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ORIGINAL ARTICLE

Relationship between trigeminal neuralgia and the C-reactive protein/albumin ratio

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ABSTRACT

Objectives: This study aimed to assess whether the C-reactive protein/albumin ratio (CAR) is a risk factor for trigeminal neuralgia (TN) development and the relationship between the CAR and TN pain frequency.

Patients and methods: In this retrospective study, 100 patients (51 females, 49 males; mean age: 58.6±14.1 years; range, 31 to 88 years) with idiopathic TN and 70 healthy controls (38 females, 32 males; mean age: 54.1±15.7 years; range, 21 to 89 years) were included between January 2020 and December 2022. Patients were divided into two groups by weekly and monthly pain frequency. The laboratory findings and CARs were compared.

Results: The CAR values were significantly different between the patient and control groups ($p<0.05$) and were significantly different among TN subgroups divided according to attack frequency ($p<0.05$).

Conclusion: Since there was a significant relationship between TN and CAR as a prognostic predictor, this relationship demonstrated once again that inflammation plays a role in the etiopathogenesis of TN. As opposed to previous studies that investigated the effect of only inflammation, the effects of both inflammation and malnutrition could be investigated by evaluating CAR in this study.

Keywords: C-reactive protein/albumin ratio, inflammation, trigeminal neuralgia.

Trigeminal neuralgia (TN) is a chronic, neuropathic, trigeminal nerve pain syndrome. It is the most common form of facial pain, associated with burning, stinging, and repetitive paroxysmal problems in the orofacial region.[1,2] It is subclassified as primary or idiopathic and secondary or symptomatic, depending on the cause. Idiopathic TN (approximately 10% of all cases) is diagnosed when no obvious cause is apparent.[3-5] Inflammation plays a role in TN pathogenesis. Proinflammatory cytokines, such as interleukin-1 beta (IL-1β) and tumor necrosis factor (TNF), modulate neuronal activity;[6] both are nociceptor activators that increase trigeminal neuron excitability and sensitivity.[7,8] Interleukin-1β, TNF, IL-6, and CCL2 trigger neuropathic pain.[9-14] One study that investigated the relationship between the neutrophil-to-lymphocyte ratio, the monocyte-to-lymphocyte ratio, and TN reported that elevated levels of inflammatory markers might be risk factors for TN.[15]

C-reactive protein (CRP) is a positive acute-phase reactant secreted by the liver. The blood level of CRP increases within hours after inflammation and infection commence.[16] Albumin (Alb) is a negative acute-phase reactant secreted by the liver[17] and is the most abundant protein in plasma, maintaining the plasma osmotic pressure and modulating fluid distribution among the various bodily compartments.[18] It has antioxidant and anti-inflammatory properties.[19] The CRP/Alb ratio (CAR) is a new prognostic marker of inflammation severity and mortality.[20] An increased CAR is associated with poor prognosis of migraine, Crohn's disease, and Guillain-Barré syndrome.[21-23]

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Hematological and biochemical tests are simple, inexpensive, and readily interpretable; the CRP and Alb levels are routinely assayed. It is also important that it is more easily accessible than inflammatory cytokines such as IL-6, IL-1β, and TNF-alpha.[24-26]

Since inflammation can play a role in nerve damage and pain pathways, a higher CAR might suggest a more pronounced inflammatory response in individuals with TN. In other chronic conditions, the CRP/Alb ratio has been used to predict outcomes and disease progression. While specific studies on TN are limited, the CRP/Alb ratio might offer similar prognostic information, helping to identify patients at higher risk of severe disease or complications. No study has yet reported a relationship between TN and the CAR. Hence, this study aimed to explore whether a high CAR increased the risk for TN and whether the CAR was associated with the TN pain frequency.

