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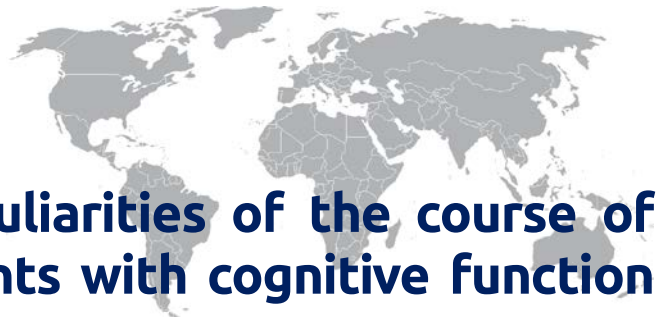

Clinical and instrumental peculiarities of the course of arterial hypertension in patients with cognitive function impairments

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ABSTRACT

Objective: Cognitive impairments (CIs) appear to be commonly encountered in patients with arterial hypertension (AH). Hence, our study was aimed at examining the frequency of cognitive impairments (CIs) in the physician's outpatient practice, as well as at determining clinical and instrumental peculiarities of the course of AH in patients with and without CIs.

Method: We carried out comprehensive examination of three hundred and fifty 50-to-80-year-old hypertensive patients followed up in the setting of a polyclinic and tested by means of neuropsychological scales (MMSE, Mini-Cog test, Montreal Cognitive Assessment Scale, Hospital Anxiety and Depression Scale), duplex scanning of extracranial vessels, and magnetic resonance tomography (MRT) of the brain.

Results: The findings of neuropsychological testing demonstrated the presence of CIs in 83.5% of hypertensive patients, with CIs reaching the level of dementia in 16.9% and being combined with depressive symptoms in 40.3%. Hypertensive patients with CIs as compared with those without CIs were found to have more pronounced lesions to white matter of the brain: periventricular (71.1%) and/or subcortical (15.8%) leukoaraiosis. Subcortical leukoaraiosis of the frontal lobes of the brain was associated with an elevated level of systolic arterial pressure (SAP). It was confirmed that impaired circadian rhythm of AP with stable persistence of nocturnal hypertension resulted in the most pronounced structural and morphological damage of the brain.

Conclusion: High incidence of CIs in hypertensive patients has been confirmed. Structural and morphological impairments of strategically important regions of the brain (subcortical leukoaraiosis of the frontal lobes) in hypertensive patients with CIs were associated with elevated SAP.

Keywords: cognitive impairments, arterial hypertension, neuropsychological tests, subcortical leukoaraiosis

INTRODUCTION

Despite advances and possibilities of modern pharmacotherapy, cognitive impairments (CIs) belong to the number of the most widely occurring syndromes encountered in everyday practice of a physician (1).

Recent years have seen growing interest in the problem of elevated arterial pressure (AP) as a risk factor for disorders of cognitive function (CF) (2-4). There exists a direct relationship between the level of AP at the age of 50 years and the condition of CF at 70 years of age: "the lower AP, the better CF", however, this position has recently been a matter of debate (5-6).

Brain damage is considered as one of the most important criteria of additional risk for cardiovascular complications in patients with arterial hypertension (AH) (7-10). This is related to both high incidence of AH amongst elderly people and the pattern of a specific lesion of cerebral vessels (11-13).

Currently, ever growing attention has been attracted by an intermediate stage of the development of CIs when they have not yet achieved the degree of dementia but are already beyond the limits of the age-related norm. The duration of this stage may vary within considerable time intervals – from several months to many decades (14, 15). Formerly these mild impairments were often interpreted as age-related changes (16) and they are currently regarded as a prodromal stage of a severe cognitive defect and referred to as "moderate cognitive impairments" (MCIs) (17-20).

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Table 1: *General clinical characteristics of the examined patients with AH*

Parameters		Number of patients	
		abs.	%
Men/women		168/182	48/52
Average age, years		64.5±9.6	
Education	higher	147	42
	secondary	203	58
Average anamnestic duration of AH, years	less than 10 years	96	27.4
	10–20 years	148	42.3
	more than 20 years	106	30.3
Degree I/II/III AH		117/211/22	33.4/60.3/6.3
Stage I/II/III AH		11/173/166	3.1/49.4/47.4
SAP, mm Hg.		164.88±6.73	
DAP, mm Hg.		103.67±4.97	
Presence of regular AHT		247	70.6
Taking vascular and nootropic drugs:	permanently	15	4.28
	course treatment	188	53.7
	not taking	147	42

Currently available findings of clinical trials strongly suggest that modification of risk factors and appropriate treatment initiated at an earlier stage may prove effective and would make it possible to delay further deterioration in cognitive function (CF) (21-24).

