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Evaluation of traditional and emerging cardiovascular risk factors in patients with non-arteritic anterior ischemic optic neuropathy: a case-control study

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Abstract
Background Non-arteritic anterior ischemic optic neuropathy (NAION) is a multifactorial disease that is caused by an infarction of the vessels that supply the optic nerve head. This study aims at evaluating the role of traditional and emerging cardiovascular risk factors on the development of NAION.
Methods A total of 85 newly diagnosed NAION patients and 107 age- and gender-matched healthy controls were studied. All participants underwent blood testing for homocysteine and lipoprotein(a). Plasma levels of vitamin B6 and B12, and folic acid were also determined. Plasma values of all these parameters were evaluated as continuous variables, by a logarithmic transformation. In addition, traditional cardiovascular risk factors were considered.
Results With univariate analysis, higher values of homocysteine and Lp(a) (OR 4.24, 95% CI 2.01–8.94, $p<$ 0.0001; OR 1.32, 95% CI 1.04–1.67, p=0.03, respectively) and lower values of vitamin B6 (OR 0.44, 95% CI 0.25–0.76, p=0.003) were significantly associated with NAION. At multivariate analysis, adjusted for age, gender, smoking habit, hypertension, dyslipidemia, diabetes, sleep apnea, and thrombophilic risk factors, the higher homocysteine and Lp(a) values (OR 5.74, 95% CI 2.41–13.67, p = 0.0001; OR 1.27, 95% CI 1.01–1.63, p=0.04) and lower vitamin B6 values (OR 0.42, 95% CI 0.23–0.77, p=0.005) maintained their significant relationship with NAION.
Conclusions This study demonstrated that elevated plasma homocysteine and lipoprotein(a) levels, as well as low vitamin B6 levels, may increase the risk of developing NAION. A screening for these thrombophilic markers could be useful in subjects experiencing NAION.

Keywords Homocysteine · Lipoprotein(a) · Non-arteritic anterior ischemic optic neuropathy · Thrombophilia · Vitamins

Introduction

Non-arteritic anterior ischemic optic neuropathy (NAION) is a relatively frequent cause of severe visual impairment in subjects older than 50 years [7, 31]. It is a multifactorial disease that occurs because of an acute perfusion insufficiency in short posterior ciliary arteries (SPCAs) leading to optic nerve head (ONH) ischemia.

A variety of risk factors for NAION have been identified. The disease was associated with genetic factors, as a small and crowded disc, and traditional cardiovascular risk factors, as arterial hypertension, diabetes mellitus, dyslipidemia, sleep apnea, and coronary artery disease [3, 10, 11, 14, 18, 21, 22, 28, 32]. Since the late 1990s, several observations have suggested that hypercoagulable states may also be pathogenetically relevant [5, 15, 25, 26, 29, 35, 37]. Among thrombophilic markers, elevated homocysteinemia and lipoprotein(a) [Lp(a)] plasma levels seem to be particularly significant [15, 26, 29, 30, 37, 39]. They have to be

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considered as predisposing factors. However, the development of NAION is strongly related to acute ONH hypoperfusion, which is mostly due to nocturnal hypotension [14, 19–21, 23].

Aim of the present case-control study was to investigate the role of traditional and emerging risk factors, that is homocysteine and lipoprotein(a), on the occurrence of NAION.

Materials and methods

A total of 85 consecutive patients with a first episode of acute unilateral NAION who had referred to the Eye Clinic of the University of Florence were included in the study. Diagnosis of NAION was based on clinical findings (decrease in visual acuity, dyschromatopsia, absence of ocular pain, relative afferent pupillary defect, sectorial or diffuse ischemic papillary oedema, peripapillary hemorrhages, visual field defects consistent with the ophthalmoscopic features). Erythrocyte sedimentation rate and C-reactive protein serum levels were determined to exclude arteritic anterior ischemic optic neuropathy. One hundred and seventy age- and gender-matched healthy subjects were recruited from relatives or friends of patients and considered as controls. All participants gave signed informed consent; the study was approved by the local Ethics Committee and applies with the Declaration of Helsinki. Patients and controls with a personal history of abnormal liver or renal function, thyroid disease, and any other ocular pathologies other than NAION were excluded. Patients and controls underwent a detailed interview addressed to the presence of cardiovascular diseases and risk factors, including arterial hypertension, diabetes mellitus, dyslipidemia, smoking habit, and sleep apnea, and a complete physical and ophthalmic examination. The subjects were classified as having hypertension and diabetes according to the guidelines of European Society of Hypertension/European Society of Cardiology and to those of the American Diabetes Association, respectively [8, 13]. Dyslipidemia was defined following the criteria of the ATP III Expert Panel of the US National Cholesterol Education Program [27].

