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Monocyte to high-density lipoprotein ratio and neutrophil to lymphocyte ratio in trigeminal neuralgia patients: A retrospective cohort study

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The study was approved by the Dokuz Eylül University Faculty of Medicine ethics committee (date: March 5, 2018, number: 32151665-210.03-18389).
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

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Abstract

Background/Aim: Trigeminal neuralgia (TN) is a prevalent cranial nerve disorder. While inflammation has been implicated in neuropathic pain in numerous recent studies, its role in TN has remained uncertain. Given the increasing significance of neuroinflammation, this study aims to explore the association between inflammation and TN and to assess whether there are disparities in the monocyte to high-density lipoprotein ratio (MHR) and neutrophil to lymphocyte ratio (NLR) values between TN patients and healthy individuals. There is a dearth of literature concerning the link with MHR, a parameter extensively studied in cardiac research but unexplored in the context of TN.

Methods: This retrospective cohort study encompassed 48 patients diagnosed with classical TN and 40 healthy controls treated at the neurology and pain clinic of Dokuz Eylül University. Demographic and clinical variables, such as age and gender, along with monocyte, neutrophil, lymphocyte, and high-density lipoprotein (HDL) levels, were retrospectively retrieved from medical records. Inflammation markers, namely MHR and NLR, were calculated. Nonparametric tests were employed to compare these markers between TN patients and healthy controls.

Results: Regarding sociodemographic data, the average age of the patient group was 59.8, while that of the healthy group was 47.4. A significant age difference was observed between the patient and healthy groups (P<0.001). However, no significant differences between the groups regarding MHR or NLR values were detected.

Conclusions: These findings may suggest the presence of an inflammatory process characterized by local neurogenic inflammation in the pathophysiology of TN. Further comprehensive studies are required to assess the utility of MHR as a readily applicable marker in neurological disorders with neuroinflammatory and neuropathic pain etiologies.

Keywords: inflammation, neutrophil to lymphocyte ratio, monocyte to high-density lipoprotein ratio, trigeminal neuralgia

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Introduction

Trigeminal neuralgia (TN), defined by the third edition of the International Classification of Headache Disorders (ICHD-3), is characterized by recurrent, unilateral pain that abruptly initiates and terminates, resembling a brief electric shock. This pain is localized to one or more branches of the trigeminal nerve and can be triggered by seemingly innocuous sensory stimuli [1]. The second and third branches of the trigeminal nerve are predominantly affected. Incidence rates in various studies range from 4.3 to 27 per 100,000 individuals, with a lifetime prevalence estimated between 0.016% and 3% in population-based studies. While the age of onset can vary, classical trigeminal neuralgias typically manifest around age 53, whereas secondary trigeminal neuralgias tend to appear at age 43. The primary cause of classical TN is often attributed to the trigeminal nerve compression by arterial structures in the cerebellopontine system or morphological alterations. Anatomical investigations have revealed a gradual transition from Schwann cell myelinization to oligodendroglia within the proximal 25% of the nerve. This transition zone is considered vulnerable to compression, particularly by vascular structures [2].

Irrespective of the underlying etiology, a common thread emerges in numerous neurophysiological, neuroimaging, and histological studies: the central pathophysiological mechanism revolves around focal demyelination of the primary trigeminal afferent at the point where the trigeminal root enters the pons. Consequently, the nerve becomes hyperexcitable as demyelination progresses to a stage where ions are permitted to flow in and out within the axon, making it challenging to maintain the resting potential at the Ranvier nodes. This phenomenon may play a role in the pathophysiological processes associated with ephaptic conduction and secondary central sensitization [2].