In this connection, an important role is played by not only early diagnosis of CIs in hypertensive patients but also timely administration of effective drugs at the stage of mild-to-moderate CIs. Currently, there exists a sufficient number of drugs exerting a positive effect on the cognitive sphere, however the possibilities of the majority of them, including vasoactive drugs, in treatment of moderate cognitive impairments have not yet been conclusively established (25, 26).

Taking into account the role of AH in the development of MCIs and dementia, of primary importance is early diagnosis of initial manifestations of disorders of higher cerebral functions, which may for a long time remain the only clinical sign of neurological ill-being.

Therefore, this study was undertaken to investigate the frequency of cognitive impairments (CIs) in the outpatient polyclinic practice of a physician, as well as clinical and instrumental peculiarities of the course of AH in patients with and without CIs.

MATERIALS AND METHODS

We examined a total of 350 ambulatory patients diagnosed with stage I-III arterial hypertension. Of these, 168 (48%) were men and 182 (52%) women, aged from 50 to 80 years (mean age 64.5±9.6 years) and complaining of headache, dizziness, memory loss, sleep disorders and decreased performance efficiency (**Table 1**).

The presence and degree of CIs in hypertensive patients were determined by means of the readily available and easy for interpretation in practicing physician's work neuropsychological tests which were as follows: Mini-Mental State Examination (MMSE), Montreal Cognitive Assessment Scale (MoCa), and Mini-Cog test.

The Mini-Cog test was used only once as screening for revealing pronounced CIs or dementia. The Mini-Mental State Examination (MMSE) was administered in dynamics for assessment of the state of the CF: perception, memory, speech, reading, etc. The MoCa test was used in dynamics in order to assess various cognitive spheres: attention and concentration, executive functions, memory, language, visual-constructive skills, abstract thinking, counting and orientation. The Hospital Anxiety and Depression Scale (HADS) was administered only once in order to rule out depression.

All patients were subjected to circadian monitoring of AP (CMAP) by means of portable recorders BR-102 («Schiller», Switzerland) during 24 hours. Sixty-five hypertensive patients (38 patients with MCIs and 27 patients without MCIs) underwent duplex scanning of the extracranial vessels using the expert-level ultrasound scanner Logiq-7 (manufactured by General Electric) for assessment of patency of the internal carotid artery (ICA), presence of deformities, shape of tortuosity of the extracranial portion of the ICA, haemodynamic disorders in the tortuosity zone.

Structural and morphological brain damages were assessed by single use of MRI of the brain in 38 hypertensive patients with MCI and 27 hypertensive patients without MCI. MRI was carried out on the MR-tomograph "Excelart Vantage" (Toshiba, Japan) with a magnetic field strength of 1.5 T.

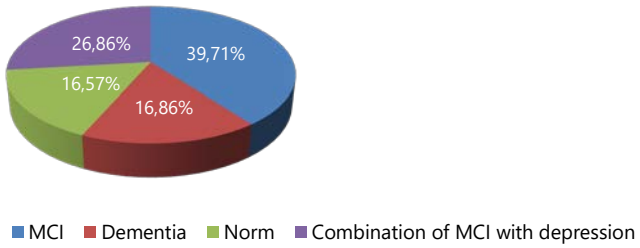

Figure 1: *Incidence of CIs in hypertensive patients enrolled into the study*

Statistical Processing

The obtained findings were statistically processed with the use of the applied programs Microsoft® Excel 2002 and SPSS 11.5, also indicating the correlation coefficient r. If the correlation coefficient was within the range from 0.8 to 0.95, the linear relationship between the parameters was considered strong, in case of $0.6<r<0.8$ – between the parameters linear correlation existed, if $0.6<r<0.4$ the correlation was weak and if $r<0.4$ the correlation coefficient was regarded non-significant.

RESULTS

The results of neuropsychological testing of 350 patients with stage I-III AH demonstrated that MCIs were observed in 66.6% of hypertensive patients; of these, 40.3% of patients were found to have CI combined with depression and 16.9% of patients were diagnosed with severe CIs. No deviations while performing neuropsychological tests were revealed in 16.6% of hypertensive patients (**Figure 1**).

