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# Clinical Significance of MRI Contrast Enhancement of the Oculomotor Nerve in Ischemic Isolated Oculomotor Nerve Palsy

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**Background and Purpose** Contrast enhancement of the oculomotor nerve in MRI was recently noticed in patients with clinical ischemic isolated oculomotor nerve palsy (iIONP). The opinions about whether this is a sign of inflammation and whether or not to administer steroids vary between doctors. The study aimed to determine the associations between this enhancement and vascular-disease risk factors (VRFs) and inflammatory factors in iIONP patients.

**Methods** The study recruited patients who had experienced iIONP during the previous 2 years. They were divided into groups A and B based on whether or not they exhibited an enhanced oculomotor nerve in MRI of the cavernous sinus using thin-section, fat-suppressed, and contrast-enhanced sequences. VRFs, inflammatory factors, and improvement scores were compared between the two groups.

**Results** Most (71.1%) of the 45 included iIONP patients had enhanced oculomotor nerves in MRI. VRFs, periorbital pain, elevated C-reactive protein and erythrocyte sedimentation rate, the neutrophil-to-lymphocyte ratio, and the platelet-to-lymphocyte ratio were not significantly associated with the enhancement. Four of the five patients in group A exhibited an elevated cerebrospinal fluid (CSF) IgG synthesis rate. The improvement score of eight patients who received 80 mg of methylprednisolone in addition to the routine therapy was not significantly different from the scores of the other patients ($p$=0.485).

**Conclusions** More than half of the iIONP patients had an enhanced oculomotor nerve in MRI. A few of them also had elevated CSF IgG synthesis rate, but no further evidence for inflammation was found. The administration of steroids seemed to have no benefit other than increasing the blood glucose level.

**Key Words** oculomotor nerve palsy, neuroimaging, ischemia, inflammation.

## INTRODUCTION

The oculomotor nerve (cranial nerve III) arises from the midbrain and divides into two branches after entering the orbit. This nerve innervates the eye muscles to enable the eye to move inward, upward, and downward. It can also raise the eyelid and control pupillary constriction and accommodation. Damage to the oculomotor nerve can therefore result in complex clinical symptoms and signs.

Isolated oculomotor nerve palsy (IONP) is a condition in which only the oculomotor nerve is affected, and there are no associated or localizing neurological symptoms or signs, with periorbital pain either being present or absent. The main causes of acquired IONP—which includes the third, fourth, and sixth cranial nerves—are microvascular ischemia and inflammatory disorders in adults. The other causes are categorized into aneurysm, stroke,

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trauma, neoplasm, carotid cavernous fistula, undetermined, and others.[1-4]

Microvascular ischemic IONP (iIONP) is diagnosed based on clinical presumption. It has been assigned frequently in patients aged ≥50 years with certain vascular-disease risk factors (VRFs), whose MRI brain scan and laboratory tests did not reveal an alternative cause, and whose symptoms and signs often resolved spontaneously within 3 months.[1,2,5-8]

However, we have found contrast enhancement of the oculomotor nerve in MRI of the cavernous sinus in most iIONP patients, while brain MRI of these patients has produced normal findings. In 2013, Tamhankar et al.[2] similarly found enhancement of the oculomotor nerve in one of their IONP patients, but the clinical significance of the enhancement was not explained.

The present retrospective study was performed to reassess clinically iIONP patients and investigate the associations with the enhancement of the oculomotor nerves, VRFs, and inflammatory factors. We estimated the effects of steroids on patients with enhanced oculomotor nerves.

## METHODS

The study recruited all of the patients who were discharged with a recorded diagnosis of 'ischemic oculomotor nerve palsy' or 'diabetic oculomotor nerve palsy' in the neurology department of our hospital from 2017 to 2019. We excluded patients who 1) had definite autoimmune diseases, such as connective-tissue disease, 2) did not recover within 3 months, as determined in telephone follow-ups, 3) were lost to follow-up, or 4) had incomplete data. We finally enrolled 45 IONP patients who had no prior history of orbital diseases, congenital oculomotor palsy, cranial trauma, brainstem infarction, nuclear or supranuclear disorders, aneurysm, intracranial space-occupying lesion, neuromuscular junction disorders, or Miller-Fisher syndrome during the hospitalization period.

