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Original Research Paper

RISK FACTORS FOR NON-ARTERITIC ANTERIOR ISCHEMIC OPTIC NEUROPATHY IN SPECIALIZED EYE CENTERS IN IRAQ

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ABSTRACT:

Background: Non-arteritic ischemic optic neuropathy (NAION) is the most common acute optic neuropathy and a common cause of sudden, painless loss of vision present commonly on awakening from sleep in patients over the age of 50 years. **Aim:** The aim of this retrospective case-control study was to assess the risk factors associated with NAION in an Iraqi population. **Patients and methods:** This study was conducted in Baghdad, Iraq, from January 2020 to December 2021. It was a retrospective case – control study and the cases included were those having new onset NAION and underwent thorough ophthalmological examination. Cases and control groups were evaluated for having hypertension, diabetes mellitus and hyperlipidemia and if they were smokers or not. **Results:** Patients with NAION had significantly more often diabetes mellitus (47.5% vs. 25%, P<0.001), hypertension (58.3% vs. 22.5%, P<0.001) and hyperlipidemia (15% vs. 5%, P=0.016). The presence of crowded optic disc and high IOP were significantly associated with the occurrence of NAION (crowded optic disc, OR 11.01, 95% CI 3.3-36.71, P<0.001; high IOP, OR 1.37, 95% CI 1.22-1.54, P<0.001). Diabetes mellitus, hypertension and hyperlipidemia had a strong correlation with NAION (diabetes, OR 2.25, 95% CI 1.11-4.57, P=0.024; hypertension, OR 5.78, 95% CI 2.73-12.2, P<0.001; hyperlipidemia, OR 8.59, 95% CI 2.43-30.28, P<0.001). Diabetes mellitus was seen significantly more often among persons with bilateral NAION (66.7% in bilateral vs. 41.9% in unilateral, P=0.023). **Conclusion:** In this study we showed that crowded optic disc, high IOP, diabetes, hypertension and hyperlipidemia are associated with the onset of NAION.

Keywords: NAION, hypertension, diabetes, hyperlipidemia

INTRODUCTION:

Non-arteritic anterior ischemic optic neuropathy (NAION) is the most frequent reason for optic disc swelling as well as optic neuropathy in the population age more than fifty years and it is considered as a significant reason for blindness [1]. NAION results from poor blood perfusion and ischemia to the head of the optic nerve without vessel inflammation and is called "non-arteritic" compared to the arteritic type which is caused by giant cell arteritis (GCA) [2]. This condition is also referred to as "anterior" as the front-most part of the optic nerve is the site of the damage, while "ischemic" is attributed to a decreased flow of blood as the pathogenic cause of the damage. The ischemic injury of the optic nerve is attributed to a disruption of the transfer of optical signals from the globe to the cerebral lobe, the reason why it is called "optic neuropathy". In contrast, decreased flow of blood to whatever area beyond the disc is called posterior ischemic optic neuropathy (PION) and does not result in disc edema [1]. It generally affects patients older than fifty years, with an average occurrence in the range between fifty-seven and sixty-five years old. Additionally, NAION also occurred in subjects younger than forty years of age that either have or not the attributable factors (i.e., NAION of the young-NAIONY) [3]

Previous researches demonstrated that the presence of NAION could be associated with ocular and systemic risk factors [17].

1. Ocular risk factors: small ONH diameter, crowded disc, cup/disc proportion of less than or equal to 0.3 and drusen of the disc of the optic nerve (it causes axonal compression inside the rigid scleral tunnel [18]).

2. Systemic attributable factors: diabetes mellitus, hypertension, tobacco smoking, sleep apnea, hyperlipidemia and phosphodiesterase-5 inhibitors use.
Some of these elements might contribute to NAION's vascular etiology, including intimal thickening and arteriosclerosis [19].

AIM OF THE STUDY:

The aim of this retrospective case-control study was to assess the risk factors associated with NAION in an Iraqi population.

PATIENTS AND METHODS:

Through the review of patient files, we enlisted participants in this retrospective case-control study, 120 persons with new onset NAION, and were evaluated at the neuro-ophthalmology clinic of Jenna ophthalmic center in Baghdad, Iraq. For the control group, there were randomly selected 120 persons matched for age and sex (1:1), without NAION, who underwent visual health examination at Ibn Al-Haitham eye teaching hospital, Baghdad, Iraq, from January 2020 to December 2021. NAION was identified as having an optic neuropathy onset that started two weeks of an initial examination, existence of relative afferent pupillary defect, acute unilateral painless sight disturbance, compatible with NAION visual field defect, slit lamp examination using non-contact 90D lens and in fundus photography, optic disc swelling seen at initial evaluation. The study included subjects with new onset NAION in either eye and a history of NAION in the fellow eye.

