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Assessment of plasma cytokine and complete blood count parameters in nitroglycerin migraine model

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Abstract

Migraine, characterized by headaches, is very common and that may be associated with immunogenic and neurogenic inflammation. Cytokines involved in neurogenic switching in migraine are TNF-α and IL10. The immune cells in peripheral blood play roles in peripheral inflammatory responses. Increased levels of peripheral inflammation may occur in patients with migraine and may be involved in the pathogenesis of migraine. In this study, 12 rats divided into two groups. The first six groups were normal rats and the last were rats that inoculated with nitroglycerin. Complete blood count (CBC) was compared between these two groups. SPSS was used for statistical analysis. There was positive correlation between TNF-α and IL10 with leukosit, platelet, hematokrit, eritrosit, neutrophils, lymphocytes, and neutrophil-to-lymphocyte ratio counts. The results of TNF-α and IL10 in migraine group were higher than control group significantly. In our study, we found that TNF-α and IL10 was higher in migraine than control group. TNF-α, IL10, leukosit, limfosit and neutrophils and lymphocytes ratio can be used as an inflammatory marker for migraine.

Keywords: cytokine, complete blood count, migraine, nitroglycerin.

Introduction

Migraine is a recurrent neurovascular headache characterized by unilateral throbbing headache, accompanied by nausea, vomiting, photophobia, phonophobia, interfering with physical activity[1–3]. The World Health Organization reveals that migraine is one of the most common headache conditions worldwide, and is the most frequent cause of headache consultations in America, Europe, Southeast Asia and the Western Pacific. Migraine prevalence reached an average of 18% [4].

Some studies suggest that migraine is a sterile form of neurogenic inflammation. Neurogenic plasma extravasation and plasma leakage may be seen during trigeminal ganglion stimulation. Other studies have also shown that there is a sterile inflammatory process in the trigeminal nerve that releases vasoactive neuropeptides[5]. The concept of the neurogenic switching hypothesis predicts an interaction between immunogenic inflammation and neurogenic inflammation resulting in an increase in local inflammation. This increase in local inflammation will increase antidromic impulses to the central nervous system. Biomarkers involved in neurogenic switching in migraine are TNF-α, IL1, IL6 and IL10 [1,2]. In an inflammatory model, treatment of mice with IL37 led to a decrease in inflammatory cytokines from the IL-1 family and an increase in anti-inflammatory IL10, thereby demonstrating, together with other compounds, its therapeutic effectiveness against inflammatory processes including migraine [6].

Despite its prevalence and impact, the pathophysiology of migraine is not fully understood. Part of the challenge of this research is using animal simulations where it is shown between the clinical presentation of humans and the behavioral responses of animals. Although rodents have been used in pain research for more than six decades, attempts to validate migraine simulations are relatively recent. Animal simulations have informed our understanding of the genetic basis of familial hemiplegic migraine and the role of aura. An animal model of migraine with peripheral administration of nitroglycerin (NTG) produces attacks that are phenotypically similar to spontaneous migraine attacks and sensitizes the trigeminal and cortical structures

underlying migraine pain. One recent study showed that a model using repeated NTG injections holds promise for studying migraine disorders [7,8].

Nitroglycerin or glyceryl trinitrate is a highly lipophilic organic nitrate and is currently used in the treatment of unstable angina pectoris, myocardial infarction and heart failure. Neuroscientists say the use of NTG causes one of the most common side effects headaches. Intravenous administration of NTG often causes headaches of moderate intensity, usually throbbing but not associated with other migraine symptoms. After nitroglycerin was injected, the rats showed typical symptoms such as redness of the ears, frequent scratching of the head with the front paws, and photophobia, which lasted at least 3 hours and was followed by reduced activitya and calm [9,10]. Repeated administration of NTG can increase white blood cell count, average platelet volume and decrease platelet count in rats, which is consistent with decreased platelet levels in migraine sufferers as well as an increase in the release of proinflammatory cytokines that cause neuroinflammation and increase pain transmission [8].

The response to stress in the systemic circulation causes an increase of neutrophils and lymphocytes. Therefore, their proportions were used as markers of inflammation. The neutrophil/lymphocyte ratio (NLR) is an easily quantifiable marker of a complete blood count (CBC). As a marker of subclinical inflammation, NLR is associated with the prognosis of many diseases [11]. Based on literature, we aimed to observe changes in leukocyte, neutrophil, lymphocyte, NLR, hemoglobin, erythrocyte, platelet, platelet aggregation, TNF-α and IL10 which are known markers of inflammation that occur during migraine attacks.