Recent evidence suggests a correlation between neuroinflammation mediated by the chemokine-cytokine network and neuropathic pain. In the peripheral nervous system, inflammatory cells begin to aggregate around the affected nerve following nerve damage, releasing chemokines and cytokines, ultimately leading to chronic neuroinflammation and peripheral sensitization. Initially, the myelin component in sensory nerves, composed of Schwann cells and resident macrophages, becomes activated. Subsequently, circulating leukocytes, primarily neutrophils during the initial stages, accumulate around the injured nerve. Previously activated leukocytes then bolster macrophages. Macrophages play a pivotal role in driving the progression of neuroinflammation, clearing debris, facilitating tissue repair in Wallerian degeneration, and activating lymphocytes. Ultimately, lymphocytes congregate around the damaged nerve, contributing to the development of neuropathic pain [3]. In 2011, it was observed that patients with complex regional pain syndrome exhibited a significantly higher inflammatory phenotype in their monocytes compared to healthy controls [4].

Microglial cells are specialized, resident macrophage-like cells within the central nervous system (CNS). They are responsible for maintaining the CNS microenvironment and regulating immunity. Microglial cells initiate a classical pro-inflammatory response in response to threats or pathogens. Ideally, once the threat is controlled, an immunomodulatory response should engage, dampening the inflammatory reaction and restoring homeostasis. However, any disruptions in this process can lead to increased damage, potentially resulting in cell death and neurodegeneration. It is believed that the pro-inflammatory activation of microglia may contribute to the pathogenesis of neurodegenerative diseases such as Parkinson's disease and multiple sclerosis (MS) [5].

Previous studies have identified leukocytes and specific lymphocyte subtypes as inflammatory markers in cardiovascular diseases. The neutrophil to lymphocyte ratio (NLR) can be readily determined by assessing neutrophil and lymphocyte counts in peripheral blood samples. Previous research has underscored its potential as a novel inflammatory marker in cardiac conditions and non-cardiac diseases [6].

Collateral neuronal damage often accompanies primary neuroinflammatory diseases and may also represent a potential outcome of primary neurodegeneration. Current research has shed light on intriguing parallels between Alzheimer's disease and MS [7].

Seeking to shift the phenotype of macrophages from a pro-inflammatory state to an anti-inflammatory one may present a more favorable therapeutic approach than outright inhibition of their function within the damaged nerve. This is crucial because macrophages are pivotal in nerve repair [8].

Recently, the monocyte to high-density lipoprotein ratio (MHR) value, calculated by dividing the monocyte count by the high-density lipoprotein (HDL) level, has emerged as a noteworthy inflammatory marker in the cardiovascular domain. Several studies in the field of neurology have suggested its potential significance as a novel prognostic marker [9]. While the involvement of inflammation in neuropathic pain has been proposed in numerous recent investigations, its role in TN has remained elusive. Given the growing emphasis on neuroinflammation, the current study explores the connection between inflammation and TN, aiming to discern any disparities in MHR and NLR values between TN patients and healthy individuals.

Materials and methods

This retrospective cohort study was conducted at the Dokuz Eylül University Faculty of Medicine, Department of Neurology and Pain in İzmir, Turkey. The study received approval from the Dokuz Eylül University Faculty of Medicine Ethics Committee on 5 March 2018, with the reference number 32151665-210.03-18389, and it was carried out following the principles outlined in the Helsinki Declaration.

In this study, we conducted a retrospective analysis of blood values in patients who presented to our Pain and Neurology Headache Outpatient Clinic and were diagnosed with classical TN. We focused on patients undergoing blood tests to assess their MHR and NLR values. We examined patient records from 2007 to 2017, extracting demographic and clinical data, including age, gender, monocyte levels, neutrophil levels, lymphocyte levels, and HDL levels from their medical records. To serve as a control group, we calculated MHR and NLR values, which serve as inflammation markers, for 40 healthy

individuals who met similar exclusion criteria, had no comorbidities, and had visited the outpatient clinic within the last month.

The exclusion criteria for this study encompassed individuals with the following conditions: diagnosed chronic inflammatory diseases, infections, diabetes mellitus, severe liver and chronic kidney diseases, rheumatic and hematological diseases, coronary artery disease, heart disease, individuals undergoing steroid therapy, and those with a history of cancer.