The VRFs were defined as aged ≥65 years, diabetes mellitus (DM), hypertension, atherosclerosis, previous stroke or myocardial infarction, coronary artery disease, and smoking. The total VRF score was calculated for each patient based on each of the above terms counting as 1 point, except for the age term scored as 2 points if the age was >75 years.

The inflammatory factors investigated in this study were periorbital pain, elevated C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR), the neutrophil-to-lymphocyte ratio (NLR), and the platelet-to-lymphocyte ratio (PLR). The cerebrospinal fluid (CSF) IgG synthesis rate and oligoclonal bands of patients who received lumbar punctures were also recorded.

All of the MRI images of the brain and cavernous sinus of these patients were read again by experts of radiology and neurology to reconfirm the results. The main MRI sequences for the cavernous sinus[9] were thin-section, fat-suppressed, T1-weighted sequences in the axial and coronal planes after intravenously injecting gadolinium-based contrast material. The section thickness was 3 mm. Different imaging manifestations of the oculomotor nerve between the left and right sides could indicate the presence of pathological changes.

Eight of the 45 patients received methylprednisolone therapy. All patients were treated with methylcobalamin or adenosine cobalamin, aspirin, and statin. Their blood pressure and glucose levels had also been controlled.

To assess the effects of steroids, we scored the degree of oculomotor nerve palsy in all patients on the first and last hospital days according to the physical examination records and the Ocular Motor Nerve Palsy Scale.[10] The difference in the scores on the two days corresponded to the improvement score for each patient. The score was obtained using the five assessment items. Because of the lack of data for maximum deviation angle, diplopia was dichotomized into two levels: presence and absence. The other items had three to five levels based on the degrees of inward, upward, and downward eye movements, the size of the eyelid fissure, the size of the pupil, and the sensitivity of the pupillary light reflex.

Appropriate descriptive statistics, Mann-Whitney tests, and Kruskal-Wallis tests were applied using the Statistical Package for the Social Sciences (version 24 IBM Corp., Armonk, NY, USA), with $p<0.05$ considered significant.

The study was performed in accordance with the ethical standards of the ethics committee of Beijing Tongren Hospital of Capital Medical University (Institutional Review Board number: TRECKY2020-112) and with the 1964 Helsinki Declaration and its amendments or comparable ethical standards.

## RESULTS

The 45 patients included in this study comprised 35 males (77.8%) and 10 females (22.2%) aged 63.07±11.47 years (mean±standard deviation), with 23 (51.3%) of the patients being older than 65 years. The oculomotor nerves were enhanced in MRI images of the cavernous sinus in 32 (71.1%) patients (Fig. 1), who were allocated to group A, while group B comprised those patients without oculomotor nerve enhancement.

DM was present in 36 (80.0%) of the patients: 27 (84.4%) patients in group A and 9 (69.2%) patients in group B. However, no significant difference was found after applying continuity correction in the chi-square test ($p=0.459$). The prevalence of atherosclerosis (68.9%), hypertension (60.0%), and