PATIENTS AND METHODS

All medical records of patients who visited the neurology outpatient clinic of Inonu University Medical Faculty who were diagnosed with idiopathic TN between January 2020 and December 2022 were retrospectively analyzed. One hundred patients (51 females, 49 males; mean age: 58.6±14.1 years; range, 31 to 88 years) diagnosed with idiopathic TN using the criteria of the ICHD-3 (third edition of the International Classification of Headache Disorders) were included.[27] The inclusion criteria were primary TN, specific TN treatment, absence of hematological or current infectious disease, hyperpyrexia, metabolic disorder, severe heart disease, severe kidney or liver dysfunction, a neoplasm, an autoimmune or inflammatory disease, and not being on medication to treat an inflammatory condition. Positive stool culture, positive blood culture, positive urine culture, infiltrates on chest X-ray, documented skin infection, fever over 38°C, and patients with otitis symptoms were not included in the study. Each patient underwent magnetic resonance imaging using a 1.5 T superconductive scanner (Siemens Magnetom® Avanto; Siemens AG, München, Germany). Patients with symptomatic TN attributable to meningiomas, multiple sclerosis, or epidermoid cysts in the cerebellopontine angle were excluded. All patients were divided into two groups by pain frequency: those with pain at least weekly (Group 1; n=58) and those with pain once a month or less (Group 2; n=42). A control group of 70 healthy individuals (38 females, 32 males; mean age: 54.1±15.7 years; range, 21 to 89 years) was included. Healthy controls were frequency-matched to the patients by age, sex, educational level, and comorbidities.

Fasting peripheral blood samples were collected from all patients. Hematological parameters, including erythrocyte sedimentation rate (ESR), were measured using an automated nephelometric system (Sysmex Corporation 1-5-1, Wakinahama-kai Gandari Chuo-ku, Kobe, Japan) and kits from the same company. C-reactive protein levels were assayed employing another automated nephelometric system (BNII; Dade Behring, Deerfield, IL, USA), and kits from that company. Total serum levels of protein and Alb were measured via automatic spectrophotometry (Abbott Laboratories Diagnostics, Abbott Park, IL, USA) using kits from that company. The CAR was calculated. Patients with TN and control subjects were compared in terms of demographics, laboratory findings, and CARs.

Statistical analysis

Statistical analyses were performed using IBM SPSS version 26.0 (IBM Corp., Armonk, NY, USA). The normality of continuous variables was verified using the Shapiro-Wilk test ($n<50$) and Kolmogorov-Smirnov test ($n\geq50$). Differences between patients with TN and healthy controls were assessed using the Mann-Whitney U test for independent nonnormally distributed variables and independent t-tests for normally distributed variables. Receiver operating characteristic (ROC) curves were used to determine optimal cutoff values for CARs in terms of predicting TN and TN attack frequency. All statistical tests were two-tailed, and p-values <0.05 were assumed to indicate statistical significance.

RESULTS

The levels of total protein, CRP, Alb, and CARs, significantly differed ($p<0.05$ unless stated otherwise) between patients and controls. All values were significantly higher than those of controls, except for Alb, whose levels were significantly lower. There were no significant differences in age or ESR between patients and controls (Table 1).

The mean CRP and Alb levels, and the CARs of TN patients, significantly differed by pain frequency; all were significantly higher in Group 1 than Group 2, but ESR, total protein level, and disease duration did not differ between the groups (Table 2).

Receiver operating characteristic curve analysis and the Youden index were used to determine the

TABLE 1
Sociodemographic characteristics and laboratory findings

	Controls (n=70)		Patients (n=100)		
	Mean±SD	Min-Max	Mean±SD	Min-Max	*p*
Age (year)	54.13±15.67	21-89	58.64 ±14.11	31-88	0.069
Erythrocyte sedimentation rate (mm/h)	9.61±8.05	1-33	11.6±10.74	1-52	0.301
Total protein (g/dL)	6.99±0.59	5.6-8.3	7.19±0.56	5.2-8.1	0.006*
CRP/Alb ratio	0.11±0.1	0.05-0.63	0.21±0.22	0.06-1.46	0.000*
CRP (mg/dL)	0.5±0.45	0.3-3	0.84±0.95	0.3-7	0.000*
Albumin (g/dL)	4.37±0.46	3-5.3	4.04±0.55	2-5.6	0.000*

SD: Standard deviation; CRP: C-reactive protein; * Statistically significant at the 0.05 level. All variables were analyzed by the Mann-Whitney U test.