The patient group's follow-up period was meticulously documented. During their visits to the outpatient clinic, blood tests and lipid profiles, including low-density lipoprotein (LDL) and HDL, were assessed either on the date of their appointment or within a 6-month timeframe. Furthermore, we calculated the average HDL values from their multiple hospital admissions between 2007 and 2017. Any additional coexisting medical conditions were duly recorded.

To ensure accuracy and reliability, we separately calculated the MHR at the first presentation and the MHR based on mean HDL values. Multiple HDL measurements were averaged to enhance the precision of our calculations.

Statistical analysis

We employed IBM SPSS Statistics software version 24.0 (IBM SPSS, Inc., Tokyo, Japan) for our statistical analyses. Descriptive statistics were presented using mean values, standard deviations, and medians. Due to the non-normal distribution observed between the patient and healthy groups, we applied the independent samples Mann-Whitney U test, a nonparametric statistical method. Results with a *P*-value below 0.05 were considered statistically significant.

Results

In a retrospective review of records spanning the past 10 years, 90 patients diagnosed with classical TN were included in the study. Twenty-four patients were excluded due to concurrent medical conditions, while 18 patients were excluded due to incomplete blood test results. The final patient group comprised 48 individuals. Additionally, 40 individuals without any concurrent medical conditions were selected as healthy controls from the retrospective records.

The average age of the patient group was 59.8 years (range: 24.0 to 85.6), while the healthy group had an average age of 47.4 years (range: 23.3 to 69.8). The patient and healthy groups had a significant age difference ($P<0.001$). Gender distribution among healthy subjects and patients, along with age averages and the patient's years of follow-up, are presented in Tables 1–3.

Table 1: Numbers and percentages of healthy and patient groups (number given as n)

	Healthy group	Patient group
Gender		
Female, n (%)	22 (55)	28 (58.3)
Male, n (%)	18 (45)	20 (41.7)
Total, n	40	48

Table 2: The mean age, minimum, maximum and standard deviation values of the healthy and patient groups

	Healthy group		Patient group	
Variable	**Min.-Max.**	**Mean (SD)**	**Min.-Max.**	**Mean (SD)**
Age	23.3-69.8	47.4 (12.1)	24.0-85.6	59.8 (15.4)

SD: standard deviation

Table 3: Number of patient group follow-up years

Patient group	n (%)
Follow-up years	
0-1 years, n (%)	23 (47.9)
2-5 years, n (%)	17 (35.4)
> 5 years, n (%)	7 (14.6)
>10 years, n (%)	1 (2.1)
Total n	48

The Mann-Whitney U test, a nonparametric statistical method, was employed for the independent samples. The analysis revealed no significant differences in white blood cell and monocyte values between the patient and healthy groups.

HDL data was available for 29 patients in the patient group and 39 subjects in the healthy group. No significant differences were observed between the groups regarding either MHR or NLR values. For the average HDL and MHR values, data was obtained from the records of 20 patients in the patient group and 12 subjects in the healthy group. The results and corresponding *P*-values are in Tables 4 to 6 and Figures 1 and 2.

Table 4: The median, minimum and maximum values of the NLR, MHR initial and MHR average of the healthy and patient group are shown

	Healthy group		Patient group	
	Median	Min.-Max	Median	Min.-Max
NLR	1.82	1.00-7.75	1.81	0.85-4.5
MHR initial	0.146	0.059-0.278	0.142	0.060-0.286
MHR average	0.009	0.006-0.029	0.008	0.003-0.018

NLR: neutrophil to lymphocyte ratio, MHR: monocyte to high-density lipoprotein ratio

Table 5: The *P*-values in the comparison between the healthy and the patient group using the independent samples Mann-Whitney U test are shown

	P-value
HDL initial	0.118
HDL average	0.192
LDL initial	0.687
LDL average	0.922
NLR	0.880
MHR initial	0.828
MHR average	0.058

LDL: low-density lipoprotein, HDL: high-density lipoprotein, NLR: neutrophil to lymphocyte ratio, MHR: monocyte to high-density lipoprotein ratio

