



Association between C-reactive protein and normal tension glaucoma

Povezanost između vrednosti C-reaktivnog proteina i normotenzivnog glaukoma

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Abstract

Background/Aim. C-reactive protein (CRP) is a systemic inflammatory marker associated with risk for cardiovascular disease (CVD). Some risk factors for CVD are associated with normal tension glaucoma (NTG), but the association between CRP and NTG has not been well defined yet. The aim of our study was to compare high-sensitivity CRP (hs-CRP) levels in plasma between patients with NTG and normal controls. **Methods.** We studied 20 patients (4 males and 16 females) with the NTG diagnosis and compared their CRP values to those obtained in 25 controls (5 males and 20 females) with no ocular disease. Both groups had similar demographic parameters (age, sex, body mass index – BMI) and similar vascular risk profile. **Results.** Plasma CRP levels were comparable between patients with NTG and controls (mean values 4.99 ± 0.77 mg/L, median 4.50 mg/L, range 2.50–18.90 mg/L and mean value 4.19 ± 0.30 mg/L, median 3.50 mg/L range 2.20–8.50 mg/L, respectively, $p > 0.5$). **Conclusion.** The results obtained in this study suggest that CRP levels are not altered in NTG patients.

Key words:

low tension glaucoma; c-reactive protein; atherosclerosis.

Apstrakt

Uvod/Cilj. C-reaktivni protein (CRP) je sistemski inflamatorni marker koji je povezan sa rizikom od nastanka kardiovaskularnih bolesti (KVB). Određeni faktori rizika od KVB su ujedno i faktori rizika od razvoja normotenzivnog glaukoma (NTG), ali povezanost između CRP i NTG još uvek nije jasno definisana. Cilj ove studije bio je da se ispita povezanost između vrednosti visokosenzitivnog CRP u plazmi kod bolesnika sa NTG i u kontrolnoj grupi. **Metode.** Ispitano je ukupno 20 bolesnika sa NTG (4 muškaraca i 16 žena) i 25 osoba iz kontrolne grupe (5 muškaraca i 20 žena). Obe grupe ispitanika imale su približno iste demografske karakteristike (godine, pol i indeks telesne mase) i kod obe grupe bili su prisutni vaskularni faktori rizika u istom procentu. **Rezultati.** Vrednosti CRP u plazmi bolesnika sa NTG i u kontrolnoj grupi bile su poredive: srednja vrednost iznosila je 4.99 ± 0.77 mg/L, mediana 4.50 mg/L, opseg 2.50–18.90 mg/L kod bolesnika sa NTG, dok su te vrednosti u kontrolnoj grupi bile: 4.19 ± 0.30 mg/L, 3.50 mg/L, odnosno 2.20–8.50. **Zaključak.** Rezultati dobijeni u ovoj studiji pokazuju da vrednosti CRP nisu povećane kod bolesnika sa NTG.

Ključne reči:

glaukom, normotenzivni; c-reaktivni protein; ateroskleroza.

Introduction

Glaucoma is a group of diseases characterized by progressive optic neuropathy and loss of retinal nerve fiber layer with corresponding visual field defects. Elevated intraocular pressure (IOP) has been identified as the most important risk factor, but not the only one¹.

Normal tension glaucoma (NTG) is a special type of primary open angle glaucoma characterized by intraocular pressure levels in normal statistical range, but resulting in a progressive optic neuropathy^{2,3}. This type of glaucoma is associated with vascular risk factors such as vascular dysregulation with systemic hypotension and vasospasm^{4,5}. In the optic nerve head (ONH) in these patients, disk hemo-

rhages, notching of the neuroretinal rim and peripapillary atrophy are often encountered⁶. Patients with NTG have an increased endothelin-1 plasma level^{7,8}.

C-reactive protein (CRP), an important serum marker of inflammation, the levels of which increase in response to acute inflammatory processes, is synthesized in the liver and regulated by cytokines⁹. CRP has recently been proposed as a marker of chronic inflammatory processes such as atherosclerosis¹⁰. Epidemiological studies show that an elevated CRP level is a strong predictor of cardiovascular risk¹¹.

Some risk factors for cardiovascular disease are associated with NTG, but the association between CRP and NTG has not been well defined yet. While some studies found elevated levels of CRP in patients with NTG^{12,13}, other studies suggest that CRP levels are not altered in NTG patients¹⁴⁻¹⁷. The purpose of this study was to investigate CRP levels by using a highly sensitive CRP kit in NTG patients and to compare them to normal controls.