TABLE 2
Sociodemographic characteristics and laboratory findings of TN patients by pain frequency

	Group 1 (n=58)		Group 2 (n=42)		
	Mean±SD	Min-Max	Mean±SD	Min-Max	*p*
Age (year)	59.31±14.24	31-84	57.71±14.05	31-88	0.527
Erythrocyte sedimentation rate (mm/h)	12.56±11.5	2-52	10.29±9.61	1-40	0.226
Total protein (g/dL)	7.28±0.54	5.2-8.1	7.08±0.58	5.6-8	0.072
CRP/Alb ratio	0.25±0.26	0.06-1.46	0.15±0.13	0.06-0.64	0.008*
CRP (mg/dL)	1.04±1.16	0.3-7	0.57±0.45	0.3-2.32	0.001*
Albumin (g/dL)	4.2±0.47	3-5.6	3.83±0.6	2-4.8	0.002*
Duration (month)	59.98±55.46	7-336	56.09±49.99	6-247	0.772

TN: Trigeminal neuralgia; SD: Standard deviation; CRP: C-reactive protein; * Statistically significant at the 0.05 level. All variables were analyzed by the Mann-Whitney U test.

optimal CAR that could distinguish patients from controls. The area under the ROC curve for CAR was 78.6 (95% confidence interval [CI]: 0.700-0.831; Figure 1). For patients, the optimum CAR cutoff was 0.075, with a sensitivity and specificity of 55.7% and 92%, respectively; the accuracy was 77.1% (Table 3). Furthermore, ROC curve analysis and the Youden index were used to determine the CAR that could distinguish Groups 1 and 2. For Group 1, the area under the ROC curve for CAR was 65.4 (95% CI: 0.239-0.431; Figure 2). For Group 1, the optimum CAR cutoff was 0.105, and the sensitivity and specificity were 52.4% and 77.6%, respectively; the accuracy was 33% (Table 4).

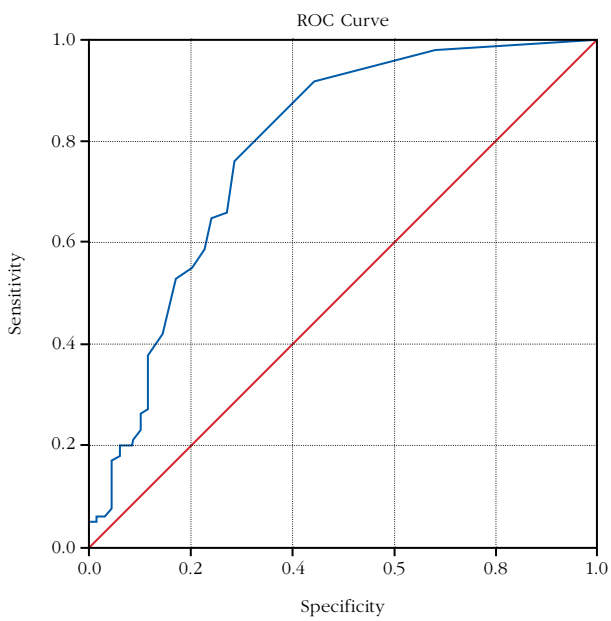

Figure 1. Control/patient CAR ROCs.
CAR: C-reactive protein/Alb ratio; ROC: Receiver operating characteristic.

DISCUSSION

We found that CAR values were significantly higher in patients with TN than in healthy controls. Furthermore, the CAR values significantly increased with TN pain frequency. To the best of our

TABLE 3
C-reactive protein/Alb ratio sensitivity and specificity (controls/patients)

	CAR
Cutoff value	0.075
Sensitivity (%)	55.7
Specificity (%)	92.0
Accuracy (%)	77.1
Area under the curve (%)	78.6
95% CI	0.700-0.831
p-value	0.000*

* Statistically significant at the 0.05 level.