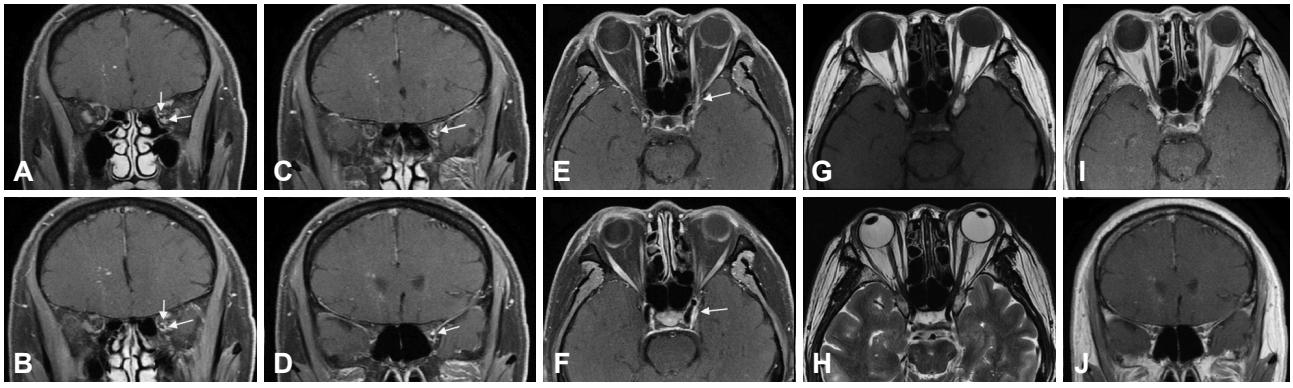


**Fig. 1.** The oculomotor nerve in MRI. Enhancement of the oculomotor nerve in MRI of the cavernous sinus (A–F). The inferior branch of the oculomotor nerve with its internal rectus and inferior rectus ends was enhanced (A and B). It was difficult to find the lesion in an T1-weighted sequence (G), T2-weighted sequence (H), and contrast-enhanced sequences without fat suppression (I and J).

smoking (44.4%) were lower than DM, while fewer of the patients had previous stroke or myocardial infarction (20%) or coronary artery disease (6.7%). The prevalence rates of these conditions did not differ significantly between the two groups (Table 1).

The total VRF score, fasting plasma glucose, and glycohemoglobin level were also compared between the two groups, which did not reveal any significant correlation between these factors and the enhancement of the third nerve in Mann-Whitney tests ($p$=0.837, 0.745, and 0.224, respectively) (Table 2).

Six inflammatory factors were collected. We found that periorbital pain was more common in group A (78.1%, $p$=0.081), which was similar to the finding of Tamhankar et al.[2] Most of the CRP levels were normal in both groups. The proportion of patients with an elevated ESR was 46.2% in group B and 15.6% in group A, but this difference was not significant ($p$=0.076). Lumbar puncture was applied to five patients in group A, which revealed slight elevations in CSF protein and IgG synthesis rate in four of them. Their CSF pressures, cell counts, and microbiology-test findings were normal, and none of them had positivity for oligoclonal bands or for serum antiganglioside antibodies. The NLR, which is a new inflammation marker, was 1.91±1.63 in group A and 2.03±1.45 in group B ($p$=0.679), while the PLR was marginally higher in group A than in group B ($p$=0.540) (Table 3). The absolute levels of neutrophils, lymphocytes, and platelets were 3.93±1.40×$10^9$/L, 2.29±0.66×$10^9$/L, and 208.59±56.95×$10^9$/L, respectively, in group A and 3.80±1.62×$10^9$/L, 2.24±0.94×$10^9$/L, and 186.08±52.20×$10^9$/L, respectively, in group B. There were also no significant intergroup differences in these parameters.

Eight patients in group A received 80 mg of methylprednisolone in addition to the routine therapy. Their median admission score for the degree of oculomotor nerve palsy was 7.5 [interquartile range (IQR)=5.8], and this did not differ significantly from those who only received the routine therapy in group A (median=8.0, IQR=5.5) and group B (median=8.0, IQR=7.5) ($p$=0.610). The condition of most of the patients improved when they were discharged. The median improve-

**Table 1.** Distribution of patients with each VRF in groups A and B

| VRF | Group A ($n$=32) | Group B ($n$=13) |
|---|---|---|
| Age ≥65 years | 17 (53.1) | 6 (46.2) |
| Diabetes mellitus | 27 (84.4) | 9 (69.2) |
| Hypertension | 19 (59.4) | 8 (61.5) |
| Atherosclerosis | 21 (65.6) | 10 (76.9) |
| Previous stroke or myocardial infarction | 7 (21.9) | 2 (15.4) |
| Coronary artery disease | 2 (6.3) | 1 (7.7) |
| Smoking | 14 (43.8) | 6 (46.2) |

Data are $n$ (%) values.
VRF: vascular-disease risk factor.