Table 6: Comparison of NLR and MHR values between genders in the patient group

Patient group	Gender	N	Mean (SD)	*P*-value
NLR	female	28	1.80 (0.66)	0.110
	male	20	2.2 (0.90)	
	n	48		
MHR initial	female	17	0.11 (0.033)	0.338
	male	12	0.17 (0.046)	
	n	29		
MHR average	female	12	0.006 (0.002)	0.066
	male	8	0.010 (0.004)	
	n	20		

NLR: neutrophil to lymphocyte ratio, MHR: monocyte to high-density lipoprotein ratio, SD: standard deviation

Figure 1: NLR frequency graphic for healthy and patient group (Graphic with blue color is patient group, and Graphic with green color is healthy group)

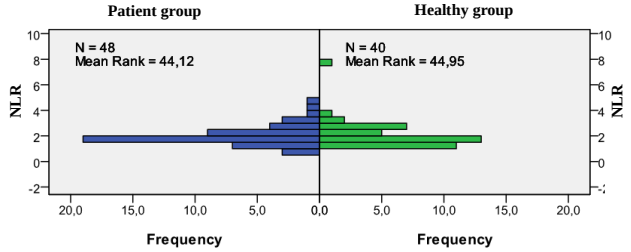
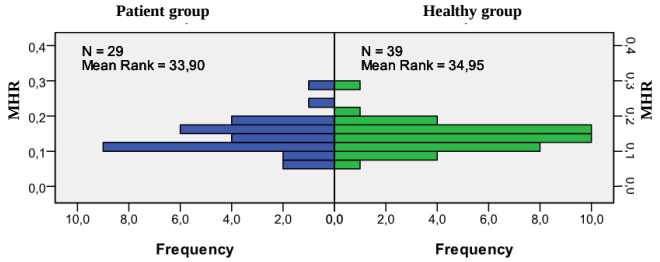


Figure 2: MHR frequency graphic for healthy and patient group (Graphic with blue color is patient group, and Graphic with green color is healthy group)



Discussion

The peripheral immune system has long been examined as a potential source of biomarkers for various disease states. NLR and MHR, which are used as noninvasive, inexpensive, and easily accessible peripheral biomarkers for many diseases, are among them. The CNS is immunologically protected, and circulating immune cells are not typically found within the CNS. However, activated microglia can secrete inflammatory mediators and induce secondary inflammatory responses in the CNS. Immune processes that impact neurodegeneration occur in the periphery and CNS.

While NLR serves as a parameter of systemic inflammation, the results from studies on Alzheimer's disease, intracranial atherosclerosis, and other neurological diseases have shown inconsistency [10-12].

Over the past two decades, there has been a growing focus on the role of glial cells in the development and persistence of chronic pain. Accumulating evidence suggests that dysregulated glial activity may contribute to chronic pain, highlighting the central role of neuroinflammation in its onset and maintenance, affecting both the CNS and peripheral nervous system. Microglial cells and other non-neuronal immune system cells are the primary sources of pro-inflammatory cytokines and chemokines, which, when released, lead to increased sensitivity to pain by activating nociceptive neurons in both the peripheral and CNS.

In the peripheral nervous system, such as in cases like sciatica and dorsal root ganglia, immune cells infiltrate the area, while in the CNS, glial cells and astrocytes become activated, resulting in the production and release of pro-inflammatory cytokines and chemokines. Numerous studies have demonstrated the involvement of microglial mitogen-activated protein kinase (MAPK) activation in the pathogenesis of neuropathic pain [5,13].

Studies have demonstrated a strong association between chronic constriction damage to the sciatic nerve and increased infiltration of macrophages after 28 days, along with the emergence of neuropathic pain-like behaviors in mice. In inflammatory events, neutrophils are often prominent but typically absent from the sciatic nerve. However, in animal experiments involving sciatic nerve damage, neutrophils appear to be implicated in the induction of neuropathic pain-like behaviors.

