ORIGINAL ARTICLE

Risk Factors for Non-arteritic Anterior Ischaemic Optic Neuropathy in a Korean Population

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ABSTRACT

To determine the risk factors for non-arteritic anterior ischaemic optic neuropathy (NAION) in Korean patients, medical records from 45 Korean patients group and 45 healthy controls group were retrospectively reviewed. 10 NAION risk factors, including age, sex, associated systemic disease, past medical/social history, and fundus findings were analyzed. Significant risk factors for NAION in Korean patients were diabetes mellitus (odds ratio (OR) = 3.613, $p = 0.020$), hypercholesterolaemia (OR = 5.200, $p = 0.001$), smoking (OR = 3.58, $p = 0.014$), microaneurysm/haemorrhage (OR = 5.375, $p = 0.024$), and crowded small cup (OR = 17.200, $p < 0.001$).

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Introduction

Patients with non-arteritic anterior ischaemic optic neuropathy (NAION) mainly present with blindness without pain or seriously impaired vision due to ischaemic damage to the anterior portion of the optic nerve, a region primarily supplied by posterior ciliary artery circulation. Characteristics of NAION include sudden and progressive monocular visual loss that evolves over several hours to days, optic nerve head swelling, delayed optic atrophy, and afferent pupillary defect.^{1–3} Visual field defects consistent with optic neuropathy are also common in NAION; arcuate or altitudinal inferior visual field defects are the most common.^{1,2} NAION is an important cause of blindness among the elderly. It may also occur in younger patients.^{1,2}

The pathogenesis of NAION has been described in many previous articles.^{1–5} However, the exact mechanism of NAION pathogenesis remains unknown.^{1–3} Previous studies have shown that NAION has various causes, including vascular disease, thromboembolic disorder, and nocturnal arterial hypotension.^{1,2} Systemic vascular diseases, particularly diabetes mellitus and hypertension

cause microvascular ischaemia and acquired neuropathies such as NAION. Other reported risk factors include advanced age, left ventricular hypertrophy (LVH), ischaemic heart disease (IHD), increased haematocrit, hypercholesterolaemia, and cigarette smoking.^{1–5} To the best of our knowledge, most studies on the risk factors of NAION have been conducted in Western populations.^{1–5} No such study has been conducted in Asian populations. Therefore, the objective of this study was to perform a retrospective study to determine the risk factors for NAION in Korean patients.

Materials and methods

We retrospectively reviewed the medical records of 45 patients diagnosed with NAION. All patients were evaluated in the Department of Ophthalmology of Chosun University from January 2009 to December 2015. Institutional review board approval was obtained from Chosun University Hospital. NAION was diagnosed with the following criteria: age greater than 50 years, new optic neuropathy onset within 2

weeks of an initial evaluation, acute unilateral painless visual disturbance, evidence of relative afferent pupillary defect, visual field defect relevant to NAION, optic disc swelling in fundus photography at initial examination, no history of trauma within the preceding 3 months, and no evidence of intracranial neoplasm, aneurysm, or inflammation on neuroimaging studies at the time of diagnosis or during follow-up. Arteritic anterior ischaemic optic neuropathy was excluded based on clinical presence with normal erythrocyte sedimentation rate, normal C-reactive protein level, and an absence of evidence of temporal arteritis. The case group (45 patients) had no systemic symptoms such as jaw claudication, headache, neck pain, malaise, scalp tenderness, or fever. Patients with sudden visual acuity or visual field loss without disc oedema, ocular pain with disc oedema, or recurrence of NAION in ipsilateral or contralateral eye were excluded. All patients were assessed for underlying diseases, particularly for evidence of thyroid disease, multiple sclerosis, glaucoma, and uveitis. Such patients were also excluded.

