DOI:10.14744/bej.2023.09815
Beyoglu Eye J 2024; 9(1): 8-13

Original Article

Understanding the Etiopathogenesis of Non-Arteritic Anterior Ischemic Optic Neuropathy with Laboratory Findings

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Abstract

Objectives: The role of inflammation and hemostasis in non-arteritic anterior ischemic optic neuropathy (NAION) was investigated by examining related blood tests. The predictive values of these laboratory indicators and their effects on prognosis were reviewed.

Methods: In this study, 48 patients diagnosed with NAION and 50 healthy volunteers were included. All subjects underwent full ophthalmological examination. All patients were treated with oral corticosteroids (methylprednisolone 1 mg/kg/day) for 15 days after that corticosteroid medication was reduced and stopped. Each patient was monitored at least for 12 months. The mean platelet volume (MPV), platelet distribution width (PDW), neutrophil/lymphocyte ratio (NLR), and red cell distribution width (RDW) values were recorded. These findings were compared with control group.

Results: The mean MPV, RDW, and NLR values were significantly higher in NAION group (respectively, $p<0.001$, $p=0.006$, and $p<0.001$). There was no statistically significant difference between group 1 and group 2 in PDW values, but the mean PDW value was higher in the patient group compared to the control group ($p=0.435$). Based on the receiver operating characteristic (ROC) curve, the NLR had the strongest predictive value. This was followed by MPV, RDW, and PDW with lower diagnostic predictive values.

Conclusion: MPV, NLR, and RDW were found to be elevated and have diagnostic predictive values in NAION patients. Easily accessible and simple laboratory methods could help us show systemic inflammation and ischemic events in NAION patients. As a result, inflammatory reactions besides ischemic changes may play a role in the etiopathogenesis of NAION. These biomarkers can be evaluated to ensure that patients with risk factors for the development of NAION.

Keywords: Mean platelet volume, neutrophil/lymphocyte ratio, non-arteritic ischemic optic neuropathy, platelet distribution width, red cell distribution width.

Introduction

Non-arteritic anterior ischemic optic neuropathy (NAION) is one of the most common causes of sudden, painless, permanent vision loss in the middle-aged and elderly population. NAION is a multifactorial disease and many risk factors may play a role in its development (1,2). The pathogenesis of this condition is unknown but acute ischemia of the optic nerve head is generally accepted in the pathogenesis of NAION (3,4).

Systemic diseases such as diabetes mellitus, hypertension,

How to cite this article: Kutlu Uzakgider N, Karaca Adiyeke S, Aytogan H. Understanding the Etiopathogenesis of Non-Arteritic Anterior Ischemic Optic Neuropathy with Laboratory Findings. Beyoglu Eye J 2024; 9(1): 8-13.

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Submitted Date: March 21, 2023 **Revised Date:** December 04, 2023 **Accepted Date:** December 10, 2023 **Available Online Date:** March 01, 2024

Beyoglu Eye Training and Research Hospital - Available online at www.beyoglueye.com

nocturnal arterial hypotension, ischemic heart disease, cerebrovascular events, and atherosclerosis constitute the main risk factors for circulatory insufficiency (4-6). Optic nerve damage is believed to be caused by an initial ischemic event. Moreover, there is evidence that secondary inflammation at the site of the ischemia may contribute to or produce greater visual loss (7-9).

The importance of mean platelet volume (MPV), platelet distribution width (PDW), neutrophil/lymphocyte ratio (NLR), and red cell distribution width (RDW) were determined in studies to investigate inflammation, oxidative stress, and platelet function in the etiopathogenesis of various diseases (10-12). Factors related to inflammation and platelet function also play an important role in the etiopathogenesis of NAION (13-18).

The role of hemostasis and inflammation in the pathogenesis of NAION was aimed to be clarified by these tests. In this study, the changes in MPV, PDW, RDW, and NLR values, which are important indicators for inflammation and platelet functions, were investigated in NAION cases. In addition, the predictive values of these tests were examined. It was desired to investigate whether these biomarkers can provide a prediction about the prognosis of the disease.