Methods

This study included 20 consecutive NTG patients who presented in our glaucoma consultations. The diagnosis of NTG was based on a clinical examination, including intraocular pressure measurements at 2-hour intervals from 8 am to 6 pm with the values consistently below 22 mmHg, open chamber angle, optic nerve head damage typical of glaucoma and glaucomatous visual field defects. There was no history or signs of other eye disease or steroid use. Control subjects also underwent clinical eye examination including measurements of intraocular pressure at two hour intervals from 8 am to 6 pm, fundoscopic and optic nerve head examination and OCTOPUS visual field analysis, program full threshold (Octopus 900, Haag Streit AG, Koeniz, Switzerland). Based on the value of the mean defect (MD), all visual fields were divided into three groups. The first group consisted of patients with initial changes in the visual field ($MD \leq 6$ dB). The second group consisted of patients with moderate changes in the visual field ($6 \text{ dB} < MD < 12 \text{ dB}$), while the third group consisted of patients with advanced changes in the visual field ($MD \geq 12 \text{ dB}$).

In both NTG and control groups, the detailed medical history was obtained. The patients and control subjects with the known systemic inflammatory disease, malignancy and/or steroid use were excluded from the study. Hypertension, hypotension, migraine, ischemic heart disease, vasospastic diathesis (positive history of cold hand and feet), cerebrovascular disease and diabetes mellitus were identified from the medical charts and history taking in each patient and subject. The control group consisted of the subjects of similar gender and age, with no ocular disease.

The quantitative determination of plasma CRP levels in all study participants was done using a highly sensitive CRP kit (Abbot AEROSET, Illinois, USA).

The study was approved by the relevant ethics committee and all the participants gave written informed consent according to the Declaration of Helsinki.

The results were analyzed by *t*-test, χ^2 test, ANOVA and Mann-Whitney *U* test. A value of $p < 0.05$ was considered significant.

Results

A total of 20 NTG cases (4 males, 16 females, mean age 65 ± 9 years) were compared with 25 controls (5 males, 20 females, mean age 63 ± 6 years) (Table 1). Both groups had similar demographic parameters (age, sex, BMI; all *p*-values > 0.05). Systemic vascular disorders identified from charts and medical history in the NTG patients were: 3 (15%) patients had hypotension, 10 (50%) had hypertension, 2 (10%) had a migraine, 2 (10%) had positive history of cold hands and feet, 2 (10%) had an ischemic heart disease and 2 (10%) had diabetes mellitus. Systemic vascular disorders that were identified in the control group were: 4 (16%) patients had hypotension, 12 (48%) had hypertension, 2 (8%) had a migraine, 2 (8%) had positive history of cold hands and feet, 3 (12%) had an ischemic heart disease and 2 (8%) had diabetes mellitus. No patient from both groups had the history of cerebrovascular disease.

Plasma CRP levels were comparable in NTG patients and controls [median (range) 4.50 (2.5–18.9) mg/L compared with 3.50 (2.2–8.5) mg/L; Mann-Whitney ($p = 0.233$)]. Also,

Table 1

Characteristics of normal tension glaucoma (NTG) cases and controls

Characteristics	NTG cases (n = 20)	Control group (n = 25)
Age (years), mean \pm SD	64 \pm 8.9	62.8 \pm 5.9
Male/Female, n	4/16	5/20
BMI (kg/m ²), mean \pm SD	25.9 \pm 4.9	26.1 \pm 3.4
Hypotension, n (%)	3 (15)	4 (16)
Hypertension, n (%)	10 (50)	12 (48)
Migraine, n (%)	2 (10)	2 (8)
Vasospastic diathesis, n (%)	2 (10)	2 (8)
Coronary artery disease, n (%)	2 (10)	3 (12)
Diabetes mellitus, n (%)	2 (10)	2 (8)
CRP (mg/L), median (range)	4.50 (2.50–18.90)	3.50 (2.20–8.50)
CRP (mg/L), mean \pm SEM	4.99 \pm 0.77	4.19 \pm 0.30

SD – standard deviation; BMI – body mass index; SEM – standard error of the mean; CRP – C-reactive protein.

the mean values (\pm standard error) were not significantly different between the patients with NTG and the controls (4.99 ± 0.77 mg/L compared with 4.19 ± 0.3 mg/L), *t*-test $p = 0.302$.