All NAION patients underwent thorough ophthalmic examinations, including a slit-lamp examination, fundus photography, and an ocular motility test. Best-corrected visual acuity was tested using the Snellen visual acuity chart under the same testing condition. All patients were administered a visual field test using automated static threshold perimetry (Humphrey 30-2 SITA [Swedish Interactive Testing Algorithm]). An Ishihara colour vision test was performed during the initial ophthalmologic examination. Systemic diseases were defined as follows. A diagnosis of hypertension was made if systolic pressure was 140 mm Hg or diastolic pressure was 90 mm Hg on three occasions or if the patient was taking oral hypertensive medication for previously diagnosed hypertension.⁶ Diabetes mellitus was indicated if the patient was taking oral hypoglycemic drugs or insulin. Some individuals were newly diagnosed in the Department of Endocrinology. Hypercholesterolaemia was defined by a random cholesterol level of 240 mg/dL or use of cholesterol reduction medications.⁷ IHD was defined by electrocardiographic documentation of myocardial infarction or a history of taking

antianginal medications. LVH was defined by enlargement and thickening of the walls of the left ventricle on electrocardiography or echocardiography or taking medications for LVH treatment.^{8,9} Patients who were active cigarette smokers at the time of diagnosis or had used tobacco in the previous 5 years were classified as smokers.^{10,11} Retinal microaneurysm/haemorrhage (Ma/Hrr) was determined based on coloured fundus photo of both eyes in patients both the NAION study group and the control group.¹² To find a small optic disc, the fundus photo of the fellow eye in the study group was compared with the ipsilateral eye in the control group.

We established a control group ($n = 45$) matched for age and sex. They were randomly selected from a pool of individuals who received health examinations at Chosun University Hospital Health Promotion Center during the same study period. Clinical and demographic features of the NAION study group and the control group were expressed as numbers and percentages for categorical variables. The mean and standard deviation were calculated for continuous variables. A paired t test was performed to determine the difference between initial visual acuity and the visual acuity at the last follow-up. Logistic regression analysis was conducted to examine the difference in risk factors between the NAION study group and the control group. An independent t test was performed to compare the average number of accompanying risk factors between the NAION study group and the control group. Linear by linear association was conducted to determine the relationship between risk factors and NAION prevalence. All statistical analyses were performed using SPSS (version 20.0; IBM, Armonk, NY, USA). Statistical significance was considered when the p value was less than 0.05.

Results

Of the 45 patients in the study group, 26 (57.8%) were females and 19 (42.2%) were males. The mean age was 63.48 ± 15.23 years. A total of 17 (37.8%) affected eyes were on the right side, whereas 28 (62.2%) were on the left. The clinical

Table 1. Clinical and demographic features of the non-arteritic anterior ischaemic optic neuropathy group and the control group used in this study.

Characteristic	Cases (<i>n</i> = 45) <i>n</i> (%)	Control (<i>n</i> = 45) <i>n</i> (%)
Sex		
Male	19 (42.2)	19 (42.2)
Female	26 (57.8)	26 (57.8)
Age (years), mean $\pm$ SD (range)	63.48 $\pm$ 15.23 (51–91)	62.42 $\pm$ 12.51 (52–89)
Affected eye		
OD	17 (37.8)	NA
OS	28 (62.2)	NA
BCVA (logMAR), mean $\pm$ SD (range)		
Initial	1.08 $\pm$ 0.89 (3–0)	0.21 $\pm$ 0.04 (0.6–0.1)
End of follow-up	1.09 $\pm$ 1.08 (3–0)	NA
Colour vision, mean $\pm$ SD (range)	7.12 $\pm$ 5.32 (0–15)	NA
Visual defect	45 (100)	NA
Altitudinal defect	23 (51.1)	
Arcuate defect	13 (28.9)	
Generalised defect	8 (17.8)	
Central scotoma	1 (2.22)	

Note. NA = not available; BCVA = best-corrected visual acuity; logMAR = logarithm of the minimum angle of resolution.

and demographic characteristics of the study group and control group are summarised in Table 1. Initial visual acuity in the NAION group varied from no light perception (logMAR +3) to 20/20 (logMAR 0). The mean initial visual acuity of the affected eyes was 1.08 ± 0.89 (logMAR). At the last follow-up, mean visual acuity was 1.09 ± 1.08 (logMAR), which was not significantly (paired *t* test, *p* = 0.913) different from the initial visual acuity. The mean initial visual acuity in the control group was 0.21 ± 0.04 (logMAR 0.6–0.1). There was a significant (Independent *t* test, *p* < 0.001) difference in the initial visual acuity between the study group and the control group. All patients had visual field defects, including altitudinal defects in 23 eyes, arcuate defects in 13 eyes, general defects in 8 eyes, and a central scotoma in 1 eye (Figure 1).

