Hemodynamic Changes in Non-Arteritic Anterior Ischemic Optic Neuropathy

Nonarteritik Anterior İskemik Optik Nöropatide Hemodinamik Değişiklikler

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ABSTRACT

Purpose: To compare hemodynamic changes at optic nerve head (ONH) in patients with acute non-arteritic anterior ischemic optic neuropathy (NAION) and age-matched controls by colour Doppler imaging (CDI).

Materials and Methods: Twenty-eight patients with acute NAION and 24 age- and sex-matched controls were included in this cross-sectional study. By means of CDI, the blood-flow velocities of the central retinal artery (CRA) and posterior ciliary artery (PCA) were measured. Peak systolic velocity (PSV), end-diastolic velocity (EDV) and resistive index (RI) were determined. Measurements on the affected side of the patients were compared to the controls.

Results: There was not any significant difference with regard to PSV, EDV, and RI values of the CRA between patients with NAION and controls. PSV and RI of the PCA were significantly increased in patients with NAION compared with controls ($P<0.001$, $P<0.0001$, respectively). EDV of the PCA showed no statistically significant difference.

Conclusion: Increased PSV and RI of PCA were found on the affected side of acute NAION compared to the controls. These findings might be potentially useful in the diagnosis and monitoring of NAION.

Key Words: Anterior ischemic optic neuropathy, colour doppler imaging, optic nerve.

ÖZ

Amaç: Akut non-arteritik anterior iskemik optik nöropati (NAİON) hastaları ile yaş uyumlu kontrol grubu optik sinir başı hemodinamik değişikliklerin renkli doppler ultrason (RDU) ile karşılaştırmak.

Gereç ve Yöntemler: Kesitsel çalışmamıza 28 akut NAİON hastası ve yaş uyumlu 24 kontrol dahil edildi. Santral retinal arter (SRA) ve posterior siliyer arter (PSA) kan akım hız ölçümleri RDU ile yapıldı. Peak sistolik akım hızı (PSAH) ve diastol sonu akım hızı (DSAH) ve rezistif indeks (RI) hesaplandı. Hastaların etkilenen tarafındaki RDU parametreleri kontrol grubu ile karşılaştırıldı.

Bulgular: Kontrol grubu ile NAİON grubu SRA' nın PSAH, DSAH ve RI parametreleri ile karşılaştırıldığında aralarında anlamlı fark bulunmadı. NAİON hastalarında kontrol grubu ile karşılaştırıldığında posterior siliyer arter PSAH ve RI' da istatistiksel olarak anlamlı artış görüldü ($P<0,001$, $P<0,0001$, sırasıyla). Posterior siliyer arter EDV değerlerinde anlamlı fark saptanmadı.

Sonuç: Akut NAİON hastalarının etkilenen göz tarafında kontrol grubuna göre artmış posterior siliyer arter PSAH ve RI değerleri bulundu. Bu bulguların NAİON hastalarının tanı ve takiplerinde muhtemel faydaları olabilecektir.

Anahtar Kelimeler: Anterior iskemik optik nöropati, renkli doppler görüntüleme, optik sinir.

INTRODUCTION

Non-arteritic anterior ischemic optic neuropathy (NAION) is the most common clinical presentation of acute ischemic damage to the optic nerve in the elderly. It is clinically characterized by acute, unilateral, painless visual loss with a relative afferent pupillary defect (RAPD), optic disc oedema and usually visual field defects.[1] Numerous risk factors systemic or local have been reported associated with NAION such as; hypertension (HT), diabetes mellitus (DM), nocturnal hypotension, hypercholesterolemia, arteriosclerosis, obstructive sleep apnea, and a small cup-to-disk ratio.[2-6]

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Several studies investigated circulatory abnormalities in patients with NAION. Fluorescein angiography studies demonstrated increased retinal arteriovenous passage time and delayed filling of optic nerve head capillaries in patients with NAION.[7, 8] Oto et al.[9] reported that Indocyanine green angiography (ICGA) had no significant advantage in terms of clinical diagnosis and management of NAION. Furthermore, patients with NAION showed decreased velocities of blood cells in the capillaries of the optic nerve head measured by laser Doppler velocimetry.[10]

Previous studies on NAION patients by CDI showed markedly different retrobulbar hemodynamics, with reduced circulation velocity in the orbital vessels [11-13]. Sanjari et al compared the blood-flow velocities of ophthalmic artery on the affected side and the contralateral healthy side of patients with unilateral NAION and found that NAION may be associated with decreased ophthalmic flow velocities and increased carotid wall thickness.[12]