Materials and Methods

Ethics, consent, and permissions

Ethics and experimental procedures were approved by the Faculty of Veterinary Medicine, Universitas Airlangga Indonesia.

Characteristics of research subjects

Method Cohort using male Rattus norvegicus wistar strain, weighing 150–250 g served as subjects for each of the two trials; animals were randomized to treatment conditions. Rats were placed in a polyethylene bath measuring 50 x 30 x 20 cm. Food and water are available ad libitum. Room temperature was maintained at 24 +/− 4 °C, and overhead fluorescent lighting was maintained on a 12/12- hour cycle. Cages were placed in house cages to allow mice to reduce exposure to lighting after NTG injection. The treatment group involved the induction of NTG 10 mg/kg. It was administered intraperitoneally 5 times.

Statistical analysis

All data were analyzed using IBM SPSS version 25.0. The significance level for statistical analyzes $p < 0.05$ was considered statistically significant.

Procedure

The control group received saline and the experimental rats received 10 mg/kg NTG intraperitoneally 5 times, on the first, third, fifth, seventh and ninth days. Rats are checked daily for clinical signs. Variable measurement studies were conducted in 12 rats, divided into two groups. The first six groups were normal rats and the last were rats that inoculated with Nitroglycerin.

Whole blood samples were collected into tubes containing ethylenediamine tetraacetic acid (EDTA) and stored at room temperature for the period between venipuncture and processing. Complete blood parameters included leukocyte count (5.4–11.6 × 10^3/mm3), neutrophil count. (12-68%), lymphocyte

count (25-33%), hemoglobin (12.4–14.6 g/dL), erythrocyte count (150-350 x 10^3/mm3), hematocrit count (38.5-45.1%), platelet count (150-350×10^3/mm3), platelet aggregation (%), TNF-α (pg/ml) and IL10 (pg/ml).

Results and Discussion

This study was conducted to evaluate TNF-α levels, IL10 levels and complete blood count parameters in migraine models. Complete blood count parameter data were in the normal range in the migraine and control groups. The levels of TNF-α and IL10, hemoglobin, hematocrit, erythrocytes, platelets, leukocytes, neutrophils, lymphocytes, ratio of neutrophils and lymphocytes, and platelet aggregation were significantly higher in the migraine model than in the control group (Table 1). TNF-α increased 1.73-fold and IL10 increased 1.04-fold in migraine models compared with controls. High levels of TNF-α, relative leukocytosis, lymphocytosis, and thrombocytosis may represent a chronic inflammatory state in migraine pathophysiology.

Characteristics of experimental animals used as models of migraine headaches and comparisons of CBC, TNF-α and IL10 in migraine and control (Table 1). There was no difference in body weight, leukocyte count, and IL10 levels ($P>0.05$). There were significant differences in hemoglobin levels, erythrocyte levels, platelet levels, hematocrit levels, lymphocyte levels, neutrophil levels, ratio of neutrophils and lymphocytes, platelet aggregation and TNF-α levels ($P<0.05$).

TNF-α levels were significantly correlated with leukocyte count, neutrophil count, lymphocyte count, ratio of neutrophils and lymphocytes, erythrocyte levels, hematocrit count, and platelet aggregation but TNF-α did not correlate with hemoglobin level. IL10 levels were significantly correlated with leukocyte count, neutrophil count, lymphocyte count, ratio of neutrophils and lymphocytes, hematocrit count, and platelet aggregation but IL10 did not correlate with erythrocyte levels and hemoglobin levels. The leukocyte count was significantly correlated with TNF-α levels, neutrophil counts, lymphocyte counts, ratio of neutrophils and lymphocytes, hemoglobin levels, erythrocyte levels, and hematocrit counts, but did not correlate with platelet aggregation (Table 2).