The values of mean defect of sensitivity were significantly higher in the patients with NTG than in the control group ($p < 0.01$). Most of the patients, 18 out of 20 (90%), belonged to the group with early and moderate changes in visual field (Table 2). The number of patients with initial changes in the visual field was 7 (35%), MD = 4.06 ± 1.02 : Moderate changes in the visual field were noted in 11 (55%) patients, MD = 8.64 ± 1.65 , while only 2 (10%) patients had advanced changes in visual field, MD = 15 ± 2.54 . Also, CRP values were not significantly different among the 3 groups of the NTG patients and the controls, ANOVA (oneway) $p = 0.347$ (Table 2).

uld be taken into account, and that should include a larger number of subjects.

C-reactive protein is not only an important serum marker of inflammation but may have a direct role in the pathogenesis of atherosclerosis. CRP has been found in atherosclerotic plaque¹⁸, and has an important role in cell adhesion molecular expression in human endothelial cells¹⁹. There are strong associations between the levels of CRP and the incidence of vascular atherosclerotic events such as myocardial infarction and stroke¹¹.

A number of studies dealing with the connection of glaucoma and systemic cardiovascular disease, despite some positive findings, did not find a strong link between atherosclerotic changes in blood vessels and the development of glaucoma²⁰⁻²⁴. Neither the Rotterdam study on a sample of

Table 2
Mean defect (MD) and C-reactive protein (CRP) values among the 3 groups of normal tension glaucoma (NTG) patients and controls

Parameters	Group I (MD < 6 dB)	Group II (6 dB < MD < 12 dB)	Group III (MD > 12 dB)	Controls
Number of patients, n (%)	7 (35)	11 (55)	2 (10)	25 (100)
MD \pm SD (dB)	4.06 ± 1.02	8.64 ± 1.65	15 ± 2.54	2.72 ± 0.60
CRP (mg/L), mean \pm SEM	4.10 ± 0.34	4.13 ± 0.32	5.30 ± 0.96	4.19 ± 0.32

NTG – normal tension glaucoma; SD – standard deviation; SEM – standard error of the mean.

Discussion

The results of this study show that CRP levels are not altered in patients with NTG as compared with the control group with no ocular disease, but with similar demographic parameters and similar vascular risk profile.

Previous researches on the connection between CRP and NTG were controversial. Our results are consistent with the findings obtained by Su et al.¹⁵ and Choi et al.¹⁶, even though they excluded patients with cardiovascular disease. That CRP is not elevated in patients with NTG when compared with normal controls, after exclusion of patients with cardiovascular and other systemic diseases has also been found by Lee et al.¹⁷ in their study. Since NTG is a multifactorial disease in which the vascular risk factors independent of IOP take increasing importance, we did not exclude from our study patients with cardiovascular disease. Taking that into consideration we tried to match NTG patients and controls well. However, our results are contrary to the prior report by Leibovitch et al.¹² who showed significantly higher levels of CRP in 20 NTG patients, when compared to the control group (mean 3.21 ± 0.6 to 0.85 ± 0.17 mg/dL, $p > 0.001$). Leibovitch et al.¹² also did not exclude patients with cardiovascular disease, but, obviously, characteristics of the patients in the control group differed from those in our control group (CRP level in their control group was lower than in our controls). A possible explanation for the different results in our and in Leibovitch's study may be the fact that patients with NTG in our study belong to the same or a similar disease stages (initial and moderate loss of the visual field). It is possible that CRP values vary in the different stages of the disease. Further research is needed so that this factor co-

3,842 subjects after 6.5 years of follow-up found an association between CRP and atherosclerosis, with the prevalence of glaucoma in a relatively healthy population¹⁴.

To the contrary, vascular dysregulation rather than atherosclerotic changes in blood vessels appears to cause reduced perfusion in the optic nerve head²⁵.

In research on NTG, vascular risk factors, in general, were considered as especially important. Interestingly, however, atherosclerosis itself and its risk factors are of minor importance. Systemic hypertension, dyslipidemia and diabetes mellitus are weak risk factors, if they are risk factors at all. Vascular dysregulation causing abnormal blood flow to the optic nerve seems to be a major risk factor. Such dysregulation may lead to systemic hypotension and to local vasospasms, but also to a disturbed autoregulation of blood flow in the optic nerve head²⁶⁻²⁸. Potential limitations of our study are relatively small group sizes of NTG subjects and normal controls. The selection process of patients must be strictly controlled to avoid all of those factors and systemic inflammatory disease that may affect the level of CRP. Patients with different types of open-angle glaucoma but at the same stage of the disease should be involved in future research.

Conclusion

Our findings suggest that CRP levels are not associated with NTG, in line with an assumption that the risk profile of atherosclerotic patients, which includes an increase in CRP, is not identical to the risk profile of NTG patients.

Declaration of interest

The authors declare no conflict of interest.

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