TABLE 4
C-reactive protein/Alb ratio sensitivity and specificity (Group 1/Group 2)

	CAR
Cutoff value	0.105
Sensitivity (%)	52.4
Specificity (%)	77.6
Accuracy (%)	33.0
Area under the curve (%)	65.4
95% CI	0.239-0.431
p-value	0.001*

* Statistically significant at the 0.05 level.

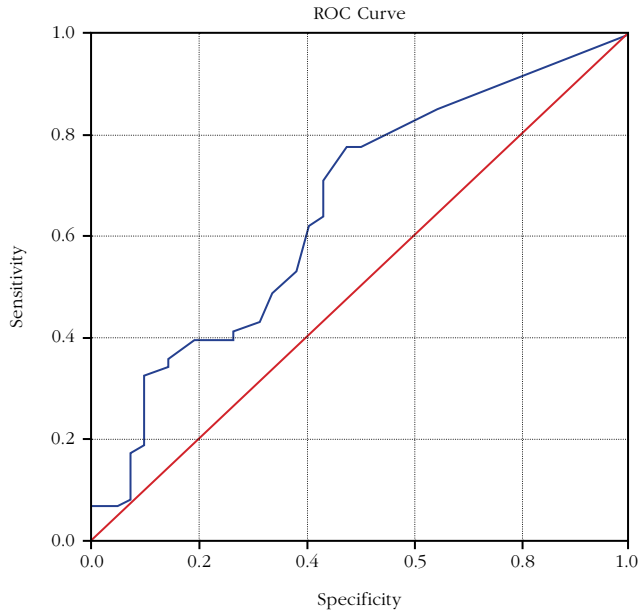

Figure 2. Group 1/Group 2 CAR ROCs.
CAR: C-reactive protein/Alb ratio; ROC: Receiver operating characteristic.

knowledge, this is the first study to show that the CAR is a novel marker of TN inflammation.

Trigeminal neuralgia is the most common form of facial pain in those aged 50 years or more. It is thought to be of neuropathic origin, caused by demyelination or remyelination associated with damage to the roots or ganglia of the trigeminal axons.[28,29] The nerve fibers become overexcitable and trigger paroxysmal pain.[29] However, the molecular mechanisms of pain generation and transmission remain unclear. It has been suggested that inflammation may be in play. Demyelination of the root entrance regions of the primary sensory trigeminal afferents may trigger secretion of inflammatory factors.[30-32] Tumor necrosis factor-alpha, IL-6, IL-8, and IL-1β contribute to neural pain.[33-36] Inflammatory mediators, including prostaglandins, proinflammatory cytokines, and chemokines, directly induce pain by increasing the sensitivities of the nociceptors that serve as the primary sensory neurons perceiving noxious stimuli.[37-39] Some studies found that proinflammatory cytokines, including IL-1, IL-2, IL-6, IL-8, TNF, and interferon, produced during inflammation activate the nerve endings of polymodal nociceptors.[40-42] Studies that used animal models of TN found many macrophages and mast cells in trigeminal root regions undergoing focal demyelination.[43,44] Thus, there may be a very close relationship between inflammation and TN.

The CAR is a new marker that is prognostic of the severity of inflammation and mortality; it was first used to identify patients with severe disease.[45] In the literature, there are studies on CAR and many diseases that are known to play a role in the etiology of inflammation.[23,46,47] There are studies showing that CAR is a prognostic factor for cancer patients.[48,49] Moreover, CAR was associated with mortality in patients with antineutrophil cytoplasmic autoantibody-related vasculopathies[50] and was significantly increased and prognostic for patients with autoimmune diseases such as Crohn's disease, Behçet's disease, and Takayasu arteritis.[23,46,47] Olgun Yazar et al.[51] reported a significant difference in the CARs of patients with restless legs syndrome and controls; the CAR significantly increased with disease severity. In another study, no significant differences were found between patients with migraine and controls, but the CAR significantly increased during migraine attacks.[22] Our findings are consistent with previous reports; the CAR was significantly higher in TN patients than in controls, particularly in those with more pain attacks.