**Table 2.** Differences in VRFs between the two groups

| VRF | Group A | Group B | $p$ |
|---|---|---|---|
| Fasting plasma glucose | 6.0 [2.2] | 5.7 [3.2] | 0.745 |
| Glycohemoglobin level | 7.4 [2.4] | 6.9 [2.7] | 0.224 |
| Total VRF score | 3.0 [2.5] | 3.0 [2.5] | 0.837 |

Data are median [interquartile range] values.
VRF: vascular-disease risk factor.

**Table 3.** Comparison of inflammatory factors between the two groups

| Inflammatory factor | Group A | Group B | $p$ |
|---|---|---|---|
| Periorbital pain | 25 (78.1) | 6 (46.2) | 0.081* |
| Elevated CRP | 4 (12.5) | 1 (7.7) | 1.000* |
| Elevated ESR | 5 (15.6) | 6 (46.2) | 0.076* |
| Elevated IgG synthesis rate | 4/5 | - | |
| NLR | 1.6 [0.9] | 1.5 [1.4] | 0.679† |
| PLR | 94.3 [45.7] | 94.8 [86.7] | 0.540† |

Data are n, $n$ (%), or median [interquartile range] values.
*chi-square test, †Mann-Whitney test.
CRP: C-reactive protein, ESR: erythrocyte sedimentation rate, NLR: neutrophil-to-lymphocyte ratio, PLR: platelet-to-lymphocyte ratio.

ment score of the eight patients in group A who received 80 mg of methylprednisolone was 3.5 (IQR=4.6), and for the other patients in group A and the patients in group B, they were 2.5 (IQR=3.0) and 2.0 (IQR=3.0) respectively. However, there was no significant difference according to the Kruskal-Wallis test ($p$=0.485) (Fig. 2).

## DISCUSSION

Studies have shown that microvascular ischemia is the most common cause of the acute IONP, and found that the brain MRI scans of the iIONP patients are normal. MRI of the cavernous sinus using thin-section, fat-suppressed, T1-weighted sequences and contrast-enhanced sequences could clearly reveal the oculomotor nerve.[9] Most (71.1%) of the patients who were diagnosed as iIONP had enhancement of the third nerve in MRI of the cavernous sinus. We also read the MRI images of 48 patients with abductor nerve palsy and 18 with trochlear nerve palsy who were hospitalized during the same period, and only 1 of them had an enhanced oculomotor nerve at the same time.

The clinical significance of gadolinium enhancement of the oculomotor nerve in iIONP patients has not been reported previously. Only three autopsies of diabetic oculomotor palsy patient had been reported previously. In 1970, Weber et al.[11] reported on an autopsy of a patient with presumed diabetic oculomotor palsy. The lesion was found in the subarachnoid portion of the nerve, and was associated with a significant reduction in myelin staining, milder injury of the axons, and hyaline thickening of the vasa nervorum. The other two previous autopsies of the oculomotor nerve performed by Dreyfus et al.[12] and Asbury et al.[13] both found injury in the intracavernous portion of the nerve, and the pathologies were similar to those found by Weber et al.[11] that suggested chronic vascular changes. However, there was no description of inflammatory cells.

