ORIGINAL ARTICLES

The value of ophthalmoscopy in the diagnosis of arterial hypertension in patients with ischemic brain disease

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Beside dyslipoproteinemia, one of the key risk factors for the onset of brain atherosclerosis, as well as ischemic brain disease (IBD) is arterial hypertension. Significant number of patients is not aware of their hypertension, and a paradoxical blood pressure decrease can occur at the onset of IBD, due to the failure of autoregulation mechanisms. Likewise, valid anamnestic data can not frequently be obtained due to difficulties in communication with patients. Regarding these facts, our hypothesis was that ophthalmoscopy in patients with IBD had the greatest sensitivity in the diagnosis of hypertensive disease, its duration and severity. For that reason, the purpose of this study was to determine the significance of ocular fundus examination in those patients with IBD who were not aware of their hypertension, or the high blood pressure was not registered at the admission. Study comprised 140 IBD patients selected upon the following criteria: ophthalmoscopy was performed by the same ophthalmologist, and IBD was diagnosed according to clinical criteria and by brain computerized tomography. Results of the study demonstrated that 26 (18.6%) patients, although not aware of having hypertensive disease, had grade I hypertonic fundus, 14 (10%) had grade II, and 8 (5.5%) had grade III hypertonic fundus, which indicated the high sensitivity of ophthalmoscopy in the diagnosis of hypertensive disease, as well as its duration and severity. This is particularly important in patients with negative history of hypertension, and also suggests the significance of routine ophthalmoscopy in normotensive patients.

Key words: **hypertension; cerebral ischemia; ophtalmoscopy; fundus oculi; severity of illness index.**

Introduction

Brain vascular diseases are ranked the third as the leading cause of both morbidity and mortality of the great majority of world population (1). These are typical diseases of the elderly, and due to the prolongation of life span they can be expected to occur more frequently. The fact that the patients develop a great degree of physical and mental disability is also very important, which is a great health, social and economic problem for every community. Ischemic brain disease, represented with three fourths of all brain vascular diseases, is dominated in this clinical entity. Atherothrombotic mechanism of IBD onset is dominated in this group. In certain patients IBD is the result of fibrinoid degeneration of penetrating cerebral arteries, as the sequela of non-regulated hypertension. Recently, ischemic lesions of cardiogenic embolic mechanism are more frequently found due to the better understanding of physiopathological processes and diagnostic procedures (2–6).

A number of correlating factors, such as hemodynamic disorders and blood hypertension as the most important, is included in IBD etiology and pathogenesis (7–9).

Arterial hypertension, as well as the other significant diseases (10–14) frequently remain unrecognized because of the well-known clinical indicators that in the majority of patients with IBD adequate anamnestic data of the disease onset and/or some earlier relevant diseases cannot be obtained due to the disease nature, with the possibility of break down of autoregulational mechanisms during the acute ischemia of brain parenchyma. For that reason, and upon the scientifically confirmed data about the blood hypertension sequelae on many organic systems, especially on small blood vessels, which can be the marker of the presence and severity of hypertensive disease, the following working hypothesis was established:

1. ocular fundus examination in patients with IBD, with no data suggesting hypertensive disease and/or in the absence of high blood pressure values, had the greatest sensitivity in diagnosis of presence, duration and severity of hypertensive disease, and the degree of fundus changes was in positive correlation with the severity of IBD.

The following aims of the study were formulated for hypothesis testing:

1. in IBD patients without the data of hypertensive disease and/or high values of blood pressure not recorded during the clinical observation, ophthalmoscopy should be performed in order to establish the changes suggesting hypertensive disease;
2. degree of fundus changes should be evaluated according to the accepted criteria;
3. CT-scan of the brain should be done in all patients 3-10 days after IBM was detected for the confirmation of ischemic lesion of brain parenchyma;
4. IBD severity should be graded in all patients included in the study according to the internationally accepted criteria;
5. appropriate statistic analysis should be used to determine the significance of fundus changes for sensitivity of presence, duration and severity of hypertension in relation to IBD severity.