Sensitivity of the MoCa test for detection of MCIs in hypertensive patients turned out to be higher as compared with that of the MMSE. CIs were diagnosed with the help of the MoCa test in 43.1% of hypertensive patients having successfully performed the MMSE test.

Analysing demographic characteristics of hypertensive patients with and without MCIs demonstrated that in the group of hypertensive patients with preserved CF the average age amounted to 59.4±9.6 years which was significantly lower than in the groups of hypertensive patients with CIs ($p<0.05$); the educational level – 14.5±2.1 years, which also differed significantly from the patients with CF impairments ($p<0.05$).

Hypertensive patients with CIs had a longer history of AH (15.1±9.6 years) as compared with the group of patients without CF impairments (9.5±4.9 years). 34.5% of patients with CI received no regular AHT, 39.6% did not control the AP level (in the group of patients without CIs – 21% and 24.1% of patients, respectively).

Individual analysis of affective disorders showed the presence of subclinical impairment of the anxiety-and-depression spectrum in 40.3% of hypertensive patients with CIs.

The results of clinical measurement of AP in the group of hypertensive patients with CIs were comparably similar when compared with the group of patients without CIs: in the group of patients with CIs clinical SAP averagely amounted to 163.4±18.5 mm Hg, in the group of patients without CIs – 156.6±11.9 mm Hg ($p>0.05$); clinical DAP – 103.8±10.3 mm Hg and 99.8±10.7 mm Hg in the groups of hypertensive patients with and without CIs, respectively ($p>0.05$) (**Table 2**).

Analysing the findings of CMAP in the group of patients with CIs showed an increase in the baseline values of average circadian SAP – 161.7±9.1 mm Hg and average circadian DAP – 103.3±9.4 mm Hg.

Hypertensive patients without CIs also demonstrated elevation of the baseline values of mean circadian SAP – 150.4±16.9 mm Hg and mean circadian DAP – 95.6±9.6 mm Hg, with both these indices being significantly lower than the mean circadian values of SAP and DAP in hypertensive patients with CIs ($p<0.05$).

The findings of CMAP showed that patients with CIs had elevation of the baseline values of SAP and DAP in all periods: mean circadian SAP and DAP amounted to 161.7±9.1 and 103.3±9.4 mm Hg, mean diurnal SAP and DAP – 165.1±11.7 and 105±9.8 mm Hg, mean nocturnal SAP and DAP – 159.2±16.3 and 99.7±10.3 mm Hg, respectively. These patients were also found to have high indices of hypertensive load: the time index for SAP and DAP at all time intervals was 2-3-fold higher than the normal values ($p<0.05$).

The correlation analysis revealed that the CF is influenced predominantly by SAP: the level of SAP correlated with a decrease in the values of the neuropsychological tests: MMSE ($r=-0.3$; $p<0.05$ (**Figure 2**), MoCa ($r=-0.3$; $p<0.05$) (**Figure 3**). Thus, elevation of SAP is one of significant factors for progression of CIs.

Table 2: *Baseline parameters of clinical measurement and circadian monitoring of AP in hypertensive patients with and without CIs (M±m; Me (25th, 75th percentile)*

Parameter	HP patients with CIs (n=91)	HP patients without CIs (n=58)	p
Clinical SAP, mm Hg	163.4 ± 18.5	156.6±11.9	>0.05
Clinical DAP, mm Hg	103.8 ± 10.3	99.8±10.7	>0.05
Mean circadian SAP, mm Hg	161.7 ± 9.1	150.4±16.9	<0.05
Mean circadian DAP, mm Hg	103.3 ± 9.4	95.9±9.6	<0.05 >0.05
Mean diurnal SAP mm Hg	165.1 ± 11.7	158.5±17.0	>0.05
Mean diurnal DAP, mm Hg	105.1 ± 9.8	98.6±9.2	<0.05
Mean nocturnal SAP, mm Hg	159.2 ± 16.3	145.1±15.7	<0.05
Mean nocturnal DAP, mm Hg	99.7 ±1 0.3	90.6±10.9	>0.05
SAP NDD (%)	8.0 (-7.8; 18.9)	12.4 (-2.1; 17.0)	>0.05
DAP NDD (%)	11.42 (-8.9; 21.1)	14.6 (-0.9; 19.4)	<0.05
SAP TI (%)	80.5 ± 16.9	59.7±18.1	<0.05
DAP TI (%)	78.1 ± 17.1	64.2±21.0	

Note: NDD – nocturnal drop degree, TI – time index.

