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Insulin Resistance Is an Important Risk Factor for Cognitive Impairment in Elderly Patients with Primary Hypertension

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Purpose: Insulin resistance plays a role in the development of dementia and hypertension. We investigated a possible relationship between cognitive impairment and insulin resistance in elderly Chinese patients with primary hypertension. **Materials and Methods:** One hundred and thirty-two hypertensive elderly patients (>60 years) were enrolled in this study, and assigned into either the cognitive impairment group (n=61) or the normal cognitive group (n=71). Gender, age, education, body mass index (BMI), waist hip ratio (WHR), total cholesterol (TC), triglyceride (TG), C-reactive protein (CRP), high density lipoprotein cholesterol (HDL-C), low density lipoprotein cholesterol (LDL-C), creatinine (Cr), fasting plasma glucose (FPG), fasting insulin (FINS), homeostasis model of assessment for insulin resistance index (HOMA-IR), systolic blood pressure, diastolic blood pressure, smoking history, atherosclerosis and the proportion of uncontrolled hypertension were compared between the two groups. Multi-factorial logistic regression analysis was performed. **Results:** No significant differences were found in gender, age, TC, CRP, HDL-C, LDL-C, Cr, BP, smoking history, atherosclerosis and the proportion of uncontrolled hypertension between the two groups. The cognitive impairment group had lower education levels, and higher BMI, WHR, TG, FPG, FINS, and HOMA-IR levels than the control group. Logistic regression analysis revealed the levels of education, BMI, WHR, and HOMA-IR as independent factors that predict cognitive impairment in patients. **Conclusion:** Our study demonstrates that poor education and increased BMI, WHR, and HOMA-IR are independent risk factors for cognitive impairment in elderly patients with hypertension. Insulin resistance plays an important role in the development of cognitive impairment in primary elderly hypertensive patients.

Key Words: Hypertension, insulin resistance, cognitive impairment, elderly, risk factor

INTRODUCTION

With the aging of the Chinese population, the prevalence of hypertension and dementia has been steadily rising. This, in turn, has had major adverse effects on the well-being of the elderly. Alzheimer's disease (AD) is a leading cause of dementia, which is characterized by progressive deterioration of memory and cognition. AD

is a major source of morbidity and mortality worldwide, and its strain on our society, in general and particularly on the affected individuals, is enormous. Mild cognitive impairment (MCI) is an intermediate state that separates normal aging-associated cognitive changes from pathological dementia. Many studies have found that insulin resistance (IR) plays an important role in the occurrence and development of hypertension and dementia.[1] Sporadic AD, which alters the brain insulin signaling pathway, is now recognized as type 3 diabetes mellitus (T3DM).[2,3] Peripheral IR without T2DM is a risk factor and facet for AD.[4-6] It is associated with reduced basal and insulin-induced activation of cerebral IRs, higher cerebral neuritic plaque loads, lower hippocampal volume and cognitive performance, inhibited cerebrocortical glucose metabolism, and reduced memory recall.[7-11] IR causes cognitive dysfunction, and increases the risk of developing dementia. Therefore, it is of a great importance to explore its critical role in the development of cognitive impairment in primary elderly hypertensive patients to appropriately apply therapeutic interventions that may hinder the progression of the disease.

The intertwined epidemics of hypertension and IR pose a major public health challenge.[12] A variety of mechanisms link IR and hypertension. Of note, essential hypertension related genes such as AGT, NOS3, NPPA, ADRB2, ADD1, and SCNN1A are known to be IR-related gene markers.[13-15] IR increases the expression of insoluble amyloid beta protein (Aβ), and activates signaling pathways related to the development of cognitive impairment and AD by increasing the production of advanced glycation end (AGEs) product.[16] The incidence of MCI is associated with IR.[17] To our best knowledge, however, it remains unknown whether IR is an important risk factor for cognitive impairment in primary elderly hypertensive patients. In the present study, we aimed to explore the relationship between cognitive impairment and IR in elderly hypertensive Chinese patients.

MATERIALS AND METHODS

Participants

Elderly patients (average age of 68.03±9.71 years) with primary hypertension (n=132, male=91, female=41), were recruited from the Department of Geriatrics, Xuanwu Hospital, Capital Medical University from August 2008 to October 2011. Inclusion criteria consisted of advanced age (≥60 years) suffering from primary hypertension. Exclusion criteria included secondary hypertension, diabetes, cancer, recent acute infection, severe cardiac, liver or kidney dysfunction, cerebrovascular disease, severe Parkinson's disease, depression or anxiety, hypothyroidism, intracranial space-occupying, alcohol dependence, cognitive dysfunction after traumatic brain injury, alcohol and drug abuse. Hypertension was defined as systolic blood pressure (SBP) ≥140 mm Hg, diastolic blood pressure (DBP) ≥90 mm Hg, current treatment with antihypertensive medication, or a self-reported diagnosis of hypertension. All the participants underwent a standardized clinical assessment, which included a medical history, and physical and neurological examination together with the Mini Mental State Examination (MMSE) tests, Montreal Cognitive Assessment (MoCA) tests, psychometric evaluation and MRI. Normal cognitive function was defined as MoCA >26 (if schooling <12 years, the boundary value was set at 25) and MMSE >24. MCI was diagnosed according to the revised Petersen criteria.[18] These criteria included a decline in memory, objectively verified by neuropsychological testing in combination with a precise history from the participant, proxy, or both, and adjusted for age and education, or a decline in other cognitive domains, with normal functional activities.[19] Patients with vascular cognitive impairment were excluded in the study. Participants were assigned to either the hypertension with cognitive impairment group (case group, n= 61) or the hypertension with normal cognitive function group (control group, n=71). All patients were under antihypertensive medication treatment. Informed consent was obtained from all participants prior to the study. This clinical investigation was approved by the Ethics Committee of Xuanwu Hospital, Capital Medical University, China.