Methods

The study comprised 140 patients admitted to the Clinic of Neurology of the Military Medical Academy for the acute ischemic brain disease (AIBD) of the following types: TIA – transient ischemic attack with the withdrawal of clinical neurological phenomenology within the first 24 hours, RIA – reversible ischemic attack with complete recovery of neurological deficiency within the first seven days and BI – brain infarction.

None of the patients had positive history of hypertensive disease and/or the high blood pressure values were not recorded within the first three days after the admission (blood pressure was measured three times a day).

Patients included in the study were not on the antihypertensive therapy before ophthalmoscopy was performed.

Ischemic lesion of brain parenchyma was confirmed by CT-scan of the brain.

The severity of fundus changes was determined by ophthalmoscopy performed by the same ophthalmologist, and grading was done according to internationally accepted criteria (15).

Degree of IBD severity was determined according to J. Grotta modified scale (16).

Results were analyzed using parametric (Student's t-test), and nonparametric statistics (linear and multiple regression analyses).

Results

Study comprised 140 patients of both sexes, 78 males and 62 females. Mean age was 64.6 years. Transient ischemic attack was found in 27 patients, brain infarction of mild degree in 26 patients, of moderate degree in 45 and of severe degree in 42 patients. Five patients died during the treatment. General characteristics and severity of IBD are presented in Tables 1 and 2.

Table 1

General characteristics

Patients (n=140)	Male	Female	Age		
			male		female
	78	62	67.4	($\bar{x}$=64.6)	62.6

Table 2

Severity of IBD

Severity of IBD/ frequency	Patients n (%)	
TIA	27 (19.2%)	
RIA	26 (18.5%)	
BI-M	45 (32.1%)	
BI-S	42 (30.0%)	5 patients died

TIA-transient ischemic attack; RIA-reversible ischemic attack; BI-M - brain infarction-moderate; BI-S - brain infarction-severe

Hypertensive fundus changes (three-degree scale) were observed in 48 patients (34.2 %) by ophthalmoscopy. Distribution of fundus changes in total patient group, and then in correlation with IBD severity is shown in Table 3.

Table 3

Distribution of fundus changes and correlation with IBD severity

IBD/ FC	Normal finding	FH-I	FH-II	FH-III
Total (n=140)	92 (65.7%)	26 (18.6%)	14 (10%)	8 (5.5%)
TIA (n=27)	19 (70.5%)	6 (22.2%)	2 (7.3%)	0
RIA (n=26)	19 (72%)	5 (20%)	2 (8 %)	0
BI-M (n=45)	31 (68.9%)	7 (15.5%)	5 (11.1%)	2 (4.5%)
BI-S (n=42)	23 (66%)	8 (19.04%)	5 (11.9%)	6 (13.8%)

FC - fundus changes; FH-I - hypertonic fundus, grade I.

Linear regression analysis revealed significant correlation of severe fundus changes and most severe cases of cerebral ischemic disease.

Significance level in total group was $r=0.399$ ($p<0.05$). The same level was confirmed in patients with transient ischemic attack, i.e., mild and moderate brain infarction. Correlation was $r=0.487$ ($p<0.01$) for the most severe cases of cerebral ischemic disease. Influence of hypertension duration on fundus changes was confirmed by subsequent detailed heterohistory and/or history of those patients who were not able to provide relevant data due to the neurologic deficit (aphasia, etc.) in the acute phase. This group comprised 29 patients, and significant correlation was observed between the duration of hypertensive disease and the severity of fundus changes – $r=0.478$ ($p<0.01$).

Discussion

At the very beginning it should be pointed out that the knowledge in reactive oxidative matters interactions, calcium homeostasis mechanisms, excitatory neurotransmitters and mechanisms of excitoneurotoxicity, nitric oxide, platelet activating factor, cytokines and neurotrophins, both in physiological and pathological conditions, is necessary for the adequate understanding of complex physiopathological mechanisms of cerebral ischemic disease, as well as atherosclerosis. All those factors and their interactions are of the utmost importance for the normal functioning of the body. Nevertheless, under the certain conditions they can become mediators of pathological cascade. In clinical conditions certain easily controlled disorders or risk factors influencing atherosclerosis and IBD should not be disregarded in clinical conditions (1).