Blood samples were collected into evacuated plastic tubes (Vacutainer) from the basilic vein, after an overnight fasting. Cholesterol and triglyceride values were determined by means of enzymatic and colorimetric methods, respectively. To determine homocysteine (Hcy) and C677T methylenetetrahydrofolate reductase (MTHFR) polymorphism, whole venous blood was collected in tubes containing ethylenediaminetetraacetate (EDTA) 0.17 mol/L, immediately put in ice, and centrifuged within 30 min at 4°C (1,500 x *g* for 15 min). Plasma samples were stored at −20 °C until assay. Plasma levels of total Hcy (free and protein bound) were measured by fluorescence polarization immunoassay (IMX Abbott Laboratories, Oslo, Norway). C677T MTHFR polymorphism analysis was performed through electronic microchip technology (Nanogen, San Diego, CA, USA). To determine circulating vitamins (B6, B12, and folic acid) venous blood was put in tubes without anticoagulant and centrifuged at room temperature (2,000 x *g* for 15 min). Sera samples were stored at −20 °C until assay. Vitamin B6 levels were determined by using a commercial HPCL assay with fluorescence detection (Immundiagnostik AG, Bensheim, Germany), whereas sera levels of folic acid and vitamin B12 were measured by radioimmunoassay (ICN Pharmaceuticals, Orangeburg, USA). Sera for testing lipoprotein(a) were obtained by centrifuging blood collected in evacuated tubes without anticoagulant and stored at −20 °C until assay. Lp(a) levels were determined by an ELISA assay (Apo[a] ELISA, Mercodia, Uppsala, Sweden).

Results are shown as median and range or number (n) and rate (%). Statistical comparisons between groups were carried out by means of Student's *t*-test and Chi-square test. A logistic regression analysis was used to evaluate the risk of NAION according to the presence of any risk factor. All the considered variables, that means demographic data and atherosclerotic and thrombophilic risk factors, were introduced in the multivariate model. Odds ratio (OR) and 95% confidence intervals (CI) were presented. Statistical significance was set at $p<0.05$.

All statistical analyses were performed using the SPSS (Statistical Package for Social Sciences, Chicago, USA) software for Windows (Version 13.0).

Results

Demographic and clinical characteristics of the participants to the study are outlined in Table 1.

Arterial hypertension and dyslipidemia were significantly more prevalent in patients than in controls, whereas the prevalence of other traditional risk factors for atherosclerotic diseases, as smoking habit and diabetes, was not

Table 1 Demographic and clinical characteristics of NAION (non-arteritic anterior ischemic optic neuropathy) patients and controls (Student's *t*-test, Chi-square test)

	NAION	Controls	*p*-value
Age (years) *	65 (26–88)	65 (21–84)	0.4
Males, *n* (%)	39 (45.9)	75 (44.1)	0.9
Hypertension, *n* (%)	51 (60)	40 (23.5)	<0.0001
Smoking habit, *n* (%)	17 (20)	24 (14.1)	0.2
Dyslipidemia, *n* (%)	41 (48.2)	55 (32.4)	0.01
Diabetes, *n* (%)	4 (4.7)	5 (2.9)	0.5

* Median (range)

significantly different between the two groups. None of the examined subjects reported a history of sleep apnea.

Among thrombophilic risk factors, plasma levels of Hcy and Lp(a) resulted significantly higher in patients with NAION compared with controls. Significant differences for vitamin B6, but not for vitamin B12 and folic acid, were observed between patients and healthy subjects. MTHFR C677T polymorphism resulted not to be significantly different between the two groups (Table 2).