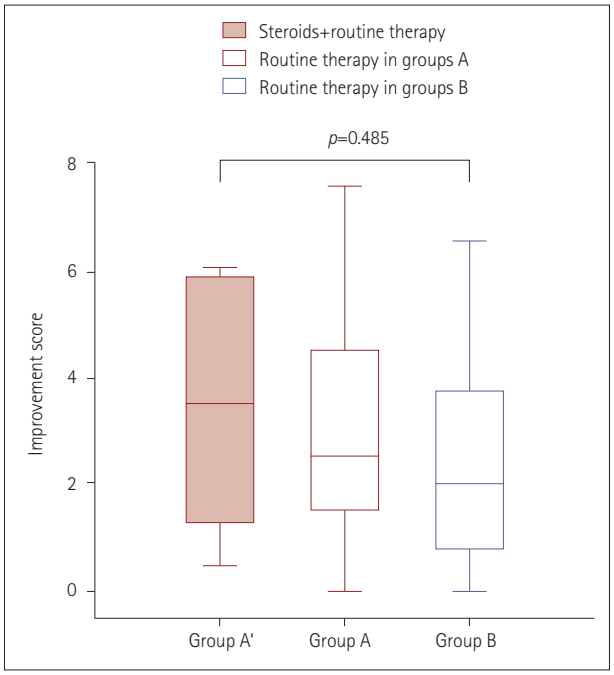


**Fig. 2.** Improvement scores in different groups with different therapies. The improvement score of the eight patients who received 80 mg of methylprednisolone in addition to the routine therapy appeared to be higher than the scores of the other patients who received routine therapy in groups A and B ($p$=0.485). Each box plot shows the median, first and third quartiles, and range.

All of the present patients had VRFs and 80.0% of them had DM. The total VRF score, fasting plasma glucose, and glycohemoglobin level did not differ significantly between the two groups. It appears that ischemic exposure might not be a critical factor in the formation of the enhancement, which has also been found in diabetic lumbosacral radiculoplexus neuropathy (DLRPN).[14,15] However, MRI of the lumbosacral plexus in DLRPN patients revealed inflammation within bilateral sciatic and femoral nerves, with a T2 signal without enhancement.[16] Some studies have also found that the early application of immunosuppression may hasten recovery and improve symptoms.[17] The pathology of DLRPN was typical of that of ischemic injury due to microvasculitis.[14]

The good prognosis of the disease and the importance of the nerve meant that we did not obtain pathological results. Instead, we used six inflammation biomarkers to explore whether microvasculitis or inflammation played an important role in the observed enhancement. The periorbital pain was not correlated with the enhancement in this study, but we did notice that patients with enhanced oculomotor nerve had worse and longer-lasting pain. Future research should investigate whether the degree and duration of periorbital pain is a significant indicator of inflammation.

The CRP level was normal in most of the patients in this study, which differs from classical inflammatory and infectious diseases. The proportion of patients with an elevated ESR did not differ significantly between the two groups. Three of the 11 patients with an elevated ESR had microalbumin in their urine. Considering that the ESR can also be elevated in DM, nephrotic syndrome, and hypercholesterolemia, metabolic disorders may play an important role in increasing the ESR in iIONP patients.

The NLR and PLR have been used as new inflammatory factors in recent years.[18] An elevated NLR is associated with the functional immune status of chronic inflammation, and may be an independent risk factor for diabetic peripheral neuropathy[19] and nonarteritic anterior ischemic optic neuropathy.[20] The PLR denotes the presence of inflammation in cardiovascular disease[21] and many inflammatory disease and

cancers, such as Behçet's disease[22] and endometrial carcinoma.[23] A high neutrophil value is a marker of a nonspecific inflammatory process, while a low lymphocyte value indicates inadequate immune regulation.[24] The present study found that the NLR, PLR, and numbers of neutrophils, lymphocytes, and platelets were not significantly associated with the enhancement of the oculomotor nerve.

Four out of five patients had an elevated CSF IgG synthesis rate and negativity for oligoclonal bands. The elevated synthesis of CSF IgG was probably associated with the damaged oculomotor nerve, since this nerve travels through the brain cisterns before reaching the cavernous sinus. Lesions in different sections of the nerve may lead to different results for the CSF IgG synthesis rate.

The eight patients who received 80 mg of methylprednisolone in addition to the routine therapy showed numerically higher improvement scores, but the difference was not statistically significant. These patients also should fluctuations in their blood glucose levels.

No significant inflammatory factors were found. However, the enhancement in MRI (which differed from diabetic neuropathy), the elevated CSF IgG synthesis rate, and the higher improvement scores with steroid treatment might be indicators of inflammation. Inflammation is a cardinal pathogenic mechanism underlying diabetic neuropathy and atherosclerosis that involves many inflammatory molecules and pathways such as inflammatory cytokines, adhesion molecules, chemokines, and nuclear factor kappa B.[25-27] The inflammation associated with iIONP is probably of low grade, and the lesion is confined to the unilateral oculomotor nerve. Future studies should attempt to identify more-sensitive inflammation biomarkers and pathologies for detecting iIONP.

