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Original Article

Intervention affects the cognitive performance of middle-aged patients with essential hypertension

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Abstract: Subject: To elucidate the characteristics associated with the cognitive performance of middle-aged patients with essential hypertension and to examine the impact of hypertension interventions on cognitive impairment. Methods: Patients with essential hypertension (n=200; age, 45-60 years) were included in the hypertension group. This group was thensubdivided into atreatment group (n=126) and a non-treatment group (n=74). The treatment group was again subdivided into a compliance group (n=72) and a non-compliance group (n=54). Another 100 healthy people were included as a control group. Clinical cognitive performance was evaluated using the Mini-Mental State Examination (MMSE), Clinical Memory Scale (CMS), and Revised Wechsler Adult Only Scale (WAIS-RC). Results: The orientation score in the MMSE, memory quotient (MQ) in the CMS, and mapping score in the WAIS-RC for the untreated group were significantly lower than those for the control group (P<0.05). The total MMSE score, MQ in the CMS, and VIQ, PIQ, and FIQ in the WAIS-RC were significantly higher for the treatment group than for the non-treatment group (P<0.05). In addition, the total MMSE, CMS, and WAIS-RC scores for the compliance group were higher than those for the non-compliance group (P<0.05). Conclusion: Middle-aged patients with essential hypertension show evidence of cognitive impairment. The onset of such impairment may be delayed by effective intervention, thereby protecting these patients from dementia.

Keywords: Cognition, dementia, hypertension, intervention

Introduction

Cognition is a higher function directed by the cerebral cortex, which enables human beings to learn and acquire knowledge [1]. The increase in the proportion of elderly people worldwide has led to an increasing trend in the incidence of cognitive dysfunction. Cognitive dysfunction is a critical characteristic for an early clinical diagnosis of Alzheimer's disease (AD) [2] and/or vascular dementia (VD) [3]. Increasing attention has been focused on the link between hypertension (a common disease among the elderly)and cognitive dysfunction and dementia [4-6]. Clearly, it is important to lower the blood pressure (BP) of hypertensive subjects; however, the relationship between hypertension and cognitive function is controversial [7]. Increased BP in midlife is associated with a higher prevalence of white matter injury in the brain and with cognitive decline; however, low BP in old age is related to poor intellectual function [8-12]. Randomized studies report thatreducing BP can have adverse effects on cognitive function. Moreover, intervention studies of antihypertensive drugsreportthe varying effects of BP reduction on cognitive function, further adding to the debate [13].

Here, we focused on middle-aged patients with essential hypertension andtried to elucidate the characteristics associated with cognitive function, memory, and intellectual disability, and examine the impact of early intervention with antihypertensive therapy on cognitive performance.

Methods and materials

Ethical statement

This was a hospital-based case-control study involving 278 patients with essential hyperten-

Table 1. Patients' characteristics between healthy group (Ctrl) and hypertension group (HT)

Characteristic	Ctrl (Mean ± SD) (n=155)	HT (Mean ± SD) (n=278)
Gender (male), n (%)	87 (56.1%)	165 (59.3%)
Age, years	55.76 ± 5.53	54.17 ± 4.22
Education, years	10.87 ± 3.24	11.05 ± 3.15
Zung index	0.33 ± 0.07	0.33 ± 0.07
FPG, mmol/L	5.00 ± 0.43	4.96 ± 0.58
Total cholesterol, mmol/L	4.42 ± 0.59	4.55 ± 0.67
Triglyceride, mmol/L	1.53 ± 0.73	1.65 ± 0.81
HDL-C, mmol/L	1.41 ± 0.31	1.40 ± 0.36
LDL-C, mmol/L	2.62 ± 0.49	2.62 ± 0.88
apolipoproteins A, g/L	1.36 ± 0.32	1.34 ± 0.35
apolipoproteins B, g/L	0.95 ± 0.24	0.95 ± 0.42

FPG, fasting plasma glucose; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

Table 2. MMSE scores between healthy group (Ctrl) and untreated group (NT-HT)