Table 1. Characteristics of rats in the migraine and control groups

Characteristic	Control	Migraine	P value
Hemoglobin (g/dL)	12.75 ± 0.12	13.15 ± 0.52	.001
Hematocrit (%)	39.300 ± 0.36	41.72 ± 0.23	.004
Erythrocyte (10^3/ mm^3)	7.28 ± 0.47	9.63 ± 0.14	.004
Platelet (10^3/ mm^3)	245.0000 ± 6.87	322.0000 ± 6.96	.000
Leukocyte (10^3/ mm^3)	7.78 ± 0.23	7.88 ± 0.57	.051
Lymfocyte (%)	34.00 ± 3.79	30.00 ± 2.14	.014
Neutrophil (%)	60.33 ± 4.80	67.17 ± 1.47	.001
Neutrophil Lymfocyte ratio	1.81 ± 0.33	2.31 ± 0.21	.004
Platelet Aggregation (%)	10.65 ± 4.51	39.39 ± 13.05	.000
TNF-α (pg/ml)	228.79 ± 104.50	395.68 ± 156.99	.054
IL 10 (pg/ml)	55.41 ± 3.30	57.41 ± 4.08	.912

Table 2. Relationship of leukocytes, TNF-α and IL10 with measured parameters inflammation of rats in the migraine

Spearman's rho		TNF-α	IL10	Leukocyte
Leukocyte	Correlation Coefficient	.004	.082	1.000
	Sig. (2-tailed)	.983	.667	.
	N	30	30	30
Neutrophil	Correlation Coefficient	.193	.205	.134
	Sig. (2-tailed)	.308	.278	.479
	N	30	30	30
Lymfocyte	Correlation Coefficient	.013	.261	.042
	Sig. (2-tailed)	.944	.164	.824
	N	30	30	30
Neutrophil Lymfocyte ratio	Correlation Coefficient	.165	.263	.091
	Sig. (2-tailed)	.384	.160	.631
	N	30	30	30
Hemoglobin	Correlation Coefficient	-.384*	.378*	.115
	Sig. (2-tailed)	.036	.039	.545
	N	30	30	30
Erythrocyte	Correlation Coefficient	.127	.732**	.069
	Sig. (2-tailed)	.505	.000	.717
	N	30	30	30
Hematocrit	Correlation Coefficient	.021	.138	-.020
	Sig. (2-tailed)	.913	.468	.915
	N	30	30	30
Platelet Aggregation	Correlation Coefficient	.351	.269	-.421*
	Sig. (2-tailed)	.057	.150	.020
	N	30	30	30

*. Correlation is significant at the 0.05 level (2-tailed).

**. Correlation is significant at the 0.01 level (2-tailed).

IL10 is found in plasma in migraine sufferers, produced by monocytes. IL10 functions as a down regulator in macrophages, reduces antigen presentation, and suppresses the production of IFN-γ, IL6, and TNF-α. IL10 plays an important role in neutralizing the pathology of macrophages in migraine. In the serum of migraine sufferers there is an increase in the level of TNF-α and an increase in the level of IL10. IL10 levels are increased during migraine attacks, this is in response to balancing the increase in plasma proinflammatory cytokine levels during attacks [12].

Immune mediators interact and activate nociceptors to send signals to the meninges; therefore, meningeal immuno-vascular interactions are an important mechanism for sensitization of nociceptors. TNF-α is a potent mast cell-derived proinflammatory cytokine, mediating the sensitization of meningeal nociceptors [13,14]. The cytokines affect the reactivity

of nociceptor signals to the brain and increase blood levels during headaches. TNF-α produced by dura mater and pia mater mast cells participates in the regulation of the blood brain barrier [15,16].

Mast cell-derived TNF-α may contribute to leukocyte collection at sites of inflammation and regulate dendritic cells as well as adaptive immunity. In addition, TNF-α is an inflammatory cytokine capable of influencing CNS physiological states where it is required for normal neuronal function [17,18]. But excess TNF-α in the brain mediates inflammatory diseases, and headaches. In addition, TNF-α can be induced by IL1 in innate immune cells including mast cells and macrophages. However, as is known IL1 induces TNF-α, by blocking IL1 with IL-37, and TNF-α induced is also decreased. Mast cell-derived TNF-α may contribute to leukocyte recruitment at inflammatory sites and regulate dendritic cells and adaptive immunity [19,20].

In the central nervous system, neuroglia are divided into microglia that protect neurons, astrocytes, oligodendrocytes and ependymal cells. Astrocytes play immune functions similar to macrophages, modulate synaptic activity, have detoxification functions, and produce pro-inflammatory members of the IL1 family. Astrocytes, in addition to producing proinflammatory cytokines, also release anti-inflammatory cytokines such as IL-10 [21].