Data collection

A comprehensive questionnaire was conducted by trained investigators. Participants' height, weight, waist circumference, and hip diameter were measured. Body mass index (BMI) and waist-hip ratio (WHR) were subsequently calculated.

Blood test

Venous blood was collected from those patients who were admitted to the hospital early in the morning following an overnight fast (with the exception of drinking water) for at least 8–10 hours, blood was collected from the patients and then coagulated at room temperature for 30 minutes. The supernatant of blood was collected after centrifugation for

15 minutes at 1000 rpm and stored at -20°C pending for analysis. Serum total cholesterol (TC), triglyceride (TG), high density lipoprotein cholesterol (HDL-C), low density lipoprotein cholesterol (LDL-C), serum creatinine (Cr), fasting blood glucose (FPG), and fasting insulin (FINS) were determined using a Hitachi 7600 automatic biochemical analyzer (Hitachi, Tokyo, Japan).

Statistical analysis

An unpaired T test was conducted using SPSS for Windows (version 12.0, SPSS Inc., Chicago, IL, USA). Data were expressed as means±standard error of the mean (SEM). The Rank Sum Test method was used for data that were not distributed normally. The education level, BMI, WHR, TC, and homeostasis model of assessment for insulin resistance index (HOMA-IR) were fixed as independent variables. A positive or negative classification of cognitive impairment was considered as the dependent variable. Logistic regression was used in multifactor analysis. Differences with a p value <0.05 and p<0.01 were considered statistically significant and very significant, respectively. In logistic regression, B>0 and p<0.05 indicate a risk factor, whereas B<0 and p<0.05 indicate a protective factor.

RESULTS

Comparison of single factors between the two groups

Shown in Table 1 are comparisons between the two groups in terms of gender, age, education level, BMI, WHR, TC, TG, C-reactive protein (CRP), HDL-C, LDL-C, Cr, FPG, FINS, HOMA-IR, SBP, DBP, smoking, atherosclerosis, and uncontrolled hypertension. The education level of the case group was lower than that of the control group, whereas BMI, WHR, TG, FPG, FINS, and HOMA-IR of the case group were higher than those of the control group. There were no differences in gender, age, course of hypertension, blood pressure level, and basic diseases between the two groups.

Logistic regression analysis

Table 2 shows that the education level (B=-1.171, p=0), BMI (B=0.980, p=0.022), WHR (B=1.020, p=0.015), and HOMA-IR (B=1.500, p=0) were independent factors of cognitive impairment in elderly patients with hypertension. High BMI, WHR, and HOMA-IR were significant risk factors, whereas a high education level was a protective factor.

DISCUSSION

To our knowledge, this is the first clinical study that systematically investigated the effects of IR on cognitive impairment in elderly Chinese patients with hypertension. Our results showed that elderly hypertensive patients with impaired cognitive function had lower education levels and higher BMI, WHR, TG, FPG, FINS, and HOMA-IR levels than those with normal cognitive function. A high degree of education has been widely recognized as a major protective factor against cognitive impairment.[20] HOMA-IR is positively associated with waist circumstances and TG.[21] Conversely, abdominal obesity and hyperlipidemia can promote IR and cognitive impairment in patients, in part due to an increased level of oxidative stress and secreted inflammatory cytokines.[22] Insulin plays an important role in maintaining normal brain function.[23,24] Insulin action requires an in-

Table 1. Factor Comparisons between the Two Groups

	Control group	Case group
Sex (male/female)	50/21	41/20
Age (yrs)	67.91±8.97	68.17±9.92
Education (≥college, %)	48 (67.61)	27 (44.26)†
BMI (kg/m^2)	22.9±2.3	26.8±2.2†
WHR	0.81±0.05	0.93±0.06†
TC (mmol/L)	5.09±0.57	5.17±0.62
TG (mmol/L)	1.7±0.5	2.3±0.6†
CRP (mmol/L)	0.47±0.11	0.48±0.13
HDL-C (mmol/L)	1.8±0.4	1.7±0.3
LDL-C (mmol/L)	2.7±0.4	2.9±0.5
Cr (mmol/L)	38.0±17.7	40.7±19.4
FPG (mmol/L)	5.2±0.9	6.1±1.3†
FINS (mU/L)	9.3±3.7	21.7±12.9†
HOMA-IR	2.1±1.3	5.9±3.1†
SBP (mm Hg)‡	138.9±39.7	140.3±42.1
DBP (mm Hg)‡	75.0±22.6	77.2±24.3
Smoking (yes, %)	17 (23.94)	15 (24.59)
Atherosclerosis (yes, %)	18 (25.35)	16 (26.22)
Uncontrolled hypertension (yes, %)	9 (12.68)	8 (13.11)