In order to investigate the possible relationship between the presence of thrombophilic risk factors and development of NAION, we logarithmically (natural logarithm [Ln]) transformed Hcy, vitamin B6, and Lp(a) plasma values, and we performed a logistic regression analysis with these parameters evaluated as continuous variables.

With univariate analysis, higher values of Hcy and Lp(a) were found to be significantly associated with the occurrence of NAION ($p<0.0001$ and $p=0.03$, respectively). Conversely, lower values of vitamin B6 resulted to be protective against this disease ($p=0.003$).

With multivariate analysis, adjusted for all the considered variables, the odds ratio for lower values of vitamin B6 and for higher levels of Lp(a) resulted slightly lower, but remained statistically significant ($p=0.005$, $p=0.04$, respectively). To what extent Hcy, its plasmatic increase was even more significantly associated with NAION, determining an almost six-fold increase in the odds of having the disease ($p<0.0001$) (Table 3).

Discussion

Non-arteritic anterior ischemic optic neuropathy has a multifactorial aetiopathogenesis. Recent reviews have summarized the conditions more frequently associated with an increased risk of developing the disease: a crowded optic disc, atherosclerosis, diabetes, dyslipidemia, hypertension, hypercoagulable states, smoking habit, sleep apnea, ischemic heart disease, and cerebrovascular diseases [23, 30].

All the mentioned conditions act as predisposing factors, which renders ONH more susceptible to ischemia. In fact, they may have a negative effect on the ONH circulation by producing an endothelial damage at SPCAs level. Nevertheless, the underlying mechanism for the development of NAION is not an atherothrombotic event, but an acute, severe blood-flow reduction in prelaminar and laminar areas of lamina cribrosa that are supplied by SPCAs. Nocturnal hypotension has been identified as the precipitating factor in individuals affected with traditional and emerging cardiovascular risk factors [14, 19–21, 23].

In this study we performed a joint analysis of traditional cardiovascular and thrombophilic risk factors in patients presenting with unilateral acute NAION. We found that arterial hypertension and dyslipidemia (but not diabetes and smoking habit) were significantly more prevalent in patients than in controls. The vast majority of the studies published by now have reported a higher prevalence of hypertension, hypercholesterolemia, and diabetes in patients with NAION, but some authors did not confirm these data [10, 22, 23, 26, 29–32, 38]. The lacking association between diabetes and NAION in our trial is certainly strange. A possible reason for this finding could be the inclusion of young patients, but we really are not able to give a credible justification.

With respect to thrombophilia, our results clearly demonstrated that in patients with NAION, compared to healthy subjects, plasma levels of Hcy and Lp(a) are increased, whereas those of vitamin B6 are reduced.

Hyperhomocysteinemia has a well-established prothrombotic effect by producing severe endothelial damage [17, 36]. This can be due to polymorphisms in genes encoding for enzymes involved in Hcy metabolism (as homozygosity to the C677T MTHFR polymorphism) or to a decrease in the uptake of vitamins B6, B12, and folic acid, cofactors of Hcy metabolism. In particular, an impaired vitamin B6 status is related to an increased risk of thrombotic events because it may induce hyperhomocysteinemia and affect

Table 2 Plasma values of homocysteine, vitamins, lipoprotein(a), and assessment of methylenetetrahydrofolate reductase (MTHFR) polymorphism in NAION (non-arteritic anterior ischemic optic neuropathy) and controls population (Student's *t*-test)

	NAION	Controls	*p* value
Homocysteine, μmol/L	12.3 (6.2–34.1)	10.8 (2.4–27.8)	0.003
Folic acid, ng/mL	3.3 (0.3–20.7)	3.4 (1.0–20.0)	0.9
Vitamin B6, ng/mL	5.6 (1.5–20.6)	7.3 (1.6–21.2)	0.003
Vitamin B12, pg/mL	343.5 (53–816)	389.0 (20–991)	0.1
Lipoprotein(a), mg/L	120.0 (1–1196)	72.5 (1–580)	0.01
MTHFR C677T			
CC, *n* (%)	18 (21.2)	41 (24.1)	
TC, *n* (%)	46 (54.1)	94 (55.3)	
TT, *n* (%)	21 (24.7)	35 (20.6)	0.1
T allele	0.52	0.48	0.2