Transient hypoperfusion and/or nonperfusion of the short posterior ciliary arteries of the optic nerve head (ONH) is the most widely agreed physiopathological mechanism for developing NAION, but the location of the associated vasculopathy and mechanism of ischemia remain uncertain.[7]

In this study we aimed to investigate the hemodynamic changes of the ONH circulation in NAION measuring the peak systolic velocity (PSV), end-diastolic velocity (EDV) and resistive index (RI) of the central retinal artery (CRA) and posterior ciliary artery (PCA) with Colour Doppler imaging (CDI) noninvasively. These parameters showing the blood flow velocities of the tissue and may give some useful information about the differential diagnosis and better understanding the pathophysiology of the disease.

MATERIALS AND METHODS

This cross-sectional study was performed between December 2010 and April 2013. The study protocol was approved by the Institutional Review Board of the Erciyes University. The research protocol adhered to the tenets of the Declaration of Helsinki for clinical research. Written informed consent was obtained from all the participants after the explanation of the purpose and possible consequences of the study.

Twenty-eight patients (19 male and 9 female) with a newly diagnosed NAION were included in the patients group. Twenty-four subjects (15 male and 9 female) constituted the control group. The distribution of DM and HT, which are risk factors for the development of NAION, were similar between the two groups. A detailed systematic medical evaluation and examination of all subjects were made prior to the study. All subjects underwent a detailed ophthalmological examination including best corrected visual acuity (BCVA), evaluation of RAPD, colour test by using pseudo-isochromatic plates, intraocular pressure measurement by Goldmann applanation tonometer, evaluation of anterior segment and fundus examination from dilated pupilla by slit-lamp biomicroscopy with +90 D lens, and examination of visual field by Octopus 900 (Haag-Streit AG, Switzerland) perimetry. NAION was diagnosed when a history of sudden usually painless loss of visual acuity (VA) with the examination of diffuse or sectoral optic disc oedema sometimes with focal microhemorrhages around the head of the optic nerve. Values of erythrocyte sedimentation rate and C-reactive protein of all cases were recorded for differential diagnosis of arteritic anterior ischemic optic neuropathy (AAION). Patients who had a suspected diagnosis of AAION by clinical presentation and erythrocyte sedimentation rate and C-reactive protein were excluded from the study. Subjects who had toxic and nutrional optic neuropathy, optic neuritis, glaucoma, history of trauma, ocular surface disease were also excluded.

Doppler Ultrasonography

Toshiba Xario (Osaka, Japan), 7.5 MHz, multifrequency linear probe was used. Measurements were taken in the supine position when the eyes were closed by applying ultrasound gel to the external surface of the eyelids. All measurements were taken blindly by the same examiner (S.D.) after the confirmation of the diagnosis. Peak systolic velocity (PSV), end-diastolic velocity (EDV) and Pourcelot's resistive index (RI: PSV-EDV/PSV;a measure of peripheral vascular resistance) of the central retinal artery (CRA) and paraoptic branches (nasal and temporal) of the short posterior ciliary arteries (PCA) of the affected eyes of the patients group and one eye of the control group which was randomly chosen were measured. These measurements were performed in the first day of the presentation to the clinic. Three separate measurements from corresponding localization of paraoptic branches were made in which highest quality spectral scans could be obtained and their average was recorded.

Statistical Analysis

In our study, 'mean', 'standart deviation', 'frequency' and 'ratio' were used among the descriptive statistics. The distribution of variables were evaluated by the Kolmogorov-Simirnov test. Student's *t* test was used for the analysis of parametric variables and Mann-Whitney *U* test for non-parametric variables. Chi-square test was used for the proportional analysis; Fisher's exact test was used if necessary. Spearman's method was used for the correlation analysis. Statistical Package for the Social Sciences (SPSS®) 15.0 version, on a Windows® based PC was used for the statistical analysis; $P<0.05$ was accepted as statistically significant.