BMI, body mass index; WHR, waist hip ratio; TC, total cholesterol; TG, triglyceride; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; CRP, C-reactive protein; Cr, creatinine; FPG, fasting plasma glucose; FINS, fasting insulin; HOMA-IR, homeostasis model of assessment for insulin resistance index; SBP, systolic blood pressure; DBP, diastolic blood pressure.
Compared to the control group, *p<0.05, †p<0.01.
‡All patients were under antihypertensive medication treatment.

Table 2. Logistic Regression Analysis

Factors	B	S.E.	Wald	df	Sig	Exp (B)	95% CI	
							Lower	Upper
Education	-1.171	0.323	12.301	1	0.000	3.212	1.671	6.200
BMI	0.980	0.437	5.171	1	0.022	2.690	1.150	6.331
WHR	1.020	0.403	8.898	1	0.015	3.002	1.075	5.711
TC	0.379	0.364	1.050	1	0.303	1.465	0.715	2.960
HOMA-IR	1.500	0.359	15.707	1	0.000	4.500	2.212	8.102

BMI, body mass index; WHR, waist hip ratio; TC, total cholesterol; HOMA-IR, homeostasis model of assessment for insulin resistance index; S.E., standard error; CI, confidence interval.

teraction with insulin receptors which are highly expressed in the hippocampus and cerebral cortex. The insulin-insulin receptor complex activates an intracellular signaling cascade including a tyrosine kinase involved in energy metabolism. It also supports and protects neurons by regulating glucose metabolism, and improves the learning and memory function by regulating the flux of neurotransmitters.[25] As glucose metabolism in the brain neurons is also regulated by insulin, IR can cause an impaired cognitive function. It has been demonstrated that an abnormal glucose metabolism significantly increases the risk of cognitive impairment in stroke patients.[26] Additionally, hippocampal volume, a recognized risk factor in the development of cognitive impairment, was significantly reduced in individuals with increased waist circumference. Importantly, a decreased hippocampal volume and an increased waste circumference are closely correlated with AD.[27]

In the present study, we have found that IR is an important risk factor for the cognitive impairment in elderly patients with primary hypertension, however, the pathogenesis remains unclear. We hypotheses that the mechanism of IR on cognitive function may involve the following factors: 1) IR promotes the metabolism of Aβ and Tau hyperphosphorylation, resulting in sugar, fat, protein, and other metabolic disorders, and neuronal degeneration together with an impaired cognitive function under hyperinsulinemia;[28,29] 2) IR protein is rich in the specific learning and memory regions of the brain.[30] IR impairs brain tissue oxygen metabolism, downregulates peroxisome proliferator-activated receptor γ (PPARγ) expression, upregulates AGE and receptor for advanced glycation end product (RAGE) levels, and enhances the phosphorylation of nuclear factor kappa B (NF-κB), thereby, facilitating interactions between the AGE-RAGE pathway and PPARγ in IR animals;[31,32] 3) Inflammatory cytokines. Although we could not find any difference in serum CRP concentration between the two groups, mild hyperinsulinemia can increase inflammatory cytokines such as interleukin (IL)-1a, IL-6, and tumor necrosis factor (TNF)-a in cerebrospinal fluid (CSF) and plasma.[33,34] AD has been confirmed to involve inflammation in the brain;[33,34] and 4) Hypercortisolism. Hyperinsulinemia can induce hypercortisolemia through the hypothalamic pituitary adrenal axis, inhibiting granule cell regeneration, modulating hippocampal long term potentiation and long term depression and ultimately impairing cognitive function. Brain IR, specifically in the hippocampal formation and the cerebellar cortex, appears to be an early and common feature of AD. It is accompanied by insulin-like growth factor 1 (IGF-1) signaling resistance and is closely associated with IRS-1-PI3K pathway dysfunction potentially triggered by Aβ oligomers, resulting in cognitive decline.[35,36]

Our present findings indicate that poor education, BMI, WHR, and HOMA-IR are all independent risk factors for the cognitive impairment in elderly patients with hypertension. Clinicians, therefore, should place emphasis on the diagnosis of IR in their attempt to attenuate the development of cognitive impairment in elderly patients with hypertension. In light of the present study, intervention toward early and effective management to reduce IR appears to have important implications for the prevention and treatment of cognitive impairment.

Conclusions

Our present study found that IR is an important risk factor for cognitive impairment in primary elderly hypertensive patients. Our findings contribute to a growing body of evidence linking IR to AD and identify risk factors for dementia-associated memory loss.

Limitations

Participation in this study was restricted to patients living in Beijing. Hence, our results may not be representative of the overall Chinese population. Moreover, since the cross-sectional study cannot reflect the association between risk fac-

tors and outcomes, a follow-up study is warranted.

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