Characteristic	Ctrl (Mean ± SD) (n=155)	NT-HT (Mean ± SD) (n=113)
Gender (male), n (%)	87 (56.1%)	68 (57.5%)
Orientation	9.93 ± 0.28	9.71 ± 0.66a
Immediate memory	2.89 ± 0.33	2.93 ± 0.29
Attention/concentration	4.41 ± 0.83	4.22 ± 1.54
Delayed recall	2.22 ± 0.91	2.28 ± 0.67
language	8.00 ± 1.02	7.89 ± 1.25
Total score	27.59 ± 2.25	26.98 ± 3.04

MMSE, Mini Mental State Examination; "a" donates $P<0.05$, untreated group versus healthy group.

sion and 155 healthy controls (the patients in both groups were aged 45-60 years), all of whom were recruited from the Hypertension Division, Department of Cardiology and Medical Center of the Fourth Affiliated Hospital of Guangzhou Medical University and Kaifeng Central Hospital from March 2008 to November 2013. None of the subjects reported consanguinity at the time of enrollment, and patientswith essential hypertension had been diagnosed for at least 1 year. Each subject provided informed consent before participation. This study was approved by the ethics committee of the Fourth Affiliated Hospital of Guangzhou Medical University and Kaifeng Central Hospital, and conformed to the guidelines outlined in the Declaration of Helsinki.

Subject selection

The inclusion criteria for essential hypertension were as follows: all subjects met the diagnostic criteria as stipulated in the Hypertension Prevention Guide China [14] andhad (1) no abnormal findings on general medical and neurological examination; (2) no obvious abnormalities on cranial CT scans; and (3) no severe stenosis of intracranial vessels in the neck on vascular ultrasound or transcranial Doppler examination. Patients were excluded if they (1) had secondary hypertension; (2) had a history of stroke, head trauma, brain tumor, diabetes, coronary heart disease, hyperhomocysteinemia, high cholesterol, metabolic abnormalities syndrome, sleep apnea syndrome, AD, vascular disease, Parkinson's disease (PD), epilepsy, neurological genetic metabolic and degenerative diseases, mental retardation, or depression or other psychiatric diseases; (3) had a family history of dementia; (4) had liver, kidney, heart, lung, or other organic illnesses; and (5) required the long-term use of sedatives for alcoholism, drug abuse, or severe insomnia.

The healthy control subjects were recruited from the medical center and were matched with the hypertension group in terms of sex, age, and educational background. Cranial CT, neck vascular ultrasound, and transcranial Doppler examination met the selection criteria used for the hypertension group. The exclusion criteria for healthy subjects were the same as those for the essential hypertension group.

Subject grouping

The 278 patients with essential hypertension were assigned to the hypertension (HT) groupand 155 healthy subjects were included in the control (Ctrl) group. The HT group was subdivided into atreatment group (T-HT group, 165 cases) and a non-treatment group (NT-HT group, 113 cases). The treatment group was further subdivided into a compliance group (CT-HT group, 102 cases) and a non-compliance group (NCT-HT group, 63 cases), according to BP status after the intervention.

Table 3. CMS scores between healthy group (Ctrl) and untreated group (NT-HT)

Characteristic	Ctrl (Mean ± SD) (n=155)	NT-HT (Mean ± SD) (n=113)
Gender (male), n (%)	87 (56.1%)	68 (57.5%)
Directed memory	16.18 ± 4.13	11.85 ± 5.02a
Associative learning	17.32 ± 4.28	14.49 ± 4.26a
Free recall	15.49 ± 4.81	11.35 ± 4.26a
Insignificant figure recognition	17.09 ± 5.88	16.69 ± 6.54
Portrait character association retrieval	16.21 ± 3.68	12.65 ± 5.78a
Total score	84.11±9.96	70.02 ± 16.53a
Memory quotient (MQ)	96.33 ± 9.72	79.91 ± 11.46a

CMS, Clinical Memory Scale of Chinese; "a" donates *P*<0.01, untreated group versus healthy group.