Methods

Study Design and Population

Records of the 117 patients admitted with NAION in our clinic between the years 2009 and 2017 were reviewed retrospectively. The study included 48 patients diagnosed with NAION (Group 1) whose blood samples were received before treatment and randomly selected 50 healthy volunteers (Group 2). Both groups were age and sex matched.

NAION was diagnosed with the presence of the following: Sudden onset of painless vision loss, relative afferent pupillary defect, visual-field defects consistent with optic neuropathy, characteristic fundus changes (swollen and pale peripapillary flame-shaped hemorrhage), and a lack of clinical findings suggesting any other diseases.

Using the clinical and laboratory findings, the diagnosis of arteritic ischemic optic neuropathy (AION) was excluded. Patients who were admitted to our center at <1 week after the onset of vision reduction were included.

Patients were excluded who had an uncontrolled systemic disease such as diabetes mellitus, hypertension, or anemia; a refractive error greater than 5.0 diopters (D) of spherical equivalent or 3.0 D of astigmatism; or previous surgery for ocular pathology. Patients with chronic heart disease, coronary artery disease, liver failure, renal failure, malignancy, infective diseases, anticoagulant or antiplatelet agents use, or smoking were also excluded. In addition, patients with ocular pathologies such as corneal scarring, retinal diseases, cataracts, or amblyopia that could affect best-corrected visual acuity (BCVA) were not included in the study.

All subjects underwent full ophthalmological examination including best-corrected visual acuity (BCVA), relative afferent pupillary defect, slit lamp, and fundus examination. All patients were treated with oral corticosteroids (methylprednisolone 1 mg/kg per day) for 15 days after that corticosteroid medication was reduced and stopped. Each patient was monitored at least for 12 months.

The study was conducted in accordance with the ethical standards of the Declaration of Helsinki and was approved by Tepecik Training and Research Hospital Institutional Local Ethics Committee (Date: 13.07.2017, No: 2017/5). The investigator obtained the informed consent of the participants to collect the data. The researchers assessed detailed medical histories of all cases and recorded demographic data including age, past medical history, sex, smoking status, and systemic and/or topical drug use.

Laboratory Tests

Peripheral blood samples were drawn from the antecubital vein. The samples were collected with minimal stasis, drawn into ethylenediamine tetraacetic acid (EDTA) vacutainer tubes, and studied within 1 h as standard clinical care to prevent in vitro platelet activation. The MPV, PDW, and RDW values were recorded from the patient's medical records. Neutrophil and lymphocyte counts were also considered to calculate the NLR.

Statistical Analysis

The data obtained from the study were entered into the database created in the IBM SPSS Statistics 20 program and statistical analysis was performed with the same program. The continuous variables' median, minimum, and maximum values are presented. The suitability of these variables for normal distribution was investigated. The normal distribution relationship between the groups was evaluated using the Kolmogorov–Smirnov and Shapiro–Wilk tests. The MPV, RDW, PDV, and NLR were evaluated with the Mann–Whitney U test. If the "p" value was less than 0.05, the difference between the groups was considered statistically significant.

Correlation analyses were evaluated by the Pearson test in normal distribution data and the Spearman test in non-normally distribution data.

A receiver operating characteristic analysis was performed to evaluate the diagnostic decision-making features of serum MPV, NLR, RDW, and PDW values in prediction. Sensitivity and specificity were calculated by measuring a cutoff threshold with the case series in this study. In the evaluation

of the area under the curve, the cases with 5% below the type 1 error level were interpreted to be statistically significant. Meanwhile, the differences in the areas under the curve (AUCs) were assessed using non-parametric methods for a comparison of the ROC curves. A $p<0.05$ was considered to be statistically significant in the comparisons.