Vascular diseases of the brain are the third leading cause of mortality and morbidity in all countries, regardless of their general development. These diseases are permanently ranked the third although the oscillating, somewhat paradoxical trend of their frequency can be observed (1, 17–28).

Ischemic brain disease is represented in 80% brain vascular diseases (1).

In the majority of patients with ischemic brain disease atherosclerosis of major brain arteries is the primary disease, and cardiogenic embolic mechanism and lacunary infarctions due to fibrinoid degeneration of penetrating brain arteries caused by blood hypertension are less frequently found (1, 28–41).

Etiology and pathogenesis of brain atherosclerosis, as well as atherosclerosis in general, are incompletely understood. However, prospective studies identified numerous factors that contributed the development of atherosclerogenesis, and evaluated their significance. Those factors are the risk factors for atherosclerosis.

Those factors in brain atherosclerosis, ranged according to their significance are: arterial hypertension, dyslipoproteinemia, diabetes and smoking, although the smoking is more frequently related to cerebral ischemic disease (1, 42–69).

Risk factors for other vascular regions have different range of significance. This is explained by poorly defined tissue factors. It is possible that certain differences in functional anatomy and physiology of circulation in different vascular regions cause different reactions of artery wall components to atherogenic factors.

Results of recent studies revealed that functional characteristics of endothelial cells might have the leading role in atherogenic effects of different factors. It was established that in endothelial cells of the major brain arteries existed strong expression of E-selectin, and in endothelial cells of brain microcirculation strong basal expression of ICAM-1, very sensitive to the stimulation of cytokines, as well as strong expression of major histocompatibility of classes I and II antigenes complex. Pronounced expression of major histocompatibility of classes II and VCAM-1 complex antigenes existed in coronary arteries of endothelial cells (1, 70–96).

These differences could also indicate the different sensitivity to certain factors during the initial phases of atherogenesis.

According to recent findings, the disbalance of lipid constitution and metabolism, as well as their interactions with functional and structural integrity of endothelial cells in arterial walls are the basis of physiopathological processes.

The knowledge of certain physiological characteristics of arterial walls is necessary for the understanding of these processes. As far as lipoprotein circulation is concerned, arterial wall functions similarly as a drain; outgoing amount of lipoproteins is irrelevant compared to that incoming to intima (1, 70–96). Degree of lipoprotein influx to arterial

wall is the result of plasma lipoprotein concentration and permeability of arterial endothelial layer. Whereas lipoprotein influx into arterial wall is linearly correlated to lipoprotein level in the plasma, permeability of arterial endothelial layer is individually variable. Determinants of arterial wall permeability for lipoproteins are the size of lipoprotein particle and endothelial surface integrity for which violation, meaning the increased risk for greater lipoprotein influx and development of atherosclerotic lesions, are responsible mechanical injuries, immunological lesions and chemical damage by smoke components such as carbon monoxide, nitric oxide and nicotine (1, 70–100).

Blood pressure is a significant factor determinating the degree of arterial wall permeability for lipoproteins; high blood pressure significantly increases the influx of LDL (low density lipoprotein). The influence of blood pressure on endothelial surface integrity is frequently disregarded. Conditions for the increase of hemostasis disorders, which are enhanced by endothelial damage occur due to turbulent stress of blood stream on blood vessel bifurcation. Thus, the blood pressure is aggraveted by the already existing damage and the process is in positive correlation with the severity and duration of hypertensive disease.

Beside the already described processes, expressed mostly on the arterial walls of medium and large lumen blood vessels, blood pressure also affects microcirculation, inducing rheological disturbances through similar mechanisms. These processes usually cannot be detected by objective diagnostic methods. Nevertheless, relatively simple method of direct ophthalmoscopy of the fundus reveals changes in blood vessel. Branches of central retinal artery are arterioles by their anatomical features, and exactly the changes affecting arterioles can be seen on retinal blood vessels. This is particularly pronounced in advanced atherosclerosis, nephritis and arterial hypertension. It should be emphasized that retina is a brain sprout, and retinal vascular system is a branch of brain vascular system. Regarding that, ophthalmoscopy has the significance of cerebroscopy for some regions (98–110).