RESULTS

Mean ages of the patients and controls were 62.39±8.01 and 61.29±6.61 years, respectively. There were 19 male and 9 female subjects in the patients group, and 15 male and

9 female subjects in the control group. There was not any significant difference between the patients and the control group with regard to age, gender, smoking and alcohol consumption, systemic diseases and drug usage (P>0.05). All demographic data and health behaviours and also systemic diseases such as DM, HT, and coronary heart disease (CHD) and drug usage of the cases were shown on Tables 1, 2, respectively. Median VA (min-max) of the affected eyes of the patients and controls were 0.75 (3.10-0.0) and 0.12 (0.80-0.0) logMAR lines, respectively (P<0.001). Patient group had statistically significantly deteriorated visual acuity. Although there was not any significant difference with regard to PSV, EDV, and RI values of the CRA between the groups (P>0.05), PSV and RI values of the PCA were significantly higher in the patients group than the control group (P<0.001, P<0.0001, respectively). Also EDV value of PCA was higher in the patients group than the control group but the difference was not statistically significant (P>0.05). All Doppler parameters of both patients and the controls were shown on Table 3.

Table 1. *Demographic data and health behaviours of the patients and controls.*

Demographic data and health behaviours		Patients Group		Control Group		
		N: 28		N: 24		*P*
Age		62.39±8.01		61.29±6.61		0.595
Sex	Male (n,%)	19	67.9	15	62.5	0.774
	Female (n,%)	9	32.1	9	37.5	
Smoking (n,%)		2	7.2	2	8.6	1.000
Alcohol consumption (n,%)		1	3.6	1	4.2	1.000

Continues variables in cells are presented as mean ± standard deviation (SD)

Table 2. *Systemic diseases and drug usage of the patients and controls.*

Systemic diseases and drug usage	Patients group		Control group	
	n	%	n	%
HT	15	53.6	12	50.0
DM	13	46.4	11	45.8
Hypercholestrolaemia	9	32.1	9	37.5
CHD	2	7.1	2	8.3
Antihypertension drug usage	15	53.6	12	50.0
Oral antidiabetics	12	42.9	6	25.0

HT: Hypertension, DM: Diabetes Mellitus, CHD: Coranary Heart Disease

DISCUSSION

In the present study, we found a significant increase in the PSV of the PCA of the patients compared to the controls. Increase in PSV was considered also increase in the amount of the blood flow to the ONH. This result could be explained by the autoregulation system which is normally found and preventing the ONH from ischemia in a certain range. We also found an increase in RI which may indicate the peripheral vascular resistance.

The physiopathology of the NAION is not fully understood today but acute transient hypoperfusion or nonperfusion of the ONH circulation is considered as the major etiopathological agent. This loss of perfusion may be due to decreased blood flow and may be due to the transient vasoconstriction.[2]

There are limited number of studies observing haemodynamic changes of the ONH circulation in patients with NAION. Bertram et al. found an increase in the retinal arteriovenous passage time by fluorescein angiography.[8] Arnold and Hepler revealed a significant delay in the filling time of the ONH capillaries in patients with NAION [14]. Leiba et al. [15] compared ONH blood circulation in the affected eyes of the NAION patients with unaffected eyes and also compared with healthy controls by using Heidelberg retinal flowmeter. They found a significant decrease in the blood flow of the affected eyes compared to both unaffected eyes and controls but also found a decrease in the unaffected eyes more than the controls. They considered that this result is associated with the structure of the optic disc. They proposed that small and crowded discs have a lower blood flow initially, and this lower blood flow causes reduced perfusion pressure which triggers ischemia at the ONH and creates a higher risk for the development of NAION. NAION is a multifactorial disease which could not be explained only with the structural property of the disc. Furthermore, Leiba and colleagues stated that there were 4 patients whose cup-to-disc ratios of the fellow eyes were 0.4 or greater in their study.[15] Structural properties of the optic disc were not reported in the present study. We found an increase in the blood flow velocity of the PCA of the patients compared to controls. This increase may show the reperfusion of the tissue due to the compensatory vasodilatation secondary to decrease of the perfusion pressure of the disc. This result is in agreement with that of Hayreh's, which claimed that after transient occlusion of the PCA, compensatory vasodilatation occurs.[7]

Ghanchi et al. found no abnormality on CDI examination of three patients with NAION where they compared NAION and giant cell arteritis in their study.[16] Initial CDI of all patients were performed within the 24 hours of presentation to the clinic. All patients with giant cell arteritis showed altered blood flow in the orbital vessels on CDI examination. However, in one patient with NAION, the blood flow was

undetectable in one of the PCAs initially, but the blood flow returned to the normal values on the 2nd day and has remained normal since. The authors suggested that this result may reflect the temporary disturbance of blood flow. The absence of detectable blood flow in the PCAs in patients with AAION may be useful in differentiating NAION from arteritic cases.