Results

In this study, 48 patients (23 females and 25 males) in the NAION group and 50 healthy subjects (24 females and 26 males) in the control group were included. The mean age of the individuals in the NAION group was 59.25±9.68 years (range 45–75 years), and the mean age of the control group was 58.26±9.25 years (range 45–85 years). There was no statistically significant difference between the two groups in terms of age (p=0.08). The mean follow-up period was 24.1±20 (12–107) months.

The mean intraocular pressure (IOP) of the affected eyes of the patients was 15.98±2.56 mmHg and the mean IOP of the control group was 15.94±3.01 mmHg. There was no significant difference in the mean IOP of both groups (p=0.866).

The mean BCVA of the NAION group's affected eyes at the time of admission was 0.72±0.65 logMAR (range 0.5–2.10 logMAR) and in the non-affected eyes was 0.15±0.52 logMAR (range 0.00–1.70 logMAR). The mean BCVA of the affected eyes evaluated at the 12th-month follow-up was 0.68±0.53 logMAR (range 0.05–1.80 logMAR).

NAION patients had significantly higher MPV, RDW, and NLR values than control group ($p<0.001$, p=0.006, and $p<0.001$, respectively). For the mean PDW value, there was no statistically significant difference between NAION and control groups, but the mean PDW value was higher in the patient group compared to the control group (p=0.435). The results are summarized in Table 1.

No significant correlation was found between the BCVA of the patients at the first admission and laboratory parameters. There was also no significant relationship between laboratory data and post-treatment follow-up BCVA.

It was observed that the NLR parameter was far from the reference line and had the highest value in terms of the AUC in the ROC curve Figure 1. Therefore, it was discovered that the laboratory data had the highest diagnostic predictive value. The MPV parameter also showed a parallel course to the NLR, but the RDW and PDW parameters gradually approached the reference line and weakened their diagnostic prediction power.

In our study group, the AUC of NLR was 0.861 (confidence interval 79%–93% range), which was significant, with a $p<0.001$. The optimal cutoff point calculated was 1.91 where the corresponding sensitivity and specificity were 80% and 75%, respectively. The positive predictive value for NLR was 76% and the negative predictive value was 78%.

The AUC of MPV was found as 0.851 (confidence interval 77%–92% range), and a cutoff point was determined >8.5. Then, sensitivity was 72%, and specificity was calculated as 74% at the cutoff point. The positive predictive value for MPV was 73% and the negative predictive value was 72%. The results for all parameters are summarized in Tables 2 and 3.

The odds ratio-estimated relative risk was calculated for the NLR, MPV, and RDW parameters with cutoff values determined by ROC analysis. The estimated relative risk was 10.8 for NLR, 8.8 for MPV, and 2.1 for RDW.

Table 1. Patient and control group MPV, PDW, RDW, and NLR value comparison

	NAION group (n=48) (mean±SD)	Control group (n=50) (mean±SD)	p
MPV (f/L)	9.28±0.90	8.05±0.71	<0.001
RDW (%)	14.94±2.5	13.634±0.89	0.006
N/L ratio	3.21±1.98	1.54±0.52	<0.001
PDW (%)	17±1.06	16.7±0.51	0.435

NAION: Non-arteritic optic neuropathy; SD: Standard deviation; MPV: Mean platelet volume; RDW: Red cell distribution width; N/L ratio: Neutrophil–lymphocyte ratio; PDW: Platelet distribution width.

