and migraine chronification are metabolic and hormonal activity of adipose tissue, augmented release of pro-inflammatory cytokines, inflammation and dysregulation of hypothalamic function [13-16]. Increased BMI is usually associated with metabolic syndrome and elevated insulin resistance that may also contribute to systemic inflmmation and increased IL-6 levels. Future studies performed in larger populations are needed to investigate this relationship.

Strengths of our study are that we only included chronic migraine patients who did not use any prophylactic medications during the study period and we assured that the episodic migraine patients were evaluated interictally by defining the 72 hour headache-free duration before and after the blood sample collection. Migraine is commonly seen in women and by including only female patients we excluded factors related to sexual dimorphism. Limitation of our study is that since this is a preliminary study, we conducted the study in a limited number of patients. Also, we focused on the role of circulating IL-6 levels and BMI in migraine chronification, therefore, other parameters associated with BMI and inflammation were not evaluated. Further investigations extensively including all of these parameters will enlighten their role in pathophysiology of migraine chronification.

Conclusion

Chronic migraine management is challenging and modifiable risk factors must be defined in order to increase the success of the treatment. We demonstrated that increased migraine attack frequency is associated with elevated systemic IL-6 levels and higher BMI in female migraneurs. New strategies to reduce systemic inflammation and improve metabolic health must be integrated to chronic migraine treatment to reach sustainability in management.

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Ethical approval

The study protocol and procedures conformed to the standards set by the Declaration of Helsinki and Gazi University Clinical Research Ethical Committee approved the study (E-22-143).

References

1. Hunter CA, Jones SA. IL-6 as a keystone cytokine in health and disease. Nat Immunol. 2015;16(5):448-57.
2. Burgos-Vega CC, Quigley LD, Trevisan Dos Santos G, Yan F, Asiedu M, Jacobs B, et al. Non-invasive dural stimulation in mice: A novel preclinical model of migraine. Cephalalgia. 2019;39(1):123-34.
3. Yan J, Melemedjian OK, Price TJ, Dussor G. Sensitization of dural afferents underlies migraine-related behavior following meningeal application of interleukin-6 (IL-6). Mol Pain. 2012;8:6.
4. Burgos-Vega CC, Quigley LD, Avona A, Price T, Dussor G. Dural stimulation in rats causes brain-derived neurotrophic factor-dependent priming to subthreshold stimuli including a migraine trigger. Pain. 2016;157(12):2722-30.
5. Avona A, Burgos-Vega C, Burton MD, Akopian AN, Price TJ, Dussor G. Dural Calcitonin Gene-Related Peptide Produces Female-Specific Responses in Rodent Migraine Models. J Neurosci. 2019;39(22):4323-31.
6. Ramer MS, Murphy PG, Richardson PM, Bisby MA. Spinal nerve lesion-induced mechanoallodynia and adrenergic sprouting in sensory ganglia are attenuated in interleukin-6 knockout mice. Pain. 1998;78(2):115-21.
7. Xu XJ, Hao JX, Andell-Jonsson S, Poli V, Bartfai T, Wiesenfeld-Hallin Z. Nociceptive responses in interleukin-6-deficient mice to peripheral inflammation and peripheral nerve section. Cytokine. 1997;9(12):1028-33.

8. Sarchielli P, Alberti A, Baldi A, Coppola F, Rossi C, Pierguidi L, et al. Proinflammatory Cytokines, Adhesion Molecules, and Lymphocyte Integrin Expression in the Internal Jugular Blood of Migraine Patients Without Aura Assessed Ictally. Headache: The Journal of Head and Face Pain. 2006;46(2):200-7.
9. Scher AI, Stewart WF, Ricci JA, Lipton RB. Factors associated with the onset and remission of chronic daily headache in a population-based study. Pain. 2003;106(1-2):81-9.
10. Perini F, D'Andrea G, Galloni E, Pignatelli F, Billo G, Alba S, et al. Plasma cytokine levels in migraineurs and controls. Headache. 2005;45(7):926-31.
11. Mansoureh T, Soodeh Razeghi J, Zeinab G, Amir G, Pegah R. Evaluation of Inflammatory State in Migraineurs: A Case-control Study. Iranian Journal of Allergy, Asthma and Immunology. 2020;19(S1).
12. Kristoffersen ES, Børte S, Hagen K, Zwart J-A, Winsvold BS. Migraine, obesity and body fat distribution – a population-based study. The Journal of Headache and Pain. 2020;21(1):97.
13. Gelaye B, Sacco S, Brown WJ, Nitchie HL, Ornello R, Peterlin BL. Body composition status and the risk of migraine: A meta-analysis. Neurology. 2017;88(19):1795-804.
14. Ornello R, Ripa P, Pistoia F, Degan D, Tiseo C, Carolei A, et al. Migraine and body mass index categories: a systematic review and meta-analysis of observational studies. J Headache Pain. 2015;16:27.
15. Peterlin BL, Sacco S, Bernecker C, Scher AI. Adipokines and Migraine: A Systematic Review. Headache. 2016;56(4):622-44.
16. Mínguez-Olaondo A, Martínez-Valbuena I, Romero S, Frühbeck G, Luquin MR, Martínez-Vila E, et al. Excess abdominal fat is associated with cutaneous allodynia in individuals with migraine: a prospective cohort study. The Journal of Headache and Pain. 2020;21(1):9.