Finally, it is worth considering the disease from another viewpoint. Many doctors will consider Tolosa-Hunt syndrome (THS) as an alternative diagnosis in a patient presenting with acute oculomotor nerve palsy and periocular pain. According to the International Classification of Headache Disorders-3,[28] the diagnosis of THS requires the presence of granulomatous inflammation in MRI or a biopsy. However, some cases are clinically diagnosed as THS with normal MRI findings, which have been named as benign THS. The border between diabetic ophthalmoplegia and THS with DM remains unclear.[29,30] The pathological mechanism is used the basis for diagnosing and treating, and it is possible that iIONP and THS are two sides of the same cause—this suggests that it is time to stop considering THS.[31]

## Author Contributions

Conceptualization: Yan Yang, Chuntao Lai, Jiawei Wang. Data curation: Yan Yang, Fei Yan, Chuntao Lai. Formal analysis: Yan Yang, Jiawei Wang. Funding acquisition: Jiawei Wang. Investigation: Yan Yang. Methodology: Yan Yang, Jiawei Wang. Supervision: Jiawei Wang. Writing—original draft: Yan Yang. Writing—review & editing: all authors.

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## Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

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## REFERENCES

1. Choi KD, Choi SY, Kim JS, Choi JH, Yang TH, Oh SY, et al. Acquired ocular motor nerve palsy in neurology clinics: a prospective multicenter study. *J Clin Neurol* 2019;15:221-227.
2. Tamhankar MA, Biousse V, Ying GS, Prasad S, Subramanian PS, Lee MS, et al. Isolated third, fourth, and sixth cranial nerve palsies from presumed microvascular versus other causes: a prospective study. *Ophthalmology* 2013;120:2264-2269.
3. Richards BW, Jones FR Jr, Younge BR. Causes and prognosis in 4,278 cases of paralysis of the oculomotor, trochlear, and abducens cranial nerves. *Am J Ophthalmol* 1992;113:489-496.
4. Pineles SL, Velez FG. Isolated ocular motor nerve palsies. *J Binocul Vis Ocul Motil* 2018;68:70-77.
5. Kung NH, Van Stavern GP. Isolated ocular motor nerve palsies. *Semin Neurol* 2015;35:539-548.
6. Chou KL, Galetta SL, Liu GT, Volpe NJ, Bennett JL, Asbury AK, et al. Acute ocular motor mononeuropathies: prospective study of the roles of neuroimaging and clinical assessment. *J Neurol Sci* 2004;219:35-39.
7. Tamhankar MA, Volpe NJ. Management of acute cranial nerve 3, 4 and 6 palsies: role of neuroimaging. *Curr Opin Ophthalmol* 2015;26:464-468.
8. Murchison AP, Gilbert ME, Savino PJ. Neuroimaging and acute ocular motor mononeuropathies: a prospective study. *Arch Ophthalmol* 2011;129:301-305.
9. Mahalingam HV, Mani SE, Patel B, Prabhu K, Alexander M, Fatterpekar GM, et al. Imaging spectrum of cavernous sinus lesions with histopathologic correlation. *Radiographics* 2019;39:795-819.
10. Zhou LY, Su C, Liu TJ, Li XM. Validity and reliability of the Ocular Motor Nerve Palsy Scale. *Neural Regen Res* 2018;13:1851-1856.
11. Weber RB, Daroff RB, Mackey EA. Pathology of oculomotor nerve palsy in diabetics. *Neurology* 1970;20:835-838.
12. Dreyfus PM, Hakim S, Adms RD. Diabetic ophthalmoplegia; report of case, with postmortem study and comments on vascular supply of human oculomotor nerve. *AMA Arch Neurol Psychiatry* 1957;77:337-349.
13. Asbury AK, Aldredge H, Hershberg R, Fisher CM. Oculomotor palsy in diabetes mellitus: a clinico-pathological study. *Brain* 1970;93:555-566.
14. Laughlin RS, Dyck PJ. Diabetic radiculoplexus neuropathies. *Handb Clin Neurol* 2014;126:45-52.
15. Greenberg JS, Singh J, Falcon N. Evaluation and rehabilitation of a patient with diabetic lumbosacral radiculoplexus neuropathy. *PM R* 2009;1:774-777.
16. McCormack EP, Alam M, Erickson NJ, Cherrick AA, Powell E, Sherman JH. Use of MRI in diabetic lumbosacral radiculoplexus neuropathy: case report and review of the literature. *Acta Neurochir (Wien)* 2018;160:2225-2227.
17. López Ruiz R, Quintas Gutiérrez S, Zapata-Wainberg G. Diabetic lumbosacral radiculoplexus neuropathy succesfully treated with in-