Exclusion criteria:

1. AAION. This condition was ruled out based on clinical characteristics with normal serum C-reactive protein, normal erythrocyte sedimentation rate, and absence of clinical evidence of temporal arteritis in addition to absence of systemic symptoms (i.e. jaw claudication, headache, neck discomfort, achy, tenderness in the scalp, elevated body temperature).
2. Neither at the time of initial evaluation nor afterward during follow-up were there any signs of an intracranial tumor, aneurysm, or inflammation.
3. Abrupt visual acuity disturbance or defect in the visual field with no disc swelling.
4. Ocular or peri-ocular pain with swelling of the disc.
5. Cases where the visual potential was impacted by any retinal or optic nerve lesions.
6. Diabetic papillopathy.
7. Thyroid eye disease.
8. Multiple sclerosis.
9. Uveitis.
10. Glaucoma.
11. Trauma history in the previous three months.

All patients diagnosed with NAION underwent ophthalmic examinations, which include best-corrected visual acuity checking on the Snellen's acuity chart within the initial examination, pupillary light reflexes, slit-lamp evaluation of anterior eye segment with fundus examination using 90D lens, fundus photography, Ishihara color vision test and ocular motility testing. A visual field assessment employing automated and static using threshold perimetry (Humphrey 30-2 SITA [Swedish Interactive Thresholding Algorithm]) was further conducted. Pneumatic tonometry is used to measure the intraocular pressure (IOP) in the affected one while in cases with previous NAION in both eyes, the IOP in the newly involved eye was used. IOP measurements are performed during visit to the neuro-ophthalmology clinic between 15:00-19:00. A 6 mm by 6 mm data cube was performed for the Huvitz HD-OCT examination of the retinal nerve fiber layer and the optic nerve head. Comparisons were made between the ONH of the fellow eye in the patient group and the matching eye from the control group in order to ascertain whether a crowded disc, low cup disc ratio, or tiny disc area is present or evidence of previous NAION by fundus examination using 90D lens and OCT. Hypertension is defined as intake of oral anti-hypertensive therapy. Diabetes mellitus is defined as intake of oral hypoglycemic medications or insulin. Hyperlipidemia is defined as intake of lipid lowering medications. Smokers were defined as patients who were currently smoking cigarettes at the time of diagnosis. Ethical approval was obtained from Ibn AL-Haitham teaching eye hospital, Arab board of health specialization.

STATISTICAL ANALYSIS:

Cases with NAION and controls were compared through a Mann-Whitney U-test for continuous variables and displayed as median±IQR (range). Categorical variables were compared by Pearson chi-square test and presented as number (n) and percentage (%). The significant variables in univariate analyses ($P<0.05$) were entered into a binary logistic regression to obtain odds ratios (ORs). We also utilized a Hosmer and Lemeshow test for the goodness of fit of the model. A P value <0.05 or a 95% confidence interval (95% CI) that didn't contain 1.0 was considered statistically significant. Each analysis was calculated utilizing SPSS version 28.0.1.0 for Mac (IBM Corp., Armonk, NY, USA).

RESULTS:

Through patients' files review a total of 120 persons were diagnosed with NAION. Demographic and co-morbidity characteristics among the persons with

NAION and healthy controls are outlined in Table 1. The type of refractive error between the two groups was significantly different. Significantly more persons with NAION had hypermetropy (62.5% vs. 41.7%, P=0.001) and crowded optic disc (25% vs. 3.3%, P<0.001) compared with the controls. The intraocular pressure (IOP) was significantly higher among persons with NAION compared with controls (median IOP; 19 mmHg vs. 16.5 mmHg, P<0.001). Persons with NAION had significantly more diabetes mellitus (47.5% vs. 25%, P<0.001), hypertension (58.3% vs. 22.5%, P<0.001) and hyperlipidemia (15% vs. 5%, P=0.016) in comparison to controls (Table 1).

Table 1: Demographics of persons with non-arteritic anterior ischemic optic neuropathy and age- and sex-matched controls.