Few studies have investigated the relationship between TN and inflammation in the literature. Yao et al.[15] showed that the white blood cell, neutrophil, and monocyte counts, the neutrophil-to-lymphocyte ratio, and the monocyte-to-lymphocyte ratio were higher in the peripheral blood of TN patients compared to controls. It was suggested that these inflammatory markers might be risk factors for TN and that they played a predictive role in diagnosing TN. Ericson et al.[52] found that the levels of many proteins that affect the immune system, particularly TNF-beta, were elevated in the cerebrospinal fluid of TN patients after surgery compared to controls. Another study reported that the serum levels of IL-1β, IL-6, IL-8, and TNF-alpha in TN patients were significantly higher than those of controls and that IL-6 concentrations were positively correlated with TN severity.[53] We found that the CAR, a new inflammatory marker, was significantly higher in TN patients than in controls.

We found that the CAR levels achieved a diagnostic accuracy of 77.1% in TN. In our study, the sensitivity and specificity of the CAR ROC analysis for the distinction between control and patient were found to be 55.7% and 92%, respectively. Although we were aware that the diagnostic accuracy was not very high, no reports in the literature were found to compare our results. Therefore, we decided to present this paper as a contribution to the literature.

There are several limitations to our study. First, not all inflammatory biomarkers were evaluated in detail. In addition, this was a retrospective cross-sectional study with a rather low number of patients. Future prospective large-scale studies are required.

In conclusion, there was a significant relationship between TN, the etiology of which is still unclear, and CAR, an inflammatory marker. The CAR could be an inflammatory prognostic marker for TN etiology and disease severity. Additionally, this study contributed to the literature by investigating the effects of both inflammation and malnutrition using the CAR. It is thought that this study will provide a new perspective to the literature in this respect.

Ethics Committee Approval: The study protocol was approved by the İnönü University Faculty of Medicine Ethics Committee (date: 24.01.2023, no: 2023/4389). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Patient Consent for Publication: A written informed consent was obtained from each patient.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

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REFERENCES

1. Bista P, Imlach WL. Pathological mechanisms and therapeutic targets for trigeminal neuropathic pain. Medicines (Basel) 2019;6:91. doi: 10.3390/medicines6030091.
2. Jones MR, Urits I, Ehrhardt KP, Cefalu JN, Kendrick JB, Park DJ, et al. A comprehensive review of trigeminal neuralgia. Curr Pain Headache Rep 2019;23:74. doi: 10.1007/s11916-019-0810-0.
3. Gambeta E, Chichorro JG, Zamponi GW. Trigeminal neuralgia: An overview from pathophysiology to pharmacological treatments. Mol Pain 2020;16:1744806920901890. doi: 10.1177/1744806920901890.
4. Smyth P, Greenough G, Stommel E. Familial trigeminal neuralgia: Case reports and review of the literature. Headache 2003;43:910-5. doi: 10.1046/j.1526-4610.2003.03172.x.
5. Denu RA, Rosenberg SA, Howard SP. Familial trigeminal neuralgia treated with stereotactic radiosurgery: A case report and literature review. J Radiat Oncol 2017;6:149-52. doi: 10.1007/s13566-017-0300-0.
6. Bałkowiec-Iskra E. The role of immune system in inflammatory pain pathophysiology. Pol Merkur Lekarski 2010;29:395-9. Polish.
7. Flake NM, Gold MS. Inflammation alters sodium currents and excitability of temporomandibular joint afferents. Neurosci Lett 2005;384:294-9. doi: 10.1016/j.neulet.2005.04.091.
8. Vaughn AH, Gold MS. Ionic mechanisms underlying inflammatory mediator-induced sensitization of dural afferents. J Neurosci 2010;30:7878-88. doi: 10.1523/JNEUROSCI.6053-09.2010.
9. Sherkheli MA, Schreiner B, Haq R, Werner M, Hatt H. Borneol inhibits TRPA1, a proinflammatory and noxious pain-sensing cation channel. Pak J Pharm Sci 2015;28:1357-63.
10. Dauvergne C, Molet J, Reaux-Le Goazigo A, Mauborgne A, Mélik-Parsadaniantz S, Boucher Y, et al. Implication of the chemokine CCL2 in trigeminal nociception

and traumatic neuropathic orofacial pain. Eur J Pain 2014;18:360-75. doi: 10.1002/j.1532-2149.2013.00377.x.

