Correlations of Cognitive Impairment with Circadian Blood Pressure Pattern and Intima-Media Thickness in Hypertensive Patients

Athena Cristina MERGEANI\textsuperscript{a,b}; Florina ANTOCHI\textsuperscript{a}; Octavia RUSU\textsuperscript{a}; Andrei CIOBOTARU\textsuperscript{a}; Catalina COCLITU\textsuperscript{a}; Ovidiu Alexandru BAJENARU\textsuperscript{a,b}

\textsuperscript{a} Emergency University Hospital, Bucharest, Romania
\textsuperscript{b} “Carol Davila” University of Medicine and Pharmacy, Bucharest, Romania

ABSTRACT

Introduction: Cognitive impairment is strongly associated with arterial hypertension and might be associated also with certain circadian blood pressure patterns. Ambulatory blood pressure monitoring (ABPM) represents a very useful tool in the evaluation of patients with hypertension. Intima-media thickness (IMT), a marker of subclinical organ damage in hypertensive patients is associated with the progression of cognitive impairment.

The aim of our study was to correlate the cognitive impairment with the hypertension pattern found with ABPM, IMT, lipid profile and inflammatory syndrome.

Materials and methods: We enrolled 40 patients aged between 47 and 88 years (69±11 years) with medical history of essential hypertension and cognitive impairment. All patients underwent neuropsychological examination, ABPM, and B-mode ultrasound of the carotid arteries.

Results: 57\% of the patients had a nondipping pattern. The blood pressure pattern inversely correlated with the results of MMSE (r=-0.33; p=0.04), patients with nondipping patterns having lower scores than the ones with dipper pattern. Increased IMT was associated with poorer performance on MoCA test (r=-0.33; p=0.005). MoCA and MMSE scores were inversely correlated with the total cholesterol (r=-0.31; p=0.04; and r=0.38; p=0.01 respectively) and with the LDL-cholesterol (r=-0.32; p=0.04; and r=-0.41; p=0.009 respectively). Patients with low scores on MMSE also had high serum levels of C reactive protein (r=-0.33; p=0.045).

Conclusions: Patients with cognitive impairment and hypertension have vascular changes characterized by increased carotid IMT, alteration of the dipping phenomenon, increased total and LDL-cholesterol, and increased C reactive protein, all related to the degree of cognitive dysfunction.

Keywords: intima-media thickness, hypertension, cognitive impairment, nondipper
INTRODUCTION

Cognitive impairment is strongly associated with arterial hypertension and might be associated also with certain circadian blood pressure patterns previously proved to rise the risk of subclinical organ damage in hypertensive patients, including the increase of intima media thickness. Dementia from all causes has a prevalence of about 8% in the population over 65 years. Between 15 and 30% of these cases are of vascular type. In the elderly, subcortical small vessel disease is known to be associated with vascular dementia(1). Hypertension leads to increased cerebralvascular resistance with diffuse lesions and multiple lacunar infarcts in the white matter (especially in the subcortical region). These lesions might be observed easily by magnetic resonance imaging. It is noted that risk factors like hypertension interfere with the impairment of cognitive function not only in patients with vascular dementia, but also in those with Alzheimer’s disease (2,3).

Hypertension is the most important modifiable risk factor linked to cerebrovascular diseases and as stated earlier one of the risk factors highly associated with the development of cognitive impairment (4). In the latest years, continuous ambulatory blood pressure monitoring (ABPM) for twenty-four hours has become a very useful tool for the for diagnosis and for the optimization of the treatment for hypertension, thus preventing the development of cerebrovascular disease (including stroke, cerebral small vessel disease consisting of lacunar infarcts, white matter lesions, microbleeds), and cognitive impairment. It is known that ABPM results correlates better with hypertension-related organ damage and has a closer association with cardiovascular events than office blood pressure (5,6). Based on this measurement one may document easier and with a high precision the dipping pattern, which may be altered by certain metabolic and cardiovascular changes (7). Blood pressure has a circadian pattern in normal individuals; a fall of more than 10% in systolic and diastolic blood pressure during nighttime monitoring compared to daytime readings is considered normal. Patients which have a fall of less than 10% during nocturnal monitoring are defined as non-dippers (8) and those with a rise in the nocturnal arterial pressure values are reverse dippers (9). The prevalence of the non-dipping pattern in the general population is about 25-35%, and can reach up to 60% in high-risk patients (1).

Recent studies found an association between ambulatory blood pressure variation and cognitive function. Non-dipper status (10), increased blood pressure variability and high systolic blood pressure (11) were important determinants of cognitive impairment (1).