	With NAION (n=120)	**Without NAION** (n=120)	**Crude P-value**
Age (years)	58±15 (23-80)	59±16 (30-85)	NS
20-29	1 (0.8%)	0 (0%)	
30-39	2 (1.7%)	3 (2.5%)	
40-49	22 (18.5%)	23 (19.2%)	
50-59	41 (34.5%)	40 (33.3%)	
60-69	37 (31.1%)	34 (28.3%)	
70-79	15 (12.6%)	18 (15%)	
80-89	1 (0.8%)	2 (1.7%)	
Sex			NS
Male	67 (55.8%)	67 (55.8%)	
Female	53 (44.2%)	53 (44.2%)	
Type of refractive error			0.002
Myopic	45 (37.5%)	70 (58.3%)	0.001
Hypermetropic	75 (62.5%)	50 (41.7%)	0.001
Previous cataract surgery	9 (7.5%)	8 (6.7%)	NS
Crowded optic disc	30 (25%)	4 (3.3%)	<0.001
Intraocular pressure (mmHg)	19±4.4 (11-35.9)	16.5±5 (9-23)	<0.001
Smoking	18 (15%)	10 (8.3%)	NS
Diabetes mellitus	57 (47.5%)	30 (25%)	<0.001
Hypertension	70 (58.3%)	27 (22.5%)	<0.001
Hyperlipidemia	18 (15%)	6 (5%)	0.016

NAION: Non-arteritic anterior ischemic optic neuropathy. Categorical variables were analyzed using Pearson chi-square test and presented as number (n) and percentage (%). Continuous variables were analyzed using Mann-Whitney U test and presented as median±IQR (range).

Table 2 summarizes the demographic and co-morbidity characteristics of persons with unilateral and bilateral NAION. Diabetes mellitus was seen significantly more often among persons with bilateral disease (66.7% vs. 41.9%, P=0.023) (Table 2).

Table 2: Demographics of persons with unilateral and bilateral non-arteritic anterior ischemic optic neuropathy.

	Unilateral NAION (n=93)	**Bilateral NAION** (n=27)	**Crude P-value**
Age (years)	56±16 (23-80)	59.5±11 (40-79)	NS
Sex			NS
Male	49 (52.7%)	18 (66.7%)	
Female	44 (47.3%)	9 (33.3%)	
Type of refractive error			NS
Myopic	35 (37.6%)	10 (37%)	

Hypermetropic	58 (62.4%)	17 (63%)	
Previous cataract surgery	8 (8.6%)	1 (3.7%)	NS
Crowded optic disc	26 (28%)	4 (14.8%)	NS
Intraocular pressure (mmHg)	19±4.7 (11-35.9)	19±4 (12-30)	NS
Smoking	12 (12.9%)	6 (22.2%)	NS
Diabetes mellitus	39 (41.9%)	18 (66.7%)	0.023
Hypertension	54 (58.1%)	16 (59.3%)	NS
Hyperlipidemia	14 (15.1%)	4 (14.8%)	NS

NAION: Non-arteritic anterior ischemic optic neuropathy. Categorical variables were analyzed using Pearson chi-square test and presented as number (n) and percentage (%). Continuous variables were assessed utilizing Mann-Whitney U test and displayed as median±IQR (range).

The existence of crowded optic disc and high IOP were significantly associated with the occurrence of NAION (crowded optic disc, OR 11.01, 95% CI 3.3-36.71, P<0.001; high IOP, OR 1.37, 95% CI 1.22-1.54, P<0.001). Moreover, the presence of diabetes mellitus, hypertension and hyperlipidemia exhibited a strong correlation with the diagnosis of NAION (diabetes, OR 2.25, 95% CI 1.11-4.57, P=0.024; hypertension, OR 5.78, 95% CI 2.73-12.2, P<0.001; hyperlipidemia, OR 8.59, 95% CI 2.43-30.28, P<0.001) (Table 3).

Table 3: Odds ratios (ORs and 95% CIs) for the association of non-arteritic anterior ischemic optic neuropathy with demographic and medical parameters.

	Non-arteritic anterior ischemic optic neuropathy OR (95% CI)	**Crude P-value**
Age	0.97 (0.94-1)	NS
Sex	0.70 (0.34-1.47)	NS
Previous cataract surgery	1.46 (0.42-5.07)	NS
Presence of crowded optic disc	11.01 (3.30-36.71)	<0.001
High intraocular pressure	1.37 (1.22-1.54)	<0.001
Smoking	1.43 (0.45-4.49)	NS
Diabetes mellitus	2.25 (1.11-4.57)	0.024
Hypertension	5.78 (2.73-12.2)	<0.001
Hyperlipidemia	8.59 (2.43-30.28)	<0.001

Odds ratios were calculated by binary multivariate logistic regression. The combined model included age and sex of the patient, previous cataract surgery, presence of crowded optic disc, intraocular pressure, smoking and previous morbidity (diabetes mellitus, hypertension, hyperlipidemia). P-values were computed utilizing the Hosmer and Lemeshow test for the goodness of fit of the model.