11. Latrémolière A, Mauborgne A, Masson J, Bourgoin S, Kayser V, Hamon M, et al. Differential implication of proinflammatory cytokine interleukin-6 in the development of cephalic versus extracephalic neuropathic pain in rats. J Neurosci 2008;28:8489-501. doi: 10.1523/JNEUROSCI.2552-08.2008.
12. Lis K, Grygorowicz T, Cudna A, Szymkowski DE, Bałkowiec-Iskra E. Inhibition of TNF reduces mechanical orofacial hyperalgesia induced by Complete Freund's Adjuvant by a TRPV1-dependent mechanism in mice. Pharmacol Rep 2017;69:1380-5. doi: 10.1016/j.pharep.2017.05.013.
13. Nassini R, Materazzi S, Benemei S, Geppetti P. The TRPA1 channel in inflammatory and neuropathic pain and migraine. Rev Physiol Biochem Pharmacol 2014;167:1-43. doi: 10.1007/112_2014_18.
14. Coelho SC, Bastos-Pereira AL, Fraga D, Chichorro JG, Zampronio AR. Etanercept reduces thermal and mechanical orofacial hyperalgesia following inflammation and neuropathic injury. Eur J Pain 2014;18:957-67. doi: 10.1002/j.1532-2149.2013.00441.x.
15. Yao Y, Chang B, Li S. Relationship of inflammation with trigeminal neuralgia. J Craniofac Surg 2020;31:e110-3. doi: 10.1097/SCS.0000000000005879.
16. Kaplan M, Ates I, Akpinar MY, Yuksel M, Kuzu UB, Kacar S, et al. Predictive value of C-reactive protein/albumin ratio in acute pancreatitis. Hepatobiliary Pancreat Dis Int 2017;16:424-30. doi: 10.1016/S1499-3872(17)60007-9.
17. Ethemoglu O, Calik M. Effect of serum inflammatory markers on the prognosis of adult and pediatric patients with Guillain-Barré syndrome. Neuropsychiatr Dis Treat 2018;14:1255-60. doi: 10.2147/NDT.S162896.
18. Fanali G, di Masi A, Trezza V, Marino M, Fasano M, Ascenzi P. Human serum albumin: From bench to bedside. Mol Aspects Med 2012;33:209-90. doi: 10.1016/j.mam.2011.12.002.
19. Gabay C, Kushner I. Acute-phase proteins and other systemic responses to inflammation. N Engl J Med 1999;340:448-54. doi: 10.1056/NEJM199902113400607.
20. Borné Y, Fagerberg B, Persson M, Östling G, Söderholm M, Hedblad B, et al. Cadmium, carotid atherosclerosis, and incidence of ischemic stroke. J Am Heart Assoc 2017;6:e006415. doi: 10.1161/JAHA.117.006415.
21. Ning P, Yang B, Yang X, Huang H, Shen Q, Zhao Q, et al. Clinical value of C-reactive protein/albumin ratio in Guillain-Barré syndrome. Neurol Sci 2021;42:3275-83. doi: 10.1007/s10072-020-04930-4.
22. Yazar HO, Yazar T, Aygün A, Kaygisiz Ş, Kirbaş D. Evaluation of simple inflammatory blood parameters in patients with migraine. Ir J Med Sci 2020;189:677-83. doi: 10.1007/s11845-019-02136-y.
23. Qin G, Tu J, Liu L, Luo L, Wu J, Tao L, et al. Serum albumin and c-reactive protein/albumin ratio are useful biomarkers of Crohn's disease activity. Med Sci Monit 2016;22:4393-400. doi: 10.12659/msm.897460.