Table 4. WAIS-RC scores between healthy group (Ctrl) and untreated group (NT-HT)

Characteristic	Ctrl (Mean ± SD) (n=155)	NT-HT (Mean ± SD) (n=113)
Gender (male), n (%)	87 (56.1%)	68 (57.5%)
Information	12.23 ± 2.45	11.04 ± 3.41
Comprehension	12.39 ± 3.02	11.77 ± 3.69
Arithmetic	8.64 ± 2.23	8.43 ± 2.72
Similarities	10.65 ± 2.01	10.33 ± 2.13
Digit span	9.64 ± 1.91	9.60 ± 2.06
Vocabulary	11.78 ± 2.95	11.23 ± 3.41
Language score	63.65 ± 9.82	62.76 ± 13.44
Verbal intelligence (VI)	107.65 ± 11.44	106.31 ± 11.98
Digit Symbol	8.12 ± 2.78	8.06 ± 2.96
Picture Completion	9.11 ± 2.98	8.43 ± 2.61a
Block Design	8.24 ± 2.12	8.05 ± 2.26
Picture Arrangement	7.51 ± 2.55	7.36 ± 2.72
Object Assembly	6.64 ± 2.17	6.38 ± 2.29
Working score	38.87 ± 8.02	38.05 ± 8.44
Performance IQ (PIQ)	94.25 ± 9.75	93.89 ± 9.53
Total score	103.81 ± 15.32	101.96 ± 16.98
IQ	99.23 ± 8.64	98.77 ± 9.46

WAIS-RC, Wechsler Adult Intelligence Scale-Revised Chinese; "a" donates P<0.05, untreated group versus healthy group.

BP measurement

According to the Chinese Hypertension Prevention Guide, the recorded BP was the average of at least two measurements. The diagnostic criterion for hypertension was a BPreading of 140/90 mmHg or higher. For the treatment group, a systolic pressure lower than 140 mmHg or a diastolic pressure lower than 90 mmHg was considered as "compliance". Here, the average value of three measurements was taken.

Assessment

All subjects meeting the inclusion criteria were tested using the Mini-Mental State Examination (MMSE) [15], Chinese Clinical Memory Scale (CMS) [16], Wechsler Adult Intelligence Scale-Revised Chinese (WAIS-RC) [16, 17]. At least three tests were applied at the same time to test cognitive function, memory, and intelligence. All tests were performed in a quiet environment and administered by neuropsychological clinicians.

Statistical analysis

Statistical analysis was performed using the SPSS 16.0 statistical package. Data sets were compared using analysis of variance (ANOVA), the Chi-square *test*, or paired *t-test*as appropriate. Multiple data sets were compared using ANOVA. Data were expressed as the mean ± standard deviation. *P*<0.05 was considered statistically significant.

Results

Comparison of general conditions between the hypertension and healthy groups

There were no significant differences between the Ctrl and HT groups in terms of gender, age, educational situation, Zung's index, or levels of

Table 5. MMSE scores between hypertension treated group (T-HT) and untreated group (NT-HT)

Characteristic	T-HT (Mean ± SD) (n=165)	NT-HT (Mean ± SD) (n=113)
Gender (male), n (%)	97 (58.8%)	68 (60.2%)
Orientation	9.74 ± 0.62	9.71 ± 0.66
Immediate memory	2.95 ± 0.36	2.93 ± 0.29
Attention/concentration	4.38 ± 1.23	4.22 ± 1.54
Delayed recall	2.39 ± 0.82	2.28 ± 0.67
language	8.12 ± 0.93	7.89 ± 1.25
Total score	28.91 ± 1.06a	26.98 ± 3.04

MMSE, Mini Mental State Examination; "a" donates *P*<0.05, treated versus untreated hypertension group.