The presence of diabetes mellitus had strong correlation with the bilateral onset of NAION (OR 2.8, 95% CI 1.07-7.33, P=0.035) (data not presented in table).

DISCUSSION:

This retrospective case-control study included 120 persons with an NAION diagnosis and 120 age- and sex-matched healthy controls, examined the correlation between NAION and the existence of ocular and systemic attributable factors. Our main finding was a significant correlation between NAION and the presence of crowded optic disc, higher IOP, diabetes mellitus, hypertension and hyperlipidemia. Significant correlation was found between diabetes mellitus and bilateral NAION. In NAION, structural findings of the optic disc frequently include a tiny or absent cup, a crowded disc and a small disc diameter (so called “disk at risk”). It has been hypothesized that “crowding” had a part in the development of NAION [12, 47]. Behbehani et al. from Kuwait found a cup-to-disc ratio of ≤0.3 in 61.5% of NAION cases [48]. Kim et al. found that the frequency of crowded small cup was 44.4%, which was far higher than it was in the control group (2.2%) [49]. Two studies showed a significant correlation between ‘disk at risk’ and NAION [49]. One previous study showed that compared to black or Hispanic individuals, white people are much more likely to acquire NAION [50]. This is because small cup-to-disc ratios are more prevalent in

white subjects. González et al., according to measurements by OCT, identified a low cup disc ratio as an attributable factor and a poor prognostic predictor for NAION [51]. The frequency of crowded small cup among patients with NAION in our study group was 25%, which was much greater than in the control group (3.3%). In accordance with our findings were the results by Sharma et al. in research of an Indian patients [52]. In our study, the prevalence of crowded small cup for patients with NAION was higher by 7.5 times than in the control group (OR 11.01, 95% CI 3.3-36.71, P <0.001).

Diabetes mellitus is significantly more prevalent among subjects with NAION, and it is an independent attributable factor of disease occurrence [7] Hyperglycemia can promote vasostatic perfusion deficiency by multiple biochemical abnormalities and also leads to leukostasis that predisposes to capillary occlusion. Jacobson et al. demonstrated that for the occurrence of NAION in Western populations, diabetes mellitus is a major risk factor [9]. A meta-analysis by Liu et al. that included 10 million patients showed that diabetes significantly increases the risk of development of NAION (*RR*=1.53, 95% *CI*: 1.36–1.73, *P*<0.00001) [53]. In our study, diabetes Mellitus was noticeably more common in the NAION patient group compared to the control group (47.5% vs. 25%). The prevalence of diabetes in our study is higher compared with that reported in Western populations and in a study from Korea (24% to 34%) [53]. However, a study by Behbehani et al. demonstrated a greater presence of diabetes (64.1%) among patients with NAION compared with our study [48]. 58.1% of the participants in our research had hypertension that was consistent with the 34%–57% of patients with hypertension reported in earlier studies [49]. The relationship between NAION and hypertension is still controversial but it well known that hypertension is linked to atherosclerosis. Few studies revealed that hypertension was not a sole contributing factor for the onset of NAION, despite the fact that it affects so many patients with the condition [54]. Surprisingly, Jacobson et al., showed that high blood pressure appears to protect against NAION. In this study, hypertension was significantly associated with NAION and this result is in line with Hayreh et al. study that revealed a significant association of hypertension and the occurrence of NAION, particularly in subjects of <50 years[1]. Furthermore, Liu et al. meta-analysis cleared that hypertension was a substantial and considerable risk factor of the condition's development (*RR* =1.28, 95% *CI* 1.2–1.37, *P* <0.00001) [53]. Atherosclerosis is attributed to hypercholesterolemia and can cause arterial narrowing or block there by decreasing or preventing blood flow, especially through small vessels, reaching vital organs [55]. In our thesis, NAION cases were shown to have significantly higher rates of hypercholesterolemia than were controls (15% vs. 5%). Hypercholesterolemia among cases with NAION in our study was less in comparison to the results from Jacobson et al., (49%) and Salomon et al., (36.1%) [9]. Salomon et al., showed that hypercholesterolemia is a significant independent attributable factor for the occurrence of NAION. In this study, hypercholesterolemia was significantly associated with NAION (OR 8.59, 95% CI 2.43-30.28, P<0.001). The mean age of subjects with NAION in our study was 58 years and 79% of the cases were older than 50 years at the onset. This is consistent with previous researches demonstrating that NAION typically manifests around the age of 60 [56]. The theory behind this finding is that older patients with a higher prevalence of previous risk factors present NAION more often. The importance of age in the onset of NAION is further supported by Scuteri et al., with the hypothesis that becoming older increases the probability of vascular events that cause NAION [60]. In our study, age was not significantly different between cases and controls due to the age matched study design used.