24. Park JE, Chung KS, Song JH, Kim SY, Kim EY, Jung JY, et al. The c-reactive protein/albumin ratio as a predictor of mortality in critically ill patients. J Clin Med 2018;7:333. doi: 10.3390/jcm7100333.
25. Ozdemir HH. Analysis of the albumin level, neutrophil-lymphocyte ratio, and platelet-lymphocyte ratio in Guillain-Barré syndrome. Arq Neuropsiquiatr 2016;74:718-22. doi: 10.1590/0004-282X20160132.
26. Akıl E, Bulut A, Kaplan İ, Özdemir HH, Arslan D, Aluçlu MU. The increase of carcinoembryonic antigen (CEA), high-sensitivity C-reactive protein, and neutrophil/lymphocyte ratio in Parkinson's disease. Neurol Sci 2015;36:423-8. doi: 10.1007/s10072-014-1976-1.
27. Headache Classification Committee of the International Headache Society (IHS) The International Classification of Headache Disorders, 3rd edition. Cephalalgia 2018;38:1-211. doi: 10.1177/0333102417738202.
28. Love S, Coakham HB. Trigeminal neuralgia: Pathology and pathogenesis. Brain 2001;124:2347-60. doi: 10.1093/brain/124.12.2347.
29. Devor M, Amir R, Rappaport ZH. Pathophysiology of trigeminal neuralgia: The ignition hypothesis. Clin J Pain 2002;18:4-13. doi: 10.1097/00002508-200201000-00002.
30. Obermann M, Yoon MS, Ese D, Maschke M, Kaube H, Diener HC, et al. Impaired trigeminal nociceptive processing in patients with trigeminal neuralgia. Neurology 2007;69:835-41. doi: 10.1212/01.wnl.0000269670.30045.6b.
31. Lutz J, Thon N, Stahl R, Lummel N, Tonn JC, Linn J, et al. Microstructural alterations in trigeminal neuralgia determined by diffusion tensor imaging are independent of symptom duration, severity, and type of neurovascular conflict. J Neurosurg 2016;124:823-30. doi: 10.3171/2015.2.JNS142587.
32. Rappaport ZH, Govrin-Lippmann R, Devor M. An electron-microscopic analysis of biopsy samples of the trigeminal root taken during microvascular decompressive surgery. Stereotact Funct Neurosurg 1997;68:182-6. doi: 10.1159/000099920.
33. Sommer C, Leinders M, Üçeyler N. Inflammation in the pathophysiology of neuropathic pain. Pain 2018;159:595-602. doi: 10.1097/j.pain.0000000000001122.
34. McMahon SB, Cafferty WB, Marchand F. Immune and glial cell factors as pain mediators and modulators. Exp Neurol 2005;192:444-62. doi: 10.1016/j.expneurol.2004.11.001.
35. Wei XH, Na XD, Liao GJ, Chen QY, Cui Y, Chen FY, et al. The up-regulation of IL-6 in DRG and spinal dorsal horn contributes to neuropathic pain following L5 ventral root transection. Exp Neurol 2013;241:159-68. doi: 10.1016/j.expneurol.2012.12.007.
36. Araki M, Matsuoka T, Miyamoto K, Kusunoki S, Okamoto T, Murata M, et al. Efficacy of the anti-IL-6 receptor antibody tocilizumab in neuromyelitis optica: A pilot study. Neurology 2014;82:1302-6. doi: 10.1212/WNL.0000000000000317.
37. Matsuda M, Huh Y, Ji RR. Roles of inflammation, neurogenic inflammation, and neuroinflammation in pain. J Anesth 2019;33:131-9. doi: 10.1007/s00540-018-2579-4.