The distributions of potential risk factors in the study group and the control group are shown in Table 2. In the study group, 24 (53.3%) of the 45 patients had hypertension, 14 (31.1%) had diabetes

Figure 1. Examples of visual field defect pattern in the NAION patients group. (A) Inferior altitudinal field loss along the horizontal meridian. (B) Inferior arcuated field defect. (C) Generalised field defect. (D) Central scotoma.

Table 2. Distribution of risk factors for the non-arteritic anterior ischaemic optic neuropathy group and the control group.

Risk factor	Cases (<i>n</i> = 45) <i>n</i> (%)	Control (<i>n</i> = 45) <i>n</i> (%)	OR	95% CI	<i>p</i> value
Hypertension	24 (53.3)	15 (33.3)	2.286	0.974–5.362	0.056
Diabetes mellitus	14 (31.1)	5 (11.1)	3.613	1.174–11.114	0.020
Hypercholesterolaemia	20 (44.4)	6 (13.3)	5.200	1.835–14.732	0.001
Smoking	16 (35.5)	6 (13.3)	3.586	1.250–10.291	0.014
Ma/Hrr	9 (20.0)	2 (4.4)	5.375	1.091–26.486	0.024
Small cup (fellow eye)	20 (44.4)	1 (2.2)	17.200	3.706–78.820	<0.001

Note. OR = odds ratio; CI = confidence intervals; Ma = microaneurysm; Hrr = retinal haemorrhage.

mellitus, 20 (44.4%) had hypercholesterolaemia, 20 (44.4%) had crowded small cup, 9 (20.0%) had Ma/Hrr, 3 (6.7%) had IHD, and 1 (2.2%) had LVH. In addition, 16 (35.5%) patients were smokers.

Diabetes mellitus was significantly more prevalent in the study group than that in the control group (odds ratio [OR]: 3.61; 95% confidence interval [CI]: 1.17–11.11). Hypercholesterolaemia (OR: 5.20; 95% CI: 1.83–14.73), smoking (OR: 3.58; 95% CI: 1.25–10.29), retinal Ma/Hrr (OR: 5.37; 95% CI: 1.09–26.48), and crowded small cup in the fellow eye (OR: 17.20; 95% CI: 3.70–78.82) were also significantly more frequent in the study group than those in the control group. Hypertension was also more common in the study group than that in the control group. However, the difference was not statistically significant (Table 2). The average number of accompanying risk factors was 2.35 ± 1.29 in the study group, which was significantly higher than that (0.82 ± 1.03) in the control group (Independent *t* test, $p < 0.001$). The percentage of patients with more than 2 but less than 4 risk factors was significantly greater in the study group ($n = 31$, 68.9%) than that ($n = 11$, 24.4%) in the control group (linear by linear, $p < 0.001$; Table 3).

Table 3. Distribution of the non-arteritic anterior ischaemic optic neuropathy group and the control group by the sum of risk factors.

Risk factor	Cases (<i>n</i> = 45) <i>n</i> (%)	Control (<i>n</i> = 45) <i>n</i> (%)	<i>p</i> value
0–1 risk factors	13 (28.9)	33 (73.3)	<0.001
2–4 risk factors	31 (68.9)	11 (24.4)	<0.001
5–6 risk factors	1 (2.2)	1 (2.2)	
Average number of accompanying risk factors	2.35 ± 1.29	0.82 ± 1.02	<0.001

Discussion

Small vessel circulatory insufficiency in the optic nerve head is the most widely accepted pathophysiology of NAION.^{1–5} However, the mechanism of the ischaemia and the location of the vasculopathy remain uncertain.^{1–3} NAION is a multifactorial disease.^{1–3} It has many risk factors, including diabetes, hypertension, hypercholesterolaemia, coronary artery disease, left ventricular hypertrophy, atrial fibrillation, chronic obstructive pulmonary disease, tobacco use, glaucoma, and family medical history of stroke or myocardial infarction.^{1–5} To the best of our knowledge, our study is the first to report the risk factors of NAION in Korean populations.