Kaup et al.[11] found that PSV and EDV of the CRA, and PSV of the PCA were significantly decreased in patients with NAION when compared with healthy controls. No significant differences were found for the RI values of all retrobulbar vessels**.** In this study, the authors stated that the mechanism of the reduction in the blood flow of the CRA is unclear. They suggested that, this reduction might be secondary due to the oedema of the optic nerve surrounding the CRA. Obuchowska et al.[17] also measured PSV, EDV and RI values of ophthalmic artery (OA), CRA and PCA in both eyes of 10 patients with NAION by CDI. They did not found any significant differences in the PSV, EDV and RI of OA and PCA between the affected and non-affected eyes. In their study, reduction of mean flow velocities and significantly increased RI value were observed in the CRA of the affected eyes. They also attributed the reduction of the blood flow of the CRA to the optic disc oedema. In this study the authors compared the results of the affected eyes only with fellow eyes of 10 patients and there was not a control group in their study. In our study, there was not any significant difference between the PSV, EDV and RI values of the CRA of the patients and the controls. CRA supplies only the surface layer of the nerve fibre layer of the ONH, therefore it has a relatively small role in the blood supply of the ONH. The main blood sources of the ONH are the paraoptic branches of the short PCAs.[18] Therefore our result is more compatible with the etiopathogenesis of the NAION.

Flaharty et al. [19] evaluated the retrobulbar haemodynamics using CDI in progressive NAION before and after optic nerve sheath decompression. They demonstrated preoperatively lower blood flow velocities in the CRA and PCA when compared with the contralateral eye. Postoperatively, they found a significant increase in blood flow velocity in the OA and CRA as well as significant decrease in vascular resistance in the PCA. There was not a control group in their study and also only 60% of their patients had a clinically normal fellow eye.

Li et al.[20] also found an increase in the RI value of the OA, CRA and PCA and a decrease in the PSV and EDV values of the CRA and PCA by CDI in a study of 40 eyes of 25 patients with NAION and 34 healthy controls. In our study, RI value of the PCA was significantly increased compared to the controls. RI value shows peripheral vascular resistance and it is inversely proportional with the blood flow of the ONH.

The results of our study must be evaluated within the context of its limitations. Firstly, optic disc topographic parameters of both patients with NAION and healthy controls were not evaluated in this study. Small or crowded discs may have a role in the pathophysiology of the NAION but the disease can not be explained only by structural factors. Sometimes there may be NAION patients with normal or even larger cup to disc ratios.[15, 21]

In our study, the flow parameters of PCA were found as increased in patients with NAION contrary to other studies.[11, 15, 20] This may show that the event is temporary in NAION and also may show compensatory vasodilatation secondary to vasoconstriction.

Another limitation of our study was that the flow parameters of the fellow eyes were not included. The risk of developing NAION in the fellow eye is approximately 30% in NAION patients and it becomes higher (42%) in patients younger than 50 years.[22] Therefore we considered that the flow parameters of both eyes of the patients with NAION would be similar. We thought it would be more accurate to compare with healthy subjects.

Kaup et al.[11] calculated the ocular perfusion pressure (OPP) and compared it with that of the controls. Although they did not found any difference between the patients and the controls regarding with OPP the mean arterial pressure was significantly higher in patients with NAION. In the present study, OPP was not calculated. According to Hayreh; the critical range of the perfusion pressure of the ONH changes to higher levels in HT differing from normal individuals, and the blood pressure (BP) measured in the brachial artery does not usually reflect the BP in the ONH vessels.[23] There is a progressive fall of BP from the carotid artery to OA and PCAs. And also some vascular changes of the PCAs induced by systemic and cardiovascular diseases may cause a decrease of the BP in the ONH capillaries.[2] Therefore measuring the perfusion pressure of the ONH before the CDI examination may not be considered as absolutely necessary.

The main difference of our study from the previous studies is that the distribution of the systemic diseases like DM, HT and CHD which make a predisposition to NAION, were similar between the patients and the control groups. Whereas, control groups of most of the previous studies were composed solely from healthy subjects.[11, 15, 20]

In conclusion, evaluation of ONH circulation in NAION by CDI can give useful information to the clinician; CDI is a non-invasive, reproducible and safe test. However it must be interpreted with caution because the event in NAION is transient and the time interval between the CDI and the onset of the symptoms can affect the results of the flow parameters while performing the examination since reperfusion may develop at this time.

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