38. Ji RR, Nackley A, Huh Y, Terrando N, Maixner W. Neuroinflammation and central sensitization in chronic and widespread pain. Anesthesiology 2018;129:343-66. doi: 10.1097/ALN.0000000000002130.
39. Julius D, Basbaum AI. Molecular mechanisms of nociception. Nature 2001;413:203-10. doi: 10.1038/35093019.
40. Zhao W, Wang Y, Fang Q, Wu J, Gao X, Liu H, et al. Changes in neurotrophic and inflammatory factors in the cerebrospinal fluid of patients with postherpetic neuralgia. Neurosci Lett 2017;637:108-13. doi: 10.1016/j.neulet.2016.11.041.
41. Hughes JP, Chessell I, Malamut R, Perkins M, Bačkonja M, Baron R, et al. Understanding chronic inflammatory and neuropathic pain. Ann N Y Acad Sci 2012;1255:30-44. doi: 10.1111/j.1749-6632.2012.06561.x.
42. Launay PS, Reboussin E, Liang H, Kessal K, Godefroy D, Rostene W, et al. Ocular inflammation induces trigeminal pain, peripheral and central neuroinflammatory mechanisms. Neurobiol Dis 2016;88:16-28. doi: 10.1016/j.nbd.2015.12.017.
43. Bennett GJ. Neuropathic pain in the orofacial region: Clinical and research challenges. J Orofac Pain 2004;18:281-6.
44. Anderson LC, Vakoula A, Veinote R. Inflammatory hypersensitivity in a rat model of trigeminal neuropathic pain. Arch Oral Biol 2003;48:161-9. doi: 10.1016/s0003-9969(02)00203-0.
45. Fairclough E, Cairns E, Hamilton J, Kelly C. Evaluation of a modified early warning system for acute medical admissions and comparison with C-reactive protein/albumin ratio as a predictor of patient outcome. Clin Med (Lond) 2009;9:30-3. doi: 10.7861/clinmedicine.9-1-30.
46. Kim M, Park YG, Park YH. C-reactive protein/albumin ratio as an indicator of disease activity in Behçet's disease and human leukocyte antigen-B27-associated uveitis. Graefes Arch Clin Exp Ophthalmol 2021;259:1985-92. doi: 10.1007/s00417-021-05207-y.
47. Seringec Akkececi N, Yildirim Cetin G, Gogebakan H, Acipayam C. The c-reactive protein/albumin ratio and complete blood count parameters as indicators of disease activity in patients with Takayasu arteritis. Med Sci Monit 2019;25:1401-9. doi: 10.12659/MSM.912495.
48. Kinoshita A, Onoda H, Imai N, Iwaku A, Oishi M, Tanaka K, et al. The C-reactive protein/albumin ratio, a novel inflammation-based prognostic score, predicts outcomes in patients with hepatocellular carcinoma. Ann Surg Oncol 2015;22:803-10. doi: 10.1245/s10434-014-4048-0.
49. Wei XL, Wang FH, Zhang DS, Qiu MZ, Ren C, Jin Y, et al. A novel inflammation-based prognostic score in esophageal squamous cell carcinoma: The C-reactive protein/albumin ratio. BMC Cancer 2015;15:350. doi: 10.1186/s12885-015-1379-6.
50. Best WR, Becktel JM, Singleton JW, Kern F Jr. Development of a Crohn's disease activity index. National Cooperative Crohn's Disease Study. Gastroenterology 1976;70:439-44.
51. Olgun Yazar H, Yazar T, Özdemir S, Kasko Arici Y. Serum C-reactive protein/albumin ratio and restless legs syndrome. Sleep Med 2019;58:61-5. doi: 10.1016/j.sleep.2019.02.022.
52. Ericson H, Abu Hamdeh S, Freyhult E, Stiger F, Bäckryd E, Svenningsson A, et al. Cerebrospinal fluid biomarkers of inflammation in trigeminal neuralgia patients operated with microvascular decompression. Pain 2019;160:2603-11. doi: 10.1097/j.pain.0000000000001649.
53. Liu MX, Zhong J, Xia L, Dou NN, Li ST. A correlative analysis between inflammatory cytokines and trigeminal neuralgia or hemifacial spasm. Neurol Res 2019;41:335-40. doi: 10.1080/01616412.2018.1564188.