In most previous studies with Western populations, diabetes mellitus is significantly more common in patients with NAION and it has been reported as an independent risk factor.^{3–5} In our study with Korean patients, diabetes mellitus was also significantly more frequent in the study group compared with that in the control group. Diabetes mellitus was observed in 14 (31.1%) of 45 patients with NAION, similar to its frequency in Western populations (range: 24%–34%).^{3–5} After controlling for other risk factors, the risk of developing NAION was 3 times (OR: 3.613, $p = 0.02$) higher in patients with diabetes than that in the non-diabetic control group of Korean patients. Jacobson et al.⁵ have reported that diabetes mellitus is a major risk factor for the development of NAION in Western populations. A case-control study by Salomon et al.⁴ also found that NAION is related to diabetes mellitus.

High cholesterol levels are linked to atherosclerosis, a disease defined by the accumulation of cholesterol-rich fatty deposits in arteries. Atherosclerosis can cause arteries to narrow or

become blocked, thus slowing or stopping the flow of blood to vital organs, especially narrow vessels.⁷ Hypercholesterolaemia was found to be significantly more frequent in our Korean NAION patients than that in the control group. It was observed in 20 (44.4%) of 45 subjects in the study group. The percentage of patients with hypercholesterolaemia in our study is similar to the result of Jacobson et al.,⁵ where 25 (49%) of 51 patients had increased cholesterol levels, but slightly higher than that reported by Salomon et al.,⁴ where 22 (36.1%) of 61 patients had increased blood cholesterol levels. Salomon et al.⁴ have confirmed that hypercholesterolaemia is an significant independent risk factor for NAION. In our Korean study patients, hypercholesterolaemia was also found to be significantly associated with NAION (OR: 5.200, $p = 0.001$).

Smoking increases vasoconstriction, platelet aggregation, and both red and white blood cell counts. It increases the risk of stroke and IHD among patients with diabetes mellitus and hypertension.¹³ Smoking also decreases high-density lipoprotein levels.¹³ The frequency of smoking in our study was 35.5% (16 of 45 patients), which was higher than the frequency (18%, 9 of 51 patients) reported by Jacobson and colleagues.⁵ The frequency of smoking found in our study was also higher than that (14.8%, 9 of 61 patients) among patients in the study of Salomon et al.⁴ Both Salomon et al.⁴ and Hayreh et al.¹⁴ have reported that there is no association between NAION and smoking. However, Moro et al.¹⁵ and Talk et al.¹⁶ have reported that cigarette smoking is an important risk factor in the development of NAION. A large (137 cases) but uncontrolled study by Chung et al.¹⁷ has concluded that smoking is a significant risk factor for NAION based on the finding that smokers developed NAION at a significantly younger age than nonsmokers. Although the mean age of smokers (63.41 years) in our analysis was older than that (51 years) reported by Chung et al.¹⁷ our analyses also showed that there was a significant association between NAION and smoking (OR: 3.586, $p = 0.014$). Our results and previous research results showing that smoking can lead to vascular diseases^{10,11,14–17} suggest that smoking might increase NAION risk. Although many research

studies have assessed the association between NAION and smoking, the effect of smoking as risk factor for NAION has not yet been completely established. In this regard, future research with a larger sample size is necessary to confirm this association.

In our study, 53.3% of patients had systemic hypertension, which was consistent with findings of a few previous studies^{3–5} showing systemic hypertension in 34%–57% of patients. Controversy still exists regarding the relationship between NAION and systemic hypertension. In a case-control study of NAION, Jacobson et al.⁵ have reported that hypertension is not an independent risk factor for NAION despite its high frequency in the NAION patients. Surprisingly, Jacobson and colleagues⁵ have shown that hypertension seems to be protective against NAION. Salomon et al.⁴ and Talks et al.¹⁶ have also reported that hypertension is not a statistically important risk factor for NAION. Despite the high frequency of hypertension in the NAION group, our analyses also showed that there was no significant association between NAION and hypertension (OR: 2.286, $p = 0.056$). In contrast, Hayreh et al.¹⁸ have found that hypertension is strongly associated with the development of NAION, especially in adults 50 years of age or younger.