Depletion of neutrophils has been shown to result in a reduction in the development of thermal hypersensitivity. Nevertheless, research suggests neutrophils may primarily contribute to the initial phase of neuropathic pain rather than its sustained presence. They release many chemokines and activate other immune cells, such as macrophages, which exhibit algogenic effects similar to mast cells [8].

T lymphocyte cells, constituting 80% of circulating lymphocytes in the blood, can be categorized into two groups with pro-inflammatory and anti-inflammatory functions. They hold a crucial position in the context of autoimmune diseases. Research has indicated a notable elevation in the number of T cells in neuropathic pain models compared to control groups, and this rise is linked to heightened sensitivity to both mechanical and thermal pain. Experiments involving mice deficient in T cells reduced neuropathic pain-like behavior [8].

In neuroinflammation, macrophages and microglia play more prominent roles than T lymphocytes. Microglia, a non-migrating glial cell, are partially derived from circulating monocytes. They adopt the morphology of activated macrophages and exhibit heightened sensitivity to damage within the CNS. In addition to the conventional "outside-in" pathology involving myelin sheath to axon interactions, Tsunado Fujinami et al. [7] have proposed an "inside-out" pathology based on observations of secondary demyelination following virus-mediated neuronal and axonal damage. Such lesions may also involve neuronal injury and oligodendroglial damage, triggering an immune response that can potentially progress to autoimmunity under specific environmental conditions.

Macrophages play a crucial role in the onset and persistence of neuropathic pain. Traumatic damage to the peripheral nerve results in the detachment of axons from the cell body and the accompanying myelin sheath, a process known as Wallerian degeneration. Macrophages assume a vital role in the phagocytosis and clearance of myelin debris. This clearance is significant because myelin debris can hinder axon regeneration, making removing such debris essential for nerve repair [8].

Numerous inflammatory pain mediators encompass a wide range of molecules, from small compounds like bradykinin and prostanoids to cytokines, chemokines, and growth factors, with their diversity steadily increasing. This group comprises many immune cells, glial cells, and neurons. Throughout this process, these inflammatory mediators exert various effects, including the sensitization and activation of nociceptive terminals, the regulation of the primary nociceptive phenotype, control over presynaptic transmitter release in the spinal cord nociceptor, and modulation of postsynaptic neuronal excitability. A crucial challenge lies in elucidating the intricate interplay among these diverse mediators and mechanisms, particularly in pain-related situations [8].

The NLR in peripheral blood has been proposed as a potential systemic inflammatory marker in various diseases, with a specific focus on rheumatological conditions [14] and cancer research [15]. The physiological immune response of circulating leukocytes to systemic inflammation typically involves increased neutrophil counts and decreased lymphocyte counts. Lymphopenia indicates weakened cellular immunity, while neutrophilia reflects the body's response to systemic inflammation. Consequently, NLR is put forward as a fundamental marker of systemic inflammation and stress across numerous diseases. Many studies interpret the ratio of these two values as a measure of the competency of the cellular immune response [16–18]. In short, NLR serves as an indirect indicator of the host's immune response [19].

Moreover, NLR offers a cost-effective means of identifying critically ill patients, as it is a readily measurable and reproducible indicator of subclinical inflammation. Its potential utility has also been explored in neurological conditions like ischemic stroke [20]. Goyal and colleagues [21] discovered that NLR on admission could be a prognostic biomarker for outcomes in patients with large vessel occlusion strokes.

Although few studies have investigated NLR in patients with MS, they have proposed a potential role in disease diagnosis and the detection of disease activity [22–27]. NLR has been validated as a poor prognostic marker for cancer and cerebrovascular diseases [28-30]. Furthermore, it has been linked to the presence and severity of atherosclerosis in carotid arteries, coronary arteries, and even peripheral arteries, suggesting that atherosclerosis is an inflammatory disorder [31-35].

In our study, we explored the role of systemic inflammation in the pathophysiology of TN using inflammatory markers such as NLR and MHR calculated from blood tests and lipid profile measurements. We did not observe any significant differences when comparing NLR and MHR values between TN patients and the control group. A similar study involving 141 TN patients found that NLR and other inflammatory markers could predict TN diagnosis and showed a close association with inflammation [36]. The variation in results between these studies may be attributed to differences in patient sample sizes. Additionally, it is worth considering that hematological parameters, such as neutrophils (NEU) and lymphocytes (LYM), which a wide range of conditions can influence, may have played a role in these findings.