Table 6. CMS scores between hypertension treated group (T-HT) and untreated group (NT-HT)

Characteristic	T-HT (Mean ± SD) (n=165)	NT-HT (Mean ± SD) (n=113)
Gender (male), n (%)	97 (58.8%)	68 (60.2%)
Directed memory	13.51 ± 4.96a	11.85 ± 5.02
Associative learning	14.99 ± 4.06	14.49 ± 4.26
Free recall	13.05 ± 4.33a	11.35 ± 4.26
Insignificant figure recognition	17.02 ± 5.89	16.69 ± 6.54
Portrait character association retrieval	13.76 ± 5.44	12.65 ± 5.78
Total score	74.91 ± 14.23b	69.72 ± 15.94
Memory quotient (MQ)	84.09 ± 11.89b	79.91 ± 11.46

CMS, Clinical Memory Scale of Chinese; "a" donates *P*<0.05, treated versus untreated hypertension group. "b" donates *P*<0.01, treated versus untreated hypertension group.

fasting plasma glucose, total cholesterol, triglycerides, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), or apolipoproteins A and B (*P*>0.05 for all; **Table 1**).

Comparison of cognitive performance between the healthy group and NT-HT groups

There were no significant differences between the Ctrl and NT-HT groups in terms of the MMSE test scores (except for the orientation score component) (*P*<0.05; **Table 2**). However, the scores for directed memory, associative learning, free recall, portrait character association retrieval, and the total score, and the scores for the memory quotient (MQ) component of the CMS test were significantly lower for the NT-HT group than for the Ctrl group (*P*<0.05; **Table 3**). Only the score for the picture completion component of the WAIS-RC was significantly lower for the NT-HT group than for the Ctrl group (*P*<0.05; **Table 4**).

Comparison of cognitive performance between the T-HT and NT-HT groups

The total MMSE scorefor theT-HT group was significantly higher than that for the NT-HT group (*P*<0.05); however, there was no difference in the MMSE subtest scores between the two groups (**Table 5**). For the CMS test, the total score and the scores for the directed memory and associative learning components, and the total scores for the MQ, were markedly higher for the T-HT group than for the NT-HT group (*P*<0.05; **Table 6**). The total score and the scores for the information, comprehension, similarities, language score, verbal intelligence (VI), picture completion, working score, and performance IQ (PIQ) componentsof the WAIS-RC test, and the IQ score, were significantly higher for the T-HT group than for the NT-HT group (*P*<0.05; **Table 7**).

Cognitive performance of the CT-HT and NCT-HT groups after hypertension intervention

The total score and the scores for the immediate memory, attention/concentration, delayed recall, and language components of the MMSE were significantly higher in the CT-HT group than in the NCT-HT group after hypertension invention (*P*<0.05; **Table 8**). All subtest scores in the CMS were significantly higher in the CT-HT group (*P*<0.05; **Table 9**). Finally, the total score and the scores for the arithmetic, similarities, and language components were significantly higher in theCT-HT group (*P*<0.05; **Table 10**).

Discussion

Cognitive impairment (CI), whichrefers to a clinical syndrome of cognitive dysfunction, includes

Table 7. WAIS-RC scores between hypertension treated group (T-HT) and untreated group (NT-HT)

Characteristic	T-HT (Mean ± SD) (n=165)	NT-HT (Mean ± SD) (n=113)
Gender (male), n (%)	97 (58.8%)	68 (60.2%)
Information	13.69 ± 2.12a	11.04 ± 3.41
Comprehension	12.71 ± 2.49b	11.77 ± 3.69
Arithmetic	8.87 ± 2.14	8.43 ± 2.72
Similarities	11.25 ± 1.56b	10.33 ± 2.13
Digit span	9.78 ± 1.83	9.60 ± 2.06
Vocabulary	11.34 ± 2.89	11.23 ± 3.41
Language score	66.48 ± 10.43b	62.76 ± 13.44
Verbal intelligence (VI)	109.13 ± 10.98b	106.31 ± 11.98
Digit Symbol	8.31 ± 2.69	8.06 ± 2.96
Picture Completion	9.71 ± 2.33b	8.43 ± 2.61
Block Design	8.23 ± 2.01	8.05 ± 2.26
Picture Arrangement	7.68 ± 2.77	7.36 ± 2.72
Object Assembly	6.15 ± 3.02	6.38 ± 2.29
Working score	43.17 ± 6.52a	38.05 ± 8.44
Performance IQ (PIQ)	97.96 ± 7.53a	93.89 ± 9.53
Total score	107.22 ± 8.71a	101.96 ± 16.98
IQ	104.53 ± 9.68a	98.77 ± 9.46

WAIS-RC, Wechsler Adult Intelligence Scale-Revised Chinese; "a" donates $P<0.05$, treated versus untreated hypertension group. "b" donates $P<0.01$, treated versus untreated hypertension group.