Table 3 Logistic regression analysis (OR 95% CI)

	Univariate analysis	Multivariate analysis *
Ln homocysteine, μmol/L	4.24 (2.01–8.94)	5.74 (2.41–13.67)
Ln Lp(a), mg/L	1.32 (1.04–1.67)	1.27 (1.01–1.63)
Ln vitamin B6, ng/mL	0.44 (0.25–0.76)	0.42 (0.23–0.77)

* Adjusted for demographic data and atherosclerotic and thrombophilic risk factors

platelet aggregation [16, 33, 34]. To date, no literature exists about the role of vitamin B6 circulating values in NAION. Currently, there is controversy regarding the hypothesis that thrombophilia may be involved in the development of NAION. In fact, several authors have observed a higher prevalence of factor V Leiden, elevated Lp(a) serum levels, and hyperhomocysteinemia in subjects with NAION [15, 25, 26, 29, 35–37, 39]. However, these findings were not confirmed in larger populations [5, 32]. Of note, the study conducted by Salomon et al. did not demonstrate an association between the disease and any inherited and acquired thrombophilic factor [32].

Lipoprotein(a) is a defined marker of hypofibrinolysis, which may determine thrombophilic states leading to cardiovascular and cerebrovascular diseases [12]. Our results are in keeping with those of Nagy et al., who stated that elevated Lp(a) was a main predictor for NAION [26].

In summary, the present study strengthens the concept that cardiovascular risk factors, both traditional and thrombophilic, are predisposing risk factors for NAION. Our study has, however, some limitations. Only fasting homocysteinemia has been considered; measurements of Hcy post-methionine plasma levels could be useful to reveal an impairment of Hcy metabolism in a number of subjects. In addition, nutritional habits have not been registered; they would be important to determine the role of diet on vitamin B6 and homocysteine circulating values.

The complex, multifactorial nature of NAION has remarkable implications on the management of affected individuals. A complete assessment of traditional cardiovascular risk factors and a screening for thrombophilia could be performed. Although there are no guidelines for therapeutical management of NAION, some interventions deserve to be recommended. Arterial hypertension, nocturnal hypertension, dyslipidemia, and sleep apnea must be treated. Discontinuation of tobacco smoking would be advisable. To what extent prothrombotic and hypofibrinolytic states, some of them do not have specific treatments, while others do. Of note, plasma levels of homocysteine can be easily and effectively lowered by daily vitamin supplementation (vitamins B6, B12, and folic acid). This treatment demonstrated to produce a considerable reduction of cardiovascular morbidity in subjects with arterial occlusive disorders [9]. Kupersmith et al. showed that aspirin treatment would prevent the involvement of the fellow eye in the 2 years after the first episode of NAION [24]. Conversely, larger studies have denied a long-term prophylactic effect [4, 6]. Thus, at present antiplatelet treatment cannot be proposed as a treatment of choice for NAION patients. However, even if referred only to our study, aspirin treatment could possibly be suitable to reduce Lp(a) plasma levels, as demonstrated by Akaike and coworkers [1].

In conclusion, the present study indicates that a complete assessment of traditional and thrombophilic risk factors could be advisable in patients with NAION. Our findings may suggest the potential utility of different and combined therapeutical approaches which aim at lowering the incidence of further cardiovascular disorders and of the involvement of the second eye: the treatment of arterial hypertension and dyslipidemia, the correction of hyperhomocysteinemia by vitamin supplementation, and, if the study by Akaike et al. is confirmed, the reduction of Lp(a) plasma levels by aspirin [1]. Longitudinal and intervention studies are needed to establish the influence of the aforesaid risk factors and their therapeutical management on the cardiovascular morbidity and the visual prognosis in subjects presenting with NAION.

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