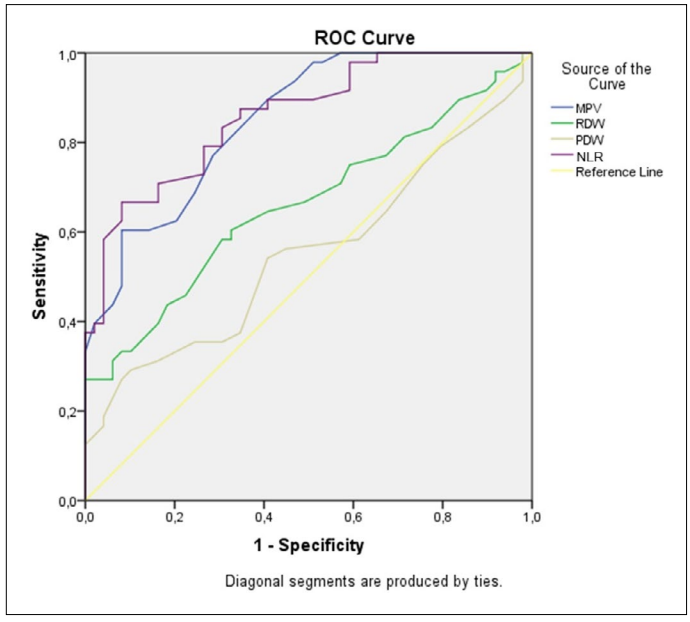

Figure 1. Receiver operating characteristics curve for neutrophil–lymphocyte ratio, mean platelet volume, red cell distribution width, and PDV values.

Table 2. AUC, P-values, cutoff points, and sensitivity-specificity of NLR, MPV, RDW, and PDW

	AUC	p	Cutoff	Sensitivity	Specificity
N/L ratio	0.861	<0.001	1.91	80%	75%
MPV (f/L)	0.851	<0.001	8.5	72%	74%
RDW (%)	0.661	0.006	13.6	65%	60%
PDW (%)	0.551	0.435	16.5	58%	60%

AUC: Area under the curve; N/L ratio: Neutrophil–lymphocyte ratio; MPV: Mean platelet volume; RDW: Red cell distribution width; PDW: Platelet distribution width, Positive predictive value.

Table 3. The NLR, MPV, RDW, and PDW parameters and positive and negative values

	Positive predictive value	Negative predictive value
NLR	76%	78%
MPV	73%	72%
RDW	61%	63%
PDW	59%	58%

N/L ratio: Neutrophil–lymphocyte ratio; MPV: Mean platelet volume; RDW: Red cell distribution width; PDW: Platelet distribution width, Positive predictive value.

Discussion

In the current study, MPV, RDW, and NLR values were significantly higher in the NAION cases compared to the control group. To the best of our knowledge, the parameters of MPV, PDW, RDW, and NLR have not been previously investigated together in the same patient group and have not been evaluated in terms of their superiority in the diagnosis of NAION. The study also tried to determine if the platelet indices RDW and NLR can be used as predictive factors and new biomarkers for NAION. The NLR parameter with the highest diagnostic predictor value seemed to be the laboratory data. The MPV parameter showed a parallel course to NLR, but the RDW and PDW parameters had weaker predictive power. Therefore, it is suggested that both hemostasis and inflammation play a role in the etiopathogenesis of the cases.

The hemostatic balance is maintained by complex interactions between the platelets, vessel wall, coagulation system, physiological anticoagulants, and fibrinolytic system. There are studies on platelet activation that investigate the role of hemostasis in the pathogenesis of NAION (13,14,19).

Hayreh suggested that serotonin released by platelet aggregation in atherosclerotic plaques may play an important role in the pathogenesis of NAION by producing transient non-perfusion or hypoperfusion of the optic nerve head (20). Nagy et al. reported that the platelet P-selectin level was increased in patients with NAION. They suggested that enlarged platelet activity may be related to NAION (16). In contrast, Salomon et al. investigated the pathogenic role of different risk factors for thrombophilia but found no significant difference in NAION patients (5).

In the Sahin et al. study, MPV values were found to be significantly higher than that of the control group and contributed to the pathogenesis of NAION. The study stated that the presence of high MPV may increase the risk of NAION (15).