Hypertension represents a major contributor to atherosclerosis, being one of the most prevalent. Intima-media thickness (IMT) is marker of generalized atherosclerosis (12) and it could be reactive to high values of blood pressure. The OPERA study, published in 2012, showed that increased mean IMT in carotid artery was associated with non-dipping pattern in ABPM (p < 0.01) regardless of conventional cardiovascular risk factors, antihypertensive or lipid lowering medications (13). Another study published in the same year found that patients with cognitive dysfunction and elevated central systolic blood pressure have changes in the vascular morphology characterized by an increased carotid IMT (2). A recent study depicted that carotid IMT is associated with the progression of cognitive impairment in the elderly and that carotid IMT was independent of other risk factors (14).

The aim of our study was to correlate the cognitive impairment with the hypertension pattern on ABPM, IMT, lipid profile and inflammatory syndrome.

MATERIALS AND METHODS

Study design and population

The study group consisted of 40 patients aged between 47 and 88 years (69±11 years) with medical history of essential hypertension and cognitive impairment ranging from mild to severe. Group features are shown in Table 1.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>69 ± 11</td>
</tr>
<tr>
<td>Hypertension duration (months)</td>
<td>119 ± 116</td>
</tr>
<tr>
<td>Hypertension treatment</td>
<td></td>
</tr>
<tr>
<td>- Treated no (%)</td>
<td>4 (10%)</td>
</tr>
<tr>
<td>- Untreated no (%)</td>
<td>36 (90%)</td>
</tr>
<tr>
<td>Mean IMT (cm)</td>
<td>0.76 ± 0.15</td>
</tr>
<tr>
<td>Total cholesterol (mg/dl)</td>
<td>190 ± 55</td>
</tr>
<tr>
<td>LDL-cholesterol (mg/dl)</td>
<td>113 ± 47</td>
</tr>
<tr>
<td>HDL-cholesterol (mg/dl)</td>
<td>55 ± 20</td>
</tr>
<tr>
<td>Triglycerides (mg/dl)</td>
<td>104 ± 47</td>
</tr>
</tbody>
</table>

TABLE 1. Group features in patients with cognitive impairment.
The exclusion criteria consisted in the history of stroke (evaluated using MRI and clinical assessment), significant hemodynamic extracranial or intracranial artery stenosis, atrial fibrillation, congestive heart failure, diabetes mellitus, severe chronic kidney disease, thyroid disease or other hormonal disorder, psychiatric illness and substance abuse. When secondary hypertension was suspected it was ruled out using renal arteries Doppler ultrasonography, measurement of metanephrines, vanillylmandelic acid and serum cortisol.

The study was approved by The Ethics Committee of the University Emergency Hospital Bucharest. All of the participants gave written informed consent.

Study participants offered information about their medical history and were submitted to complete physical and neurologic examinations. Age, gender, hypertension duration and treatment, the onset of cognitive impairment (reported by patient, members of the family or diagnosed by a neurologist), and the blood tests results were recorded.

Procedures

Blood pressure measurement

Ambulatory blood pressure was monitored using validated automatic-measuring device (BTL-08 ABPM). The monitors were programmed to measure BP during 24 hours, at 15 minutes intervals during daytime (from 6 A.M until 10 P.M) and at 30 minutes interval during nighttime (between 10 P.M and 6 A.M). The inflatable cuff was placed on the non-dominant upper limb and it was recommended to the patients to remain with the forearm extended during each ABPM session. When the ambulatory monitoring was completed, all the data were downloaded into a computer for analysis.

Carotid intima-media thickness

The carotid IMT of the left and right carotid arteries was evaluated using a 7–12 MHz linear transducer and a high resolution ultrasound (Philips, HD 7 XE) and was calculated using scans of the far wall by a standardized method, with a software that measures automatically the IMT. IMT was defined as the distance between the luminal–endothelial interface and the junction between the media and the adventitia (15). The IMT was measured over a 1 cm segment of the common carotid artery located approximately 1 cm below the carotid-artery bulb and considered not to contain any plaque (Figure 1). Patients were always examined in the supine position and the analysis was performed by a physician experienced in the evaluation of cervico-cerebral arteries. The patient’s clinical data was blinded for the examiner.

Neuropsychological assessment

The neuropsychological exam was performed by an experienced neuropsychologist who was blinded regarding the other clinical data. The battery of tests included standardized tests with established reliability and validity for all domains of cognition that helped in establishment of an accurate diagnosis. After the diagnosis was made only the results regarding the Mini Mental State Examination (MMSE), Clock Test and Montreal Cognitive Assessment (MoCA) were analyzed (16,17).

Data analyses

Normal distribution of variables was checked by Kolmogorov-Smirnov test. Continuous variables were summarized as mean ± SD, and categorical variables were reported as percentages (%). Pearson’s correlation was used to analyze the relationships between IMT, different parameters and global results of the MoCA and MMSE tests, and the serum levels of the lipid profile.

All analyses were carried out using SPSS version 20.0 (SPSS, Inc., Chicago, IL). Differences among variables were considered significant at p <0.05.