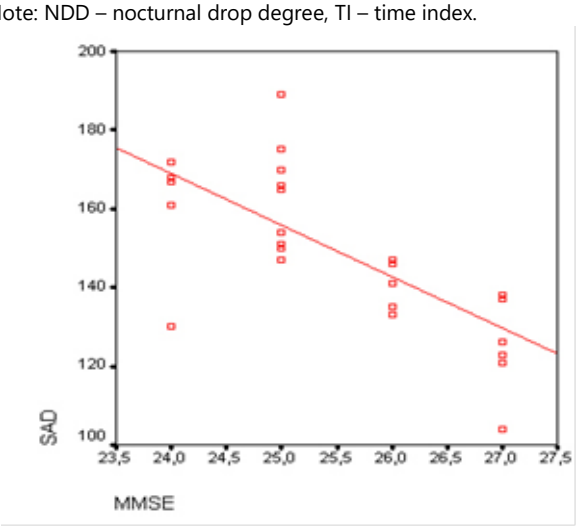

Figure 2: *Correlation analysis of SAP values and MMSE scores*

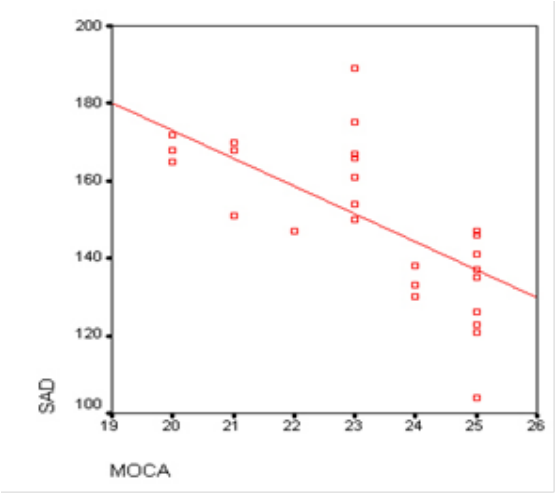

Figure 3: *Correlation analysis of SAP values and MoCa scores*

Table 3: *Baseline distribution of hypertensive patients with and without CIs by the degree of night fall in SAP and DAP*

Type of circadian curve	SAP		DAP	
	AH with CI (n=91)	AH without CI (n=58)	AH with CI (n=91)	AH without CI (n=58)
Night-peaker	17 (18.7%)*	5 (8.6%)	15 (16.5%)*	6 (10.3%)
Non-dipper	36 (39.5%)*	9 (15.5%)	28 (30.8%)*	7 (12.1%)
Over-dipper	9 (9.9%)	8 (13.8)	10 (11%)	5 (8.6%)
Dipper	29 (31.9%)	36 (62.1%)	38 (41.7%)	40 (69%)

Note: * - significant differences of the parameters between the groups (p<0.05).

As can be seen from Table 3, 68.1% of hypertensive patients with CIs were initially found to have impairment of the circadian profile of AP for SAP, 58.2% - for DAP, with 39.5% of patients demonstrating insufficient fall in SAP and 30.8% of patients for DAP at nighttime ("non-dipper").

Elevation of SAP at night hours (the so-called "night-peaker" circadian curve) was observed in 18.7% of patients, elevation of DAP in 16.5%. An excessive night fall in SAP and that in DAP was registered in nine (9.9%) and ten (11%) patients, respectively (an "over-dipper" type of the circadian curve).

A normal circadian profile with a sufficient fall in SAP ("dipper"-type circadian curve) was revealed in only 31.9% of patients and that in DAP in 41.7%. Analysing the baseline parameters of CMAP in hypertensive patients with CIs showed a tendency towards increased variability of SAP (average circadian, diurnal, nocturnal) and DAP (average diurnal) as compared with the group of hypertensive patients without CIs (**Table 3**).

We revealed correlation between the scores of neuropsychological tests MMSE and MoCa and the degree of cerebral white matter lesions: for MMSE – r=0.3; p<0.05 (**Figure 4**), for MoCa – r=0.3; p<0.05 (**Figure 5**). Patients with CIs more often demonstrated evidence of structural pathological alterations of white matter of the brain, and their burden correlating with the degree of CIs (**Table 4**). The findings we obtained confirm significance of a diffuse vascular lesion of cerebral white matter in the development of cognitive deficit.