The beneficial activity of NTG as a vasodilator is well known. On the walls of blood vessels, NTG acts intracellularly through the formation of nitric oxide (NO), which is responsible for endothelial-controlled vasodilation. NO released from endothelial cells activates a high affinity receptor, soluble guanylate cyclase (sGC), thereby increasing intracellular levels of cyclicguanosine monophosphate (cGMP) and thereby causing vasorelaxation, platelet disaggregation, and prevention of platelet adhesion [8].

On routine CBC examination, platelets are an indicator of total platelet mass. Platelets release mediators such as thromboxane that cause inflammation. Platelet values in the study of Gül Z and colleagues were higher than the control group for migraine patients but were not statistically significant [2]. Many researchers mention in migraine there is an increase in platelet activation and platelet aggregation. Research by Zeller et al. there was an increase in platelet activation and the formation of leukocyte-platelet aggregation by measuring the expression of P-selectin on platelets [11].

Zahorec's study determined the relationship between neutrophils and lymphocytes during the systemic inflammatory response. Neutrophils and lymphocytes are the main sources of proinflammatory and anti-inflammatory cells. Neutrophils are most significant in the inflammatory response of the acute phase reaction. Lymphocytes are a major component of humoral and cellular responses. NLR is produced from neutrophils and lymphocytes in the inflamed circulation. NLR is a non-invasive, easy and cost-effective measurement [11,22]. In a study conducted in the study of Gül Z and colleagues[2].

Iron metabolism can increase the frequency of headaches by lowering the pain threshold through different mechanisms, such as nitric oxide, inflammatory mediators or neurotransmitters. In a study conducted by Admont et al., the frequency of headaches decreased in cases with hemoglobin levels lower than 11.5. Decreased hemoglobin levels occurs by possibility because of existence potent anti-inflammatory cytokine factors[11].

Erythrocytes can be measured routinely as part of the CBC. Inflammatory cytokines and oxidative stress suppress bone marrow function, leading to the release of immature erythrocytes into the circulation. As a result, neurohormonal activation, chronic inflammatory states, and atherosclerotic processes occur[23]. A correlation has been established between elevated erythrocytes and inflammatory markers such as white blood cell count and sedimentation rate. High erythrocyte counts have been linked to atherosclerosis, vascular occlusive disease, inflammatory bowel disease, acute and chronic heart failure, atrial fibrillation, stroke, and other inflammatory diseases. It is explained that erythrocytes reflect an increase in inflammatory markers such as TNF-α, hepcidin, and IL6 in the blood. In the study of Gül Z and colleagues, Erythrocyte values were significantly higher in the migraine group than in the control group [2].

Increased platelet activation results in upregulation of leukocyte-specific binding, which promotes leukocyte secretion and their binding to the endothelium, a mechanism that has been shown in stroke, which may be associated with migraine. Increased platelet activation in migraine is a marker of inflammatory processes in the trigeminovascular system in the pathogenesis of migraine[24].

Conclusion

This study showed that TNF-α and IL10 was higher in migraine than control group. TNF-α, IL10, leukosit, limfosit and neutrophils and lymphocytes ratio can be used as an inflammatory marker for migraine. These markers may contribute to our understanding of the pathophysiology of migraine.

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CONFLICTS OF INTEREST

The authors have no conflicts of interest to declare.

