

(39)

Assessment of blood flow velocity in eyeball arteries in multiple sclerosis patients with past retrobulbar optic neuritis in color Doppler ultrasonography

Dopplerowska ocena przepływu krwi w tętnicach gałki ocznej u chorych z zapaleniem pozagałkowym nerwu wzrokowego w przebiegu stwardnienia rozsianego

Monika Modrzejewska¹, Danuta Karczewicz¹, Grażyna Wilk²

¹ Department of Ophthalmology, Pomeranian Medical University, Szczecin
Head of the Department: prof. Danuta Karczewicz, MD, PhD

² Department of Radiology Pomeranian Medical University
Head of the Department: prof. Grażyna Wilk, MD, PhD

Summary:

Purpose: The aim of the study was to evaluate blood flow velocity in eyeball arteries in affected and unaffected eyes in patients with past retrobulbar optic neuritis in the course of multiple sclerosis (MS).

Material and methods: Evaluation of blood flow velocity in 16 eyes of 16 patients with unilateral retrobulbar optic neuritis was performed in ophthalmic artery (OA), central retinal artery (CRA) and short posterior ciliary artery (SPCA). In the arteries the following parameters have been assessed: peak systolic velocity (PSV), end-diastolic velocity (EDV), mean flow velocity (MV), indicators of peripheral vascular resistance such as Gosling Index (PI) and Pourcelot Index (RI). The obtained values have been compared to values of blood flow in the same arteries of the control group. Using Shapiro-Wilk test, mode of distribution of each parameter was analyzed. The statistic analysis has been done between group of affected eyeballs (group 1) and control group and between group of unaffected eyeballs (group 2) in multiple sclerosis patients and control group (13 individual, 26 eyes), regarding the age. The assessment was performed with the assistance of t-Student test, and in case of lack of normal distribution, by U Mann-Whitney test. Statistically significant difference was established when p value was below 0.05 ($p \leq 0.05$).

Results: Among the analyzed parameters of blood flow velocity, statistically significant disturbances in the examined eyeball arteries were found. The most significant disturbances of blood flow were found in CRA and SPCA. The affected parameters were: diminished MV velocity in OA; PSV, MV, RI in CRA and PSV, EDV, MV and RI indices in SPCA. The similar blood flow velocity disturbances were also found in unaffected eyeball arteries.

Conclusions: In MS patients with past optic neuritis disturbances of ocular circulation can be observed. The statistically significant diminishing blood flow velocity parameters and vascular resistance indices in eyeball arteries may indicate alterations of blood flow. Lowering of systolic and mean velocities and resistance indices of blood flow are most expressed in CRA and SPCA. Reduction in blood flow parameters in the examined arteries occur both, in the eyes previously affected by past optic neuritis and in contra lateral, unaffected eyes.

Słowa kluczowe:

zapalenie pozagałkowe nerwu wzrokowego, przepływ krwi w gałce ocznej, ultrasonografia dopplerowska w kolorze, stwardnienie rozsiane.

Key words:

retrobulbar neuritis, ocular blood flow, colour Doppler ultrasound, multiple sclerosis.

Introduction

One of the factors in pathogenesis of retrobulbar optic neuritis in multiple sclerosis (MS) patients is the vascular factor. Endothelin 1 (ET-1) is produced by endothelial cells and is the main physiological factor in vascular constriction. ET-1 occurs in different organs and tissues, among others in neuronal cells, glial tissue in central nervous system (CNS) and in ocular tissues (1,2). ET – 1 is found in blood of patients suffering from autoimmune diseases, as well as diseases of vascular origin,

such as: hypertension, migraine, rheumatoid arthritis, temporal arteritis and multiple sclerosis (3,4,5,6,7,8). Considering vasoconstricting properties of ET – 1 it seems probable that this substance may play a major role in nerve fiber damaging in MS patients having disturbances of eyeball circulation and retrobulbar optic neuritis (5,6,9). The goal of the study was to establish parameters of blood flow velocity in bulbar and retrobulbar circulation in MS patients with past retrobulbar optic neuritis.

Material and Method

The examined group consisted of 16 patients with past unilateral optic retrobulbar neuritis, suffering from MS, who were hospitalized in the Department of Ophthalmology, Pomeranian Medical University in Szczecin, in years 2000-2005. The average age of the patients was 39,5 (16 to 47). In 80% of cases retrobulbar optic neuritis occurred for the first time, in 20% of cases occurred for the second time. Among studied patients 80% were women and 20% were men. The levels of individual blood flow velocity parameters were analyzed.