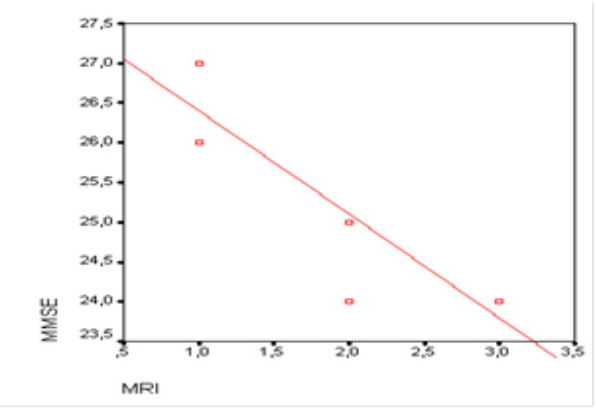

Figure 4: *Correlation analysis of cerebral white matter lesions and the MMSE scores*

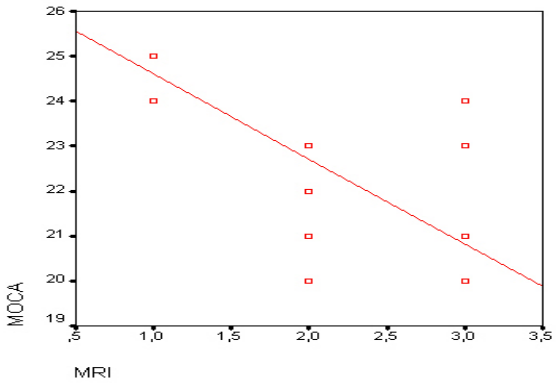

Figure 5: *Correlation analysis of cerebral white matter lesions and the MoCa scores*

Table 4: *Comparative analysis of cerebral structural alterations in hypertensive patients with and without CIs*

Parameter	AH patients with CI (n=38)	AH patients without CI (n=27)	p
Periventricular leukoaraiosis, %	71.1	11.1	<0.01
Subcortical leukoaraiosis, %	15.8	3.7	<0.05
Singular lacunae, %	26.3	7.4	<0.05

MRT signs of periventricular and subcortical leukoaraiosis were more frequently encountered in night-peakers and non-dippers (patients with the "night-peaker" and "non-dipper" circadian curve, respectively), i. e. in hypertensive patients with stable elevation of nocturnal AP and in patients with an insufficient nocturnal fall in AP for SAP and DAP. Fewer lacunar infarcts were observed in increased degree of the night fall in SAP and DAP.

The findings of assessing extracranial haemodynamics in 38 hypertensive patients with CIs and 27 patients without CIs demonstrated that 30 (79%) patients with CIs had ICA tortuosity. Of these, 19 (63.3%) patients presented with haemodynamically significant ICA tortuosities and 11 (36.7%) had haemodynamically insignificant ones. Tortuosity of the ICA was revealed in 13 (48.1%) patients without CIs, being haemodynamically significant in 4 (30.8%) and haemodynamically insignificant in 9 (69.2%) patients ($p<0.05$), with no statistically significant difference by the shape of tortuosity in both groups revealed.

Hypertensive patients with haemodynamically significant impairments of the ICA were found to have more pronounced baseline CIs (25.1±0.4 points by the MMSE scale), 83.3% of patients had degree II-III AH. Patients with haemodynamically insignificant impairments of the ICA had predominantly degree I AH, with the MMSE score amounting to 25.8±0.6.

CONCLUSIONS

1. The neuropsychological examination of 350 ambulatory patients with stage I-III AH confirmed high incidence of CIs in hypertensive patients.
2. Moderate CIs in patients with stage I-II AH were associated with age, low educational qualification, duration of AH, insufficient control of AP, impaired circadian dynamics of AP in the sleep-wakefulness cycle (predominance of pathological types of circadian curves – "non-dipper" and "night-peaker"), a tendency towards elevated circadian variability of SAP and diurnal variability of DAP, as well as with a decrease in the parameters of extracranial blood flow, thus leading to the most pronounced structural and morphological lesions of the brain. Progression of CIs correlates with an increased level of SAP ($r=-0.3$; $p<0.05$).
3. More than 80% of patients with moderate CIs had periventricular (71.1%) and/or subcortical leukoaraiosis (15.8%), with a quarter of patients found to have singular lacunar infarcts. In patients without CIs, pathological alterations of cerebral white matter were encountered considerably less often, with only 11.1% of patients diagnosed with periventricular leukoaraiosis and 3.7% of patients with subcortical one. The degree of leukoaraiosis in the group of hypertensive patients with CIs averagely amounted to 1.8 points by the Fazekas visual scale, and in the group of hypertensive patients without CIs it amounted to 0.2 point ($p<0.05$).

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