Optic disc structural features in NAION are often small in diameter with small or absent cups (so called “disk at risk”). Many researchers have suggested that “crowding” plays a role in the pathogenesis of NAION. Swelling within a tight disk may produce “compartment syndrome”, a vicious cycle of disk oedema and peripapillary haemorrhage.^{19,20} How swelling causes disk oedema and peripapillary haemorrhage remains unclear. It is possible that crowding produces intracellular axonal swelling secondary to mechanical obstruction of axoplasmic flow, particularly at the most crowded region, the cribriform plate. In Western studies, white patients are significantly more predisposed to develop NAION than black or Hispanic patients²¹ because white patients tend to have small cup-to-disc ratios. The frequency of crowded small cup in our study group was 44.4% (20 of 45 patients), which was significant higher than that (2.2%, 1 of 45) in the control group. The

relative risk (OR: 17.200, $p < 0.001$) of patients with crowded small cup was 17 times higher than that in the control group. Crowded small cup is rarely reported as an independent risk factor in Western studies. However, our results showed that crowded small cup was significantly associated with NAION. In our study, the frequency of retinal microaneurysm (Ma) and retinal haemorrhage (Hrr) was 20.0% (9 of 45) in the NAION study group and 4.4% (2 of 45) in the control group. A significantly higher frequency of patients with more than one Ma/Hrr on the fundus was found in the study group compared with that in the control group (OR: 5.375, $p = 0.024$) (Figure 2). Ma is an important predictor of progression of diabetic retinopathy.¹² Ma is defined as swellings in the retinal arteriole or capillaries caused by weakening of the vessel wall. Therefore, patients with Ma/Hrr might have a weakened posterior ciliary artery wall whose diameter is similar to that of the retinal arteriole or capillaries.²² This specific structural alteration might have an effect on laminar microcirculation in the posterior

ciliary arteries, thus causing NAION. Additional histopathological studies are needed to prove such speculation.

Although our analysis demonstrated that Ma/Hrr was related to the development of NAION, our study had following limitations. First, there might be statistical bias resulting from the fact that Ma/Hrr was only detected in the patients with diabetes mellitus patients. Therefore, the Ma risk factor might be dependent on the diabetes mellitus risk factor. No study has reported that Ma/Hrr is a risk factor for NAION. In this regard, more research studies with large samples are needed.

The evidence supporting an association between NAION and other vascular risk factors such as IHD and LVH has been inconsistent.²³ The number of patients with LVH or IHD was relatively small in our study. Therefore, we were unable to evaluate their relative risk for the development of NAION.

One strong point of this study was that it revealed a significantly higher tendency toward

Figure 2. Examples of retinal microaneurysm, retinal haemorrhage, and crowded disc in the NAION patients group. (A) Left, A fundus photograph showing superior segmental mild optic disc swelling with retinal microaneurysm (black arrows) and retinal haemorrhage. (white arrows). Right, A fundus photograph showing optic disc swelling with retinal microaneurysm (black large arrow). (B) Optic disc photographs showing crowded optic disc (disc at risk).

vasculopathic risk in the NAION study group compared with that in the control group. According to a previous study²⁴ on patients with ischaemic ocular motor nerve palsy, atherosclerotic changes in capillary vessels and arterioles in the ocular motor nerve are proportional to the number of vasculopathic risk factors. Therefore, an increasing number of vascular risk factors might result in severe pathological changes such as atherosclerosis in the optic nerve head blood vessels, thus raising the risk of developing NAION. Additional histopathological studies are needed in the future to confirm this hypothesis.

This was a retrospective single tertiary hospital-based study with a small patient sample size. Therefore, caution should be taken when generalising our results. Nevertheless, unlike previous reports involving Western populations, this research provides information regarding risk factors of NAION in an Asian population. In conclusion, diabetes mellitus, hypercholesterolaemia, smoking, microaneurysm/haemorrhage, and crowded small cup are significantly associated with NAION in Korean patients.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the article.

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