Ultrasound examinations as a routine were performed by Ultrasound Laboratory of Radiology Department of Pomeranian Medical University after obtaining consent from patients. Based on data from case histories it was established that time elapsed from the first symptoms until admission to the ultrasound examination ranged from 6 months to 2 years. The examinations of endothelin – 1 level were not performed on the studied group of patients since this was not the aim of this research.

The studied group consisted of patients with affected eyes (n = 16) – group 1 and patients with unaffected eyes (n = 16) – group 2. An eye examination including the determination of visual acuity on Snellen chart was as follows: 0.9-1.0, mean value 0.95 (sd 0.12). Ophthalmoscopic eye fundus examination was normal. The systolic and diastolic blood pressure measured during blood flow velocity investigation did not exceed values of 120 mmHg and 75 mmHg respectively. Estimation of intrabulbar pressure did not exceed 17.3 mmHg.

Control group included 13 healthy individuals, n = 26 eyes, in whom cardiac and vascular diseases and ophthalmic ailments did not occur and who were matched for age and sex with the studied group. The control group consisted of non-smoking individuals in whom application of general and ocular medications was excluded. Visual acuity in this group equaled 1.0 on the Snellen chart.

With assistance of Shapiro-Wilk test, normality of distribution of given attributes was analyzed. The average of analyzed parameters between affected eye group and control group, unaffected eye group and control group, according to age, by means of t-Student test, and in case of lack of normal distribution by means of U Mann-Whitney test, were compared. The level of significance is given in each of presented tables, and the difference was considered statistically significant at p value $p \leq 0.05$. It has been indicated in the tables which test was used depending on normality of distribution of a given attribute.

Blood flow velocity in ophthalmic (OA), central retinal (CRA) and short posterior ciliary arteries (SPCA) was measured with assistance of Acuson 128 X P10 apparatus, with color option and sector probe 7.5 MHz as a routine examination of hospitalized patients. Ultrasound probe was applied on closed eyes, using ultrasound gel, without exertion of pressure. During the exams patients were recumbent, motionless, looking straight ahead so that the best signal from the examined arteries could be achieved. During the examination, angle correction was applied to the pulsed Doppler recordings to minimize errors in the examined velocities. Ophthalmic artery was localized medially to optic nerve, 15-18 mm from posterior pole of an eyeball, after its crossing with optic nerve. Central retinal artery was localized in the head of optic nerve, 2-3 mm before its entry into the eyeball. Signals from short posterior

ciliary arteries were found in lateral and medial sections of an eyeball. Because numerous branches of short posterior ciliary arteries were available for assessment, only temporal branch was chosen for analysis. In Doppler ultrasound the following parameters were assessed: peak systolic velocity (PSV, m/s), peak end-diastolic velocity (EDV, m/s), mean flow velocity (MV, m/s), Gosling Index (PI), Pourcelot Index (RI). PSV was described as the highest value of blood flow during cardiac systole; EDV was the lowest value of blood flow at the end of cardiac diastole; RI as the quotient of difference between peak systolic and peak diastolic velocity over peak systolic velocity; PI as quotient of difference between peak systolic and peak diastolic velocity over mean flow velocity. Shifts of blood flow patterns in the examined arteries were compared between affected patients and control group.

Results

In group 1 the analysis of changes in vascular blood flow was as follows: in ophthalmic artery – PSV, EDV and MV were lower than in control group. The difference was statistically

Examined parameters Badane parametry	Past optic neuritis eyes group1 Oczy chore grupa 1 (n=16)		Control group Grupa kontrola (n=26)		p
	Mean	sd	Mean	sd	
Ophthalmic Artery					
PSV	0.4069	0.0888	0.4792	0.1414	0.1040
EDV	0.1088	0.0370	0.1408	0.0610	0.0925
MV	0.1750	0.0523	0.2277	0.0796	0.0412
PI	1.8219	0.5491	1.5962	0.4225	0.2342
RI	0.7281	0.0889	0.7115	0.0741	0.5955
Central retinal artery					
PSV	0.0944	0.0250	0.1562	0.0427	0.0001
EDV	0.0344	0.0103	0.0415	0.0234	0.2796 ¹⁾
MV	0.0456	0.0136	0.0723	0.0239	0.0008
PI	1.3731	0.2449	1.5769	0.3343	0.0689
RI	0.6406	0.1031	0.7738	0.0935	0.0012
Temporal short posterior ciliary artery					
PSV	0.1331	0.0400	0.2971	0.0946	0.0001
EDV	0.0463	0.0213	0.0764	0.0384	0.0113 ¹⁾
MV	0.0688	0.0233	0.1650	0.0592	0.0001
PI	1.3288	0.4397	1.3607	0.3784	0.8338
RI	0.6575	0.1249	0.7293	0.0968	0.0929 ¹⁾

Tab. I. The level of tested parameters of blood flow velocity in past optic neuritis eyes and in eyes of control group in ophthalmic artery (OA), central retinal artery (CRA) and short posterior ciliary artery (SPCA) among studied patients (group 1).