RESULTS

Of the 40 patients with cognitive impairment ranging from mild to severe, 17 (42.5%) of them had a dipper pattern, 20 (50%) of them were non-dippers and 3 (7.5%) of them were reverse dippers. The blood pressure pattern inversely correlated with the results of MMSE ($r=-0.33; p=0.04$); patients with reverse-dipper pattern had lower scores than non-dippers, and the dippers had the highest scores of all. However, the MoCA scores did not correlate with the blood pressure pattern. The only item from MoCA test that related to the blood pressure pattern in the same way as MMSE was orientation ($r=-0.44; p=0.04$) (Table 2).
Mean IMT of the patients was 0.76 ± 0.15 cm. Increased IMT was significantly associated with poorer performance on MoCA test ($r=-0.31; p=0.04$). However, the levels of total and LDL cholesterol correlated better with the MMSE than with the MoCA test ($r=-0.38; p=0.01$ and $r=-0.41; p=0.009$ respectively). From MoCA items, orientation was the only one correlated with the total cholesterol ($r=-0.37; p=0.02$) and LDL-cholesterol values ($r=-0.44; p=0.005$).

In a multivariate model including circadian blood pressure pattern, LDL-cholesterol and total cholesterol, only the circadian blood pressure pattern independently related to MMSE score ($\beta=-0.33, p=0.035$). Moreover if we include also the IMT in the model, circadian blood pressure pattern still remains the only factor independently related to MMSE score ($\beta=-0.35, p=0.027$).

Patients with lower scores on MMSE also had high C reactive protein levels ($r=-0.33; p=0.045$).

**DISCUSSION**

Our pilot study analyzed the relationship between IMT and hypertension pattern in the same group of patients with different degrees of cognitive impairment in whom other risk factors like diabetes, which is associated with accelerated cognitive decline (18) and an increased risk of dementia (19,20), particularly in older individuals, were excluded. In our opinion this is an important strength.

Numerous studies and reviews had investigated the correlation between blood pressure pattern and carotid IMT in patients with hypertension without cognitive impairment. It is known that hypertension is related to carotid artery hypertrophy and atherosclerotic complications, the carotid IMT being a marker of subclinical atherosclerosis (21). These studies found an increase of carotid IMT in nondipper patients. There were also studies like the recent ones described earlier that investigated the link between blood pressure pattern and cognition separately from carotid IMT and cognition (2,14,22) and all of these found an association between these parameters of vascular involvement and cognition but they did not use the same sample of patients.

In our study both carotid IMT and blood pressure pattern were correlated to cognition, so patients who performed worse on neuropsychological assessment and had severe dementia had a greater IMT than those with mild or
medium cognitive impairment. We found that less than a half of our study population had a normal dipping pattern and the percentage of nondippers was greater than in general population but smaller than in patients at high risk (1) and the lowest scores were on neurocognitive testing the blood pressure pattern was a non-dipping one. While IMT correlated best with the scores of delayed recall and abstraction items on MoCA test but in an inverse manner, the only item that correlated inversely with the blood pressure pattern was orientation.

It is to be mentioned that patients with low scores on orientation item had high values of total cholesterol and LDL-cholesterol. Total cholesterol and LDL-cholesterol are inversely linked to neurocognitive assessment scores, patients with severe dementia having high values of total and LDL-cholesterol, both being associated with atherosclerosis sustaining the data from literature that altered lipid profile have a negative impact on the cognitive function in adults (23, 24). However, the hypertension pattern was the only factor independently related with the MMSE test by comparison with total and LDL-cholesterol serum levels. The addition of the IMT into the multivariate model did not change its independent relation with the cognitive impairment in hypertensive patients.

It is well known that C reactive protein has negative impact on the cognitive function in elderly. It is well known that C reactive protein has a negative impact on the cognitive function in elderly. It is to be mentioned that patients with low values in patients with risk factors common to stroke and dementia (25). This study certifies that elevated C reactive protein is related to the severity of cognitive impairment.

A study limitation is the small sample size of the study population. However, this is only a pilot study, and we have continued with the enrollment of the patients. Another limitation would be the lack of information regarding the therapeutic control of the hypertension before the onset of cognitive impairment and also the fact that our study patients were treated with different classes of antihypertensive drugs. The impact of different therapeutic regimens on cognition is still not very clear, and further studies in this area are needed.

CONCLUSIONS

Patients with hypertension and cognitive impairment have increased carotid IMT, alteration of the dipping phenomenon, increased total and LDL-cholesterol, and increased C reactive protein values, all correlated with the degree of cognitive dysfunction.

Conflict of interests: none declared.

Acknowledgement: This paper is partly supported by the Sectorial Operational Programme Human Resources Development (SOPHRD), financed by the European Social Fund and the Romanian Government under the contract number POSDRU 141531.

REFERENCES