REFERENCES

1. Utomo H. Reducing Migraine Biomarkers Rapidly with "Assisted Drainage" Therapy (Experimental Study on Experimental Animals). Maj Kedokt Gigi Indones. 2015;1(1): 38–46.
2. Bastuğ Gül Z, Çelik RGG, Selçuk B, Aksoy S, Gül M, Soysal A. New Inflammation Indicator for Migraine: Red Blood Cell Distribution. Haydarpasa Numune Train Res Hosp Med J. 2021;61(2): 166–171.
3. Headache Classification Committee of the International Headache Society (IHS). The International Classification of Headache Disorders, 3rd edition [Internet]. IHS; 2018. Available from: https://www.ichd-3.org/wp-content/uploads/2018/01/The-International-Classification-of-Headache-Disorders-3rd-Edition-2018.pdf
4. World Health Organization. Headache Disorders [Internet]. 2016 [cited 2017 Aug 5]. Available from: http://www.who.int/mediacentre/factsheets/fs277/en/
5. Burgos-Vega C, Moy J, Dussor G. Meningeal afferent signaling and the pathophysiology of migraine. Prog Mol Biol Transl Sci. 2015; 131:537–64.
6. Liu LL, Li X, Chang G, Wang ZG, Zhang SJ, Ju XN. Sibelium in combination with dibazole in the treatment of angioneurotic headache. J Biol Regul Homeost Agents. 2017;31(3): 653–7.
7. Sufka KJ, Staszko SM, Johnson AP, Davis ME, Davis RE, Smitherman TA. Clinically relevant behavioral endpoints in a recurrent nitroglycerin migraine model in rats. J Headache Pain. 2016;17(1).
8. Demartini C, Greco R, Zanaboni AM, Sances G, De Icco R, Borsook D, et al. Nitroglycerin as a comparative experimental model of migraine pain: From animal to human and back. Prog Neurobiol. 2019; 177:15–32.
9. Moye LS, Pradhan AAA. Animal model of chronic migraine-associated pain. Curr Protoc Neurosci. 2017; 2017:9.60.1-9.60.9.
10. Targowska-Duda KM, Ozawa A, Bertels Z, Cippitelli A, Marcus JL, Mielke-Maday HK, et al. NOP receptor agonist attenuates nitroglycerin-induced migraine-like symptoms in mice. Neuropharmacology. 2020;170.
11. Karabulut KU, Egercioglu TU, Uyar M, Ucar Y. The change of neutrophils/lymphocytes ratio in migraine attacks: A case-controlled study. Ann Med Surg. 2016; 10:52–6.
12. Aydın M, Demir CF, Arıkanoğlu A, Bulut S, İlhan N. Plasma Cytokine Levels in Migraineurs During and Outside of Attacks. Electron J Gen Med. 2015;12(4).
13. Moretti S, Bozza S, Oikonomou V, Renga G, Casagrande A, Iannitti RG, et al. IL-37 Inhibits Inflammasome Activation and Disease Severity in Murine Aspergillosis. PLoS Pathog. 2014;10(11).
14. Pinho-Ribeiro FA, Verri WA, Chiu IM. Nociceptor Sensory Neuron–Immune Interactions in Pain and Inflammation. Trends Immunol. 2017;38(1):5–19.
15. Christy AL, Walker ME, Hessner MJ, Brown MA. Mast cell activation and neutrophil recruitment promotes early and robust inflammation in the meninges in EAE. J Autoimmun. 2013; 42:50–61.

16. Levy D. Endogenous mechanisms underlying the activation and sensitization of meningeal nociceptors: The role of immuno-vascular interactions and cortical spreading depression. Curr Pain Headache Rep. 2012;16(3):270–7.
17. Kempuraj D, Thangavel R, Natteru PA, Selvakumar GP, Saeed D, Zahoor H, et al. Neuroinflammation Induces Neurodegeneration. J Neurol Neurosurg spine [Internet]. 2016;1(1). Available from: http://www.ncbi.nlm.nih.gov/pubmed/28127589%0Ahttp://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=PMC5260818
18. Mukai K, Tsai M, Saito H, Galli SJ. Mast cells as sources of cytokines, chemokines, and growth factors. Immunol Rev. 2018;282(1):121–50.
19. Clark IA, Vissel B. Excess cerebral TNF causing glutamate excitotoxicity rationalizes treatment of neurodegenerative diseases and neurogenic pain by anti-TNF agents. J Neuroinflammation. 2016;13(1).
20. Conti P, Caraffa A, Kritas SK, Ronconi G, Lessiani G, Toniato E, et al. Mast cell, pro-inflammatory and anti-inflammatory: Jekyll and Hyde, the story continues. J Biol Regul Homeost Agents. 2017;31(2):263–7.
21. Ransohoff RM, Brown MA. Innate immunity in the central nervous system. J Clin Invest. 2012;122(4):1164–71.
22. Tekeşin A, Tunç A. Evaluation of inflammatory markers in patients with migraine. Arch Clin Exp Med. 2019; 4(1):37-40.
23. Raditya PPR, Ansori ANM, Notopuro PB. Immune-related pancytopenia: A rare case report in Surabaya, Indonesia. Biochem Cell Arch. 2021; 21(1): 881-884.
24. Avci AY, Akalin O. Migraine and peripheral inflammation. Acta Med. Alanya. 2017;1(3): 20-27.

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