Tab. I. Poziom badanych parametrów w oczach z przebyłym zapaleniem nerwu wzrokowego i w grupie osób zdrowych w tętnicy ocznej (OA), środkowej siatkówki (CRA) i tętnicy rzęskowej tylnej krótkiej (SPCA) u badanych pacjentów (grupa 1).

¹⁾ U Manna-Withney's test analysis

significant at $p = 0.04$ for MV parameter. Values of PI and RI indexes showed higher, but statistically insignificant numbers when compared to control group (table I).

In central retinal artery values of PSV and MV velocities were diminished in relation to age norm of the control group. Statistically significant differences were found for PSV ($p = 0.001$) and MV ($p = 0.008$). Values of PI and RI were below normal, showing statistical significance for RI ($p = 0.012$) (table I). In short temporal posterior ciliary artery diminished PSV, EDV and MV velocities were found. Of those, statistically significant were values for systolic ($p = 0.0001$) and mean velocity ($p = 0.0001$). Values for RI and PI were lowered in this artery, but insignificantly (Table I).

Shorts used in tables: peak systolic velocity (PSV), peak end-diastolic velocity (EDV), mean velocity (MV), pulsation index (PI), vascular resistance (RI), n-number of cases, sd-standard deviation, p value ≤ 0.05 .

Examined parameters Badane parametry	Unaffected eyes Group2 Oczy towarzyszące bez cech choroby Grupa 2 (n=16)		Control group Grupa kontrolna (n=26)		P
	Mean	sd	Mean	sd	
Ophthalmic Artery					
PSV	0.3869	0.1178	0.4792	0.1414	0.0655
EDV	0.1013	0.0456	0.1408	0.0610	0.0560
MV	0.1650	0.0630	0.2277	0.0796	0.0253
PI	1.7119	0.3991	1.5962	0.4225	0.4559
RI	0.7363	0.0671	0.7115	0.0741	0.3550
Central retinal artery					
PSV	0.1131	0.0326	0.1562	0.0427	0.0047
EDV	0.0325	0.0100	0.0415	0.0234	0.1728 ¹⁾
MV	0.0531	0.0149	0.0723	0.0239	0.0134
PI	1.5331	0.3665	1.5769	0.3343	0.7419
RI	0.7169	0.0766	0.7738	0.0935	0.0822
Temporal short posterior ciliary artery					
PSV	0.1575	0.0599	0.2971	0.0946	0.0000
EDV	0.0494	0.0112	0.0764	0.0384	0.0117
MV	0.0781	0.0237	0.1650	0.0592	0.0000
PI	1.2969	0.4085	1.3607	0.3784	0.6620
RI	0.6725	0.1008	0.7293	0.0968	0.1281 ¹⁾

Tab. II. The level of tested parameters of blood flow velocity of ophthalmic artery (OA), central retinal artery (CRA) and short posterior ciliary artery (SPCA) in unaffected eyes in patients with past neuritis in comparison to healthy eyes of the control group (group 2).

Tab. II. Poziom badanych parametrów w oczach towarzyszących bez cech choroby w tętnicy ocznej (OA), środkowej siatkówki (CRA) i tętnicy rzęskowej tylnej krótkiej (SPCA) u pacjentów z przebyłym zapaleniem nerwu wzrokowego i grupą kontrolną (grupa 2).

¹⁾ U Mann-Whitney's test analysis

Subsequent measurements took place in order to assess parameters of blood flow in contra lateral, theoretically unaffected eye, in which no disease was diagnosed. In ophthalmic, central retinal and in short posterior temporal ciliary artery statistical analysis of parameters of blood flow in unaffected eyes of group 2, patients showed decreased MV in OA; PSV, MV in CRA and PSV, EDV and MV velocities in SPCA. Decrease these parameters were statistically significant. Most impressive changes were observed in SPCA, where all velocities parameters of blood flow were significantly below normal, compared to control group. For PSV $p = 0.000$, for EDV $p = 0.0117$, for MV $p = 0.0000$. Indices PI and RI did not show major changes in all the examined arteries (table II).