The MPV and PDW are simple platelet indices that increase during platelet activation. However, because PDW does not increase during simple platelet swelling, unlike MPV, it is thought to be a more specific marker of platelet activation. There are also studies that have evaluated platelet and MPV values on other ocular vascular diseases such as retinal vein occlusion, (21) diabetic retinopathy, (22) retinal artery occlusion, (23) and neovascular glaucoma (24).

Recently, parameters such as MPV, PDW, and NLR have been introduced as predictors of microvascular complications of diabetes (25,26). Hematological indices, such as NLR and MPV, have become new markers of systemic inflammatory responses.

White blood cells (WBC) and NLR are used as markers of inflammation in various inflammatory conditions, particularly in cardiovascular disorders (27). Increased neutrophil counts have been shown to be associated with ischemic injury sites (10). An increase in the NLR value has appeared in various diseases such as chronic low-grade inflammation. Neutrophil-mediated cellular inflammation has also been shown to play a role in early NAION (12,28).

Polat et al. evaluated NLR in NAION patients. In this study, the WBC, neutrophil count, and NLR were significantly higher in NAION patients without any systemic disease than in the control group without systemic disease (17).

NLR combines two independent markers of inflammation and is more useful due to its stability compared to other parameters that may be affected by different pathological, physiological, and physical factors. Therefore, NLR is a more stable and reliable parameter compared to WBC and lymphocytes (29). NLR, which can be easily measured with a rapid, inexpensive, routine whole blood count analysis, can be considered a new inflammatory marker for evaluating the severity of inflammation in NAION patients (17).

Inanc et al. investigated the levels of both MPV and PDW values and found they were significantly higher in AION and NAION groups than in the controls, whereas there were no significant differences of the mean MPV and PDW values

among AION and NAION groups. The NLR values were statistically significantly higher only in the AION group compared with the NAION and the control groups (18).

Inflammation and oxidative stresses may cause RDW elevation. Currently, a simple parameter that directly measures oxidative stress and inflammatory response is not yet available. Recently, there have been studies on the relationship between RDW and coronary artery diseases, pulmonary hypertension, chronic obstructive pulmonary disease, malignancies, pulmonary thromboembolism, and sepsis (30,31). Although there are studies of RDW that can be used as a prognostic marker in cardiovascular events, there are no studies investigating the diagnostic and prognostic value of RDW in NAION. In the current study, the RDW value was higher in the patient group than in the control group. Because it is an ischemic and vascular event, RDW may be used as an inexpensive, easily accessible, and reproducible prognostic marker for morbidity in NAION.

Retrospective design is the limitation of our study. In our study, no correlation was found between visual acuity and the data we have. However, it is thought that these biomarkers can provide information about the progression of the disease in further prospective studies examining repeated blood tests from patients.

Conclusion

Inflammatory reaction in addition to ischemic changes may play a role in the etiopathogenesis of NAION. NLR and MPV values can be used as diagnostic biomarkers in NAION cases. NLR, MPV, and RDW tests can be examined for diagnosis in patients with risk factors for NAION. These biomarkers can simultaneously serve as valuable tools for monitoring NAION patients through simple and readily accessible laboratory tests. Moreover, they could be crucial for early disease detection, particularly in otherwise healthy eyes.

Disclosures

Ethics Committee Approval: The study was conducted in accordance with the ethical standards of the Declaration of Helsinki and was approved by Tepecik Training and Research Hospital Institutional Local Ethics Committee (Date: 13.07.2017, No: 2017/5). The investigator obtained the informed consent of the participants to collect the data.

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

Authorship Contributions: Concept – N.K.U., S.K.A., H.A.; Design – N.K.U., S.K.A., H.A.; Supervision – N.K.U., S.K.A.; Resource – N.K.U., H.A.; Materials – N.K.U., S.K.A.; Data Collection and/or processing – N.K.U.; Analysis and/or interpretation – N.K.U., H.A.; Literature search – N.K.U., H.A., S.K.A.; Writing – N.K.U., S.K.A.; Critical Reviews – N.K.U., S.K.A., H.A.

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