Numerous states can cause fundus changes in which the main physiopathological process is related to retinal vascular system changes. Local disturbance of hemodynamics in the eye vascular system occurs due to the pressure increase in the central retinal artery, which is easily observed by ophthalmoscopy. Nevertheless, differentiation of the real nature of the initial pathological event is frequently not possible. In such cases ophthalmoscopy provides useful information for planning the algorithm of diagnostic procedures. On the contrary, fundus changes in hypertensive disease are highly specific, and ophthalmoscopy is a procedure of choice for the evaluation of these changes. Furthermore, opthalmoscopy is significant since the duration and severity of hypertensive disease, as well as therapeutic approach can be assessed according to these changes (98–110).

However, in spite of theoretical knowledge and understanding of physiopathological cascade of this disorder, clinical trials of this problem are not so frequent. This study confirmed great sensitivity and specificity of direct ophthalmoscopy in the estimation of presence, duration and severity of hypertensive disease, even in those patients who were not aware of the disease or were not able to provide valid data on the matter. Besides, this study also revealed the correlation of the severity of fundus changes caused by hypertension and the severity of ischemic brain disease.

Conclusion

Results of the study demonstrated the great sensitivity and specificity of direct ophthalmoscopy in the diagnosis, as well as in the evaluation of the duration and severity of hypertensive disease in patients with cerebral ischemic disease.

The extent of ocular changes related to hyperetensive disease is in direct correlation with the severity degree of cerebral ischemic disease.

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Апстракт

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ВРИЈЕДНОСТ ОФТАЛМОСКОПИЈЕ У ДИЈАГНОСТИЦИ ХИПЕРТЕНЗИЈЕ КОД БОЛЕСНИКА СА ИСХЕМИЈСКОМ БОЛЕШЋУ МОЗГА

Артеријска хипертензија представља уз дислипопротеинемију један од кључних фактора ризика за развој мождане атеросклерозе, а тиме и исхемијске болести мозга (ИБМ). Међутим, значајан број болесника не зна да има хипертензивну болест, а у току настанка ИБМ може доћи до парадоксалног пада крвног притиска због слома ауторегулацијских механизама. Такође, у значајном броју случајева је отежана сарадња са болесницима, те се тако не могу добити валидни анамнестички подаци. Цијенећи ове чињенице наша хипотеза је била да офталмоскопски преглед очног дна код болесника са ИБМ, без података о хипертензивној болести, највећу сензитивност у дијагностици постојања, трајања и озбиљности хипертензивне болести. Због свега изнијетог циљ овог испитивања је био да утврди значај прегледа очног дна код болесника са ИБМ који нијесу знали за хипертензивну болест или у моменту пријема нијесу измерене повишене вриједности крвног притиска. Испитивањем је обухваћено 140 болесника са ИБМ са овако утврђеним критеријумима. Офталмоскопски преглед очног дна је обавио исти офталмолог, а ИБМ је потврђена на основу клиничких критеријума и помоћу прегледа мозга компјутеризованом томографијом. Резултати испитивања су показали да 26 (18,6%) болесника са ИБМ, и поред тога што нијесу знали за хипертензивну болест, има хипертонични фундус првог степена, 14 (10%) има хипертонични фундус другог, а 8 (5,5%) болесника хипертонични фундус трећег степена. Ово испитивање указује на високу сензитивност офталмоскопског прегледа очног дна у детекцији хипертензивне болести, али и о њеној озбиљности и трајању. Ово је посебно значајно код болесника са негативном анамнезом за хипертензију и указује на значај потребе рутинског прегледа очног дна и код болесника који су нормотензивни.

Кључне речи: **hipertenzija; mozak, veliki, ishemija; oftalmoskopija; očno dno; bolest, indeks težine.**