The brain is the body's most cholesterol-rich organ, containing nearly 25% of the total cholesterol [37]. A significant portion (70–80%) of this cholesterol resides within myelin, which plays a crucial role in insulation [38]. Astrocytes and oligodendrocytes locally synthesize brain cholesterol and is largely isolated from other cholesterol pools in the body [39]. The prevailing consensus suggests minimal net cholesterol transfer from the peripheral bloodstream to the CNS due to the blood-brain barrier, which restricts the passage of plasma lipoproteins into the brain. HDL forms both in the systemic circulation and the brain. HDL serves a diverse range of functions, including anti-oxidation, anti-inflammation, promoting endothelial function, anti-thrombosis, and modulation of immune function. Substantial evidence supports that elevated plasma levels of HDL offer protection against cardiovascular disease. An increasing body of evidence suggests that HDL also plays a beneficial role in various systems, including the CNS. Plasma HDL levels have been linked to neurodegenerative diseases such as MS [40]. Individuals in the acute stage of MS have been reported to exhibit lower HDL levels than those in remission, with a higher likelihood of developing acute inflammatory lesions, as assessed by Magnetic Resonance Imaging [40-42]. HDL promotes the formation of M2-polarized macrophages, characterized by a reduced pro-inflammatory profile, and inhibits the cytokine-induced expression of adhesion molecules in endothelial cells [43-45]. These properties may contribute to immune system suppression, thereby preventing MS relapses. Additionally, abnormalities in HDL levels have been observed in patients with psychiatric disorders [46].

The MHR has emerged as a novel inflammation marker, and its association with various diseases has been explored. One study investigated the relationship between MHR and intracerebral hemorrhage (ICH) outcomes, revealing that elevated MHR was independently linked to disability or mortality at hospital discharge and 3 months post-stroke among acute ICH patients [9]. MHR has also been strongly correlated with cardiovascular conditions. Kanbay et al. [47] were the first to report a relationship between high MHR and cardiovascular events in patients with chronic kidney disease. Canpolat et al. [48] additionally highlighted MHR as an independent predictor of atrial fibrillation recurrence following cryoballoon-based catheter ablation. Moreover, other studies have found that increased MHR is independently associated with major adverse cardiovascular events during hospitalization in patients with coronary artery disease [49,50]. Despite previous studies suggesting that MHR may serve as a novel prognostic marker for cardiovascular and neurological vascular diseases, our study found no significant difference between patients diagnosed with classical TN and healthy subjects.

Limitations

The sample size within our TN cohort was limited. Several factors contributed to the reduction in the number of patients, including the extensive exclusion criteria, incomplete data, and the absence of HDL values for all patients. Additionally, there was a notable difference in mean age between the patient and healthy groups, constituting the study's weakness. Furthermore, this study has several limitations, including the lack of evaluation of other inflammation biomarkers such as C-reactive protein, procalcitonin, sedimentation rate, and interleukin levels. We also could not exclude asymptomatic subjects with a nonspecific inflammatory response. However, the study's primary strength lies in its 10-year retrospective analysis of archived cases diagnosed with classical TN. While we aimed to maintain group homogeneity, the strict exclusion criteria resulted in a relatively small number of included patients. Nevertheless, it's worth noting that this study represents the first investigation of the MHR in the context of TN.

Conclusions

As a result, it is imperative to conduct further investigations with larger sample sizes to corroborate these preliminary findings. Expansive studies are necessary to thoroughly evaluate the significance of the MHR as a readily applicable marker in neurological diseases characterized by neuroinflammation and neuropathic pain pathogenesis. Subsequent studies could prove valuable, particularly when the differential diagnosis of classical TN is challenging or regarding its potential role in predicting acute exacerbations.

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