Discussion

In MS patients with retrobulbar optic neuritis, disturbances in bulbar arteries blood flow are observed in color Doppler ultrasound. According to many investigators' opinions it is well known that endothelin-1, as a vessel constricting agent, can disturb axoplasm flow in optic nerve. Disturbance of circulation in eye tissues can be a consequence of this substance's action (1,5,9,10). It seems that analyzing the changes of blood flow parameters in choroid and retinal arteries can give an idea about disturbances of haemodynamic in this region. Results of our study confirm that in post optic neuritis eyes, systolic, diastolic and mean velocities of blood flow are diminished in all eyeball arteries. In all of the examined patients the largest decrease of blood flow occurs in central retinal and short posterior temporal arteries and these values are statistically significant (Table I). The decreased values of the parameters are probably due to vascular spasm. In MS patients elevated levels of endothelin-1 are found (5,9). In vitro studies ET-1 exerts constricting action on ophthalmic and short posterior ciliary arteries, causing a powerful and prolonged vascular spasm and diminished blood flow in choroidea (11). ET-1 also causes powerful narrowing in retinal vessels (4). It has been shown in experimental studies that intravitreal and intravenous administration of ET-1 in animals and humans causes diminished blood flow in optic nerve papilla (6). In works of Akarsu and all, similar results to ours were obtained. The investigators found decreased blood flow in central retinal artery in post retrobulbar optic neuritis patients. Eyeball blood flow velocity studies were performed several months after optic neuritis by means of color Doppler ultrasound, as in our study (9). According to other investigators, i.e. Karaali and all, velocity of blood flow can increase in ophthalmic artery in initial period of acute inflammation of an optic nerve. They have not found changes in blood flow in other eyeball arteries (10). Still, according to other investigators, vascular resistance in eyeball arteries of MS patients does not change but increases slightly in central retinal artery. It can be due to higher concentration of ET-1 in MS patients' blood, which has edema of a retrobulbar part of an optic nerve in the course of neuritis (1,5,9,12,13). In our study we have not found major changes in Pourcelot index (RI) or Gosling index (PI) in post retrobulbar optic neuritis patients, when compared to control group. It may be a result of a decrease of inflammation features of an optic nerve, in the group of patients receiving treatment. Application of corticosteroids and calcium channel blockers generally, can partially reverse disturbances of microcirculation in optic nerve disc (14,15). In the group of the

examined patients the treatment course with steroids had been terminated, which undoubtedly influenced the healing process of inflammation and could cause reversal of disturbances in vascular resistance in central retinal artery, in which blood flow was most commonly affected. There are not many accessible reports in literature about abnormalities in vascular resistance in eyeball arteries of MS patients with retrobulbar optic neuritis. Some investigators observe slight increase of vascular resistance index (RI) in central retinal artery (8,9). In the studies of Karaali, mean elapsed time from the first symptoms of optic neuritis until the admission of Doppler ultrasound examination was 5.2 days, in Elvin's studies – 27 days (10,12). Increase of values in vascular resistance index (RI) is described in optic neuritis patients with acute clinical symptoms. According to investigators, the key issue is the period of time between appearance of symptoms of retrobulbar optic neuritis and blood flow velocity examination. It is suggested that lack of abnormalities in vascular resistance is due to quite a long period of time that has elapsed since clinical manifestations of this disease. During Doppler ultrasound examinations in the studied group, our patients went through remission of symptoms of optic neuritis (remission spanned between 6 months and 2 years).

Interesting phenomenon is an abnormally low blood flow in eyeball arteries of unaffected eyes of MS patients. In both study groups of patients statistically diminished systolic and mean velocity of blood flow and decreased RI index were observed in short posterior ciliary arteries and especially central retinal artery in comparison to control group (Table II). This may indicate that in past optic neuritis patients, circulation disturbances occur both, locally and systemically, and it can be observed in affected optic neuritis eye and in unaffected eye of the same patient. Systemic action of ET – 1 probably is responsible for the influence on retinal and choroidal arteries diameters changes and local haemodynamic of eyeball. However, in order to confirm the outcomes of this research further examinations among larger number of patients are necessary.

It is thought that Doppler ultrasonography as a non invasive and repeatable method continues to be a suitable examination of imaging the dysfunction of blood flow in vascular system of an eyeball.

Conclusions

1. The statistically significant diminishing of blood flow velocity parameters and resistance indices in studied arteries mainly in CRA and SPCA may indicate disturbances of retinal and choroidal circulation in MS patients with past retrobulbar neuritis.
2. In examined patients abnormalities in CRA and SPCA blood flow in contra lateral, unaffected eye were also found in color Doppler examination.
3. Colour Doppler ultrasound is an effective and helpful method in the assessment of haemodynamic disturbances of eye circulation in MS patients with past optic neuritis.

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Adres do korespondencji (Reprint requests to):
Monika Modrzejewska, MD, PhD
ul. Wierzbowa 21 BC/3
72-005 Szczecin