travenous immunoglobulins. *Med Clin (Barc)* 2018;150:452-453.
18. Balta S, Celik T, Mikhailidis DP, Ozturk C, Demirkol S, Aparci M, et al. The relation between atherosclerosis and the neutrophil-lymphocyte ratio. *Clin Appl Thromb Hemost* 2016;22:405-411.
19. Xu T, Weng Z, Pei C, Yu S, Chen Y, Guo W, et al. The relationship between neutrophil-to-lymphocyte ratio and diabetic peripheral neuropathy in Type 2 diabetes mellitus. *Medicine (Baltimore)* 2017;96:e8289.
20. Inanc M, Tekin K, Budakoglu O, Ilhan B, Aydemir O, Yilmazbas P. Could platelet indices and neutrophil to lymphocyte ratio be new biomarkers for differentiation of arteritic anterior ischemic neuropathy from non-arteritic type? *Neuroophthalmology* 2018;42:287-294.
21. Koseoglu HI, Altunkas F, Kanbay A, Doruk S, Etikan I, Demir O. Platelet-lymphocyte ratio is an independent predictor for cardiovascular disease in obstructive sleep apnea syndrome. *J Thromb Thrombolysis* 2015;39:179-185.
22. Hammad M, Shehata OZ, Abdel-Latif SM, El-Din AMM. Neutrophil/lymphocyte ratio and platelet/lymphocyte ratio in Behçet's disease: which and when to use? *Clin Rheumatol* 2018;37:2811-2817.
23. Pergialiotis V, Oikonomou M, Damaskou V, Kalantzis D, Chrelias C, Tsantes AE, et al. Platelet to lymphocyte and neutrophil to lymphocyte ratio as predictive indices of endometrial carcinoma: findings from a retrospective series of patients and meta-analysis. *J Gynecol Obstet Hum Reprod* 2018;47:511-516.
24. Azab B, Daoud J, Naeem FB, Nasr R, Ross J, Ghimire P, et al. Neutrophil-to-lymphocyte ratio as a predictor of worsening renal function in diabetic patients (3-year follow-up study). *Ren Fail* 2012;34:571-576.
25. Zhou J, Zhou S. Inflammation: therapeutic targets for diabetic neuropathy. *Mol Neurobiol* 2014;49:536-546.
26. Pop-Busui R, Ang L, Holmes C, Gallagher K, Feldman EL. Inflammation as a therapeutic target for diabetic neuropathies. *Curr Diab Rep* 2016;16:29.
27. Zhu Y, Xian X, Wang Z, Bi Y, Chen Q, Han X, et al. Research progress on the relationship between atherosclerosis and inflammation. *Biomolecules* 2018;8:80.
28. Headache Classification Committee of the International Headache Society (IHS) The International Classification of Headache Disorders, 3rd edition. *Cephalalgia* 2018;38:1-211.
29. Hamada K, Sakurai Y, Sugimoto I. Recurrent painful ophthalmoplegia in a patient with diabetes mellitus: is ophthalmoplegia associated with diabetes mellitus? *Cephalalgia* 2016;36:1397-1398.
30. Mullen E, Green M, Hersh E, Iloreta AM, Bederson J, Shrivastava R. Tolosa-Hunt syndrome: appraising the ICHD-3 beta diagnostic criteria. *Cephalalgia* 2018;38:1696-1700.
31. Lueck CJ. Time to retire the Tolosa-Hunt syndrome? *Pract Neurol* 2018;18:350-351.