In our study, NAION was more prevalent among men compared with women (55.8% vs. 44.2%). This is in line with earlier studies that pointed out male sex as an attributable factor for the occurrence of NAION [61].

In our analysis, the older group tended to have a higher prevalence of cigarette use. Smokers are said to experience NAION at an earlier age than those nonsmokers [62]. Smoking raises white blood cell and red blood cell counts, platelet aggregation, and vasoconstriction. It increases the risk of ischemic heart disease and stroke in people with diabetes mellitus and high blood pressure [63]. The prevalence of smokers in our study was 15% among subjects with NAION, which was lower than the frequency reported by Jacobson et al. (18%) [9] and similar to that shown by Salomon et al. (14.8%) [8]. Both Hayreh et al. and Salomon et al. have shown no correlation between smoking and the development of NAION [18, 8]. However, Moro et al. and Talk et al. showed smoking as a significant risk for the occurrence of NAION [54, 64]. Because smokers exhibit NAION at a significantly younger age than non-smokers do, Chung et al. large, uncontrolled study demonstrated smoking as a significant role in the development of NAION [65]. Previous studies showed that smoking can result in vascular events and suggested that the risk of NAION might increase by smoking [66-67].

Elevated IOP can disrupt optic nerve circulation. In this study, the mean IOP was 19 mmHg where 29% of the cases had IOP higher than 21 mmHg (not presented). Additionally, we demonstrated a strong association between higher IOP and the development of NAION.

Katz et al. showed that 44% of the patients with NAION had IOP above 21 mm Hg [68]. L. A. Mawn et al. suggest that it may be useful to use intra-ocular pressure lowering medication to prevent the progression of NAION in the affected eye and the occurrence of the condition in the unaffected one [69].

In Liu et al. meta-analysis, sleep apnea was found to be not associated with NAION occurrence in researches on Europeans, but four studies of mixed-ethnic populations found a positive correlation [53]. Guyer et al. studied NAION correlation with left ventricular hypertrophy, ischemic heart disease and other vascular risk factors and found that the correlation is inconsistent [70]. In our study, the number of subjects with ischemic heart disease, left ventricular hypertrophy or sleep apnea was small and therefore, we didn't evaluate their impact on the occurrence of NAION. Subjects having unilateral NAION have a similar risk factor profile and visual acuity results to those with bilateral NAION, demonstrating a common pathophysiology [71]. In our study, we showed a significant association with higher risk for having fellow eye involvement in cases having diabetes and that men are twice as likely as women of got affected (18 vs 9), supported by a study performed by Beri M et al. [56], came to the conclusion that those who are male and have systemic disorders, particularly diabetes, are more likely to acquire bilateral NAION. One of the possible limitations in our study is the retrospective nature of the data. This fact could include selection bias with underestimation of the systemic risk factors and used medication (t.ex. phosphodiesterase type-5 inhibitors (PDE5-Is) intake due to fear of social stigma) among the study persons. There may be underreporting of or they think it is irrelevant to their eye condition. Although **Liu B** et al. [53] showed no significant correlation between NAION and PDE5-I use, PDE5-Is may make the naturally occurring nocturnal hypotension so profound that it lowers the arterial pressure within the SPCAs. [72]. Another possible limitation is that the IOP measurement was performed between 15:00 and 19:00 and will not precisely show the range of intra-ocular pressure diurnal fluctuation. Particularly in younger patients, there are growing studies involving optic disc drusen in NAION. Ocular ultrasonography was not frequently performed in our investigation, making it probable that this was a limitation.

CONCLUSION:

By retrospectively analyzing the presence of NAION among an Iraqi population, we showed that some pre-existing ocular (crowded optic disc and high IOP) and systemic (diabetes, hypertension, hyperlipidemia) conditions could be associated with the onset of NAION.

RECOMMENDATION:

We recommend that these conditions should be taken carefully in consideration during patient counseling since most of them could effectively be controlled medically to prevent the onset of NAION. This is particularly important due to the clinical importance of NAION and the ineffective available treatments nowadays.

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