Table 8. MMSE scores between hypertension compliance group (CT-HT) and lack of compliance group (NCT-HT)

Characteristic	CT-HT (Mean ± SD) (n=102)	NCT-HT (Mean ± SD) (n=63)
Gender (male), n (%)	67 (65.7%)	30 (47.6%)
Orientation	9.81 ± 0.73	9.62 ± 0.64
Immediate memory	3.00 ± 0.37a	2.87 ± 0.32
Attention/concentration	4.32 ± 0.92	4.41 ± 1.20
Delayed recall	2.53 ± 0.71a	2.25 ± 0.74
language	8.34 ± 0.81a	7.82 ± 1.14
Total score	29.04 ± 1.62b	27.65 ± 2.18

MMSE, Mini Mental State Examination; "a" donates $P<0.05$, compliance group versus lack of compliance group. "b" donates $P<0.01$, compliance group versus lack of compliance group.

senile dementia, VD, MCI, and vascular CI. MCI is an early stage of CI, and has an estimated prevalence of 20-25% [18]. The rate of progression from MCI to dementia in patients with PD is about 6-15% per year [2]. Dementia leads to a marked reduction in the quality of life of CI patients, increases the financial burden for their family, and is a source of greatstress for their caregivers [19]. A recent study shows that hypertension is a main risk factor for cerebral arteriosclerosis and other cerebrovascular diseases, and is considered critical for the occurrence of CI [20].

Hypertension, which alters cerebrovascular structure and function [21], is also a major risk factor for stroke and dementia [22, 23]. However, the relationship between hypertension and CI remains controversial. Most studies used a single test to assess the cognitive performance of CI patients. Here, we enrolled-patients with essential hypertension that were aged 45-60 years and simultaneously applied the MMSE, CMS, and WAIS-RC tests in an effort to identify the relationship between hypertension and cognitive function. We found that, compared with a healthy control group, untreated hypertension subjects showed (1) CI, mainly with respect to orientation dysfunction; (2) reduced memory function, mainly associated with auditory, visual, and combined memory; and (3) intellectual dysfunction, mainly with respect to visual-spatial intelligence and visual comprehension. We therefore conclude that, if untreated, hypertension causes significant im pairment of cognitive function, memory, and intelligence. After appropriate treatment, the scores for the MMSE test; directed memory; associative learning; the MQ and total memory scores for the CMS test; the scores for the information, comprehension, similarities, language score, VI, and picture completion components; and the working score, PIQ, and IQ of the WAIS-RC test all increased. Haag and colleagues conducted a 15 year longitudinal study and found that antihypertensive therapy reduced the risk of CI by 8% in those aged <75 years and by 4% in those >75 years [24]. Our results are consistent with

Table 9. CMS scores between hypertension compliance group (CT-HT) and lack of compliance group (NCT-HT)

Characteristic	CT-HT (Mean ± SD) (n=102)	NCT-HT (Mean ± SD) (n=63)
Gender (male), n (%)	67 (65.7%)	30 (47.6%)
Directed memory	14.96 ± 3.48a	11.67 ± 4.31
Associative learning	16.15 ± 3.35a	13.72 ± 3.97
Free recall	14.27 ± 4.09a	11.29 ± 4.87
Insignificant figure recognition	17.95 ± 6.12a	15.83 ± 4.97
Portrait character association retrieval	15.91 ± 5.23a	12.55 ± 5.12
Total score	81.86 ± 11.85a	65.12 ± 12.43
Memory quotient (MQ)	88.84 ± 9.71a	76.52 ± 10.84

CMS, Clinical Memory Scale of Chinese; "a" donates P<0.05, compliance group versus lack of compliance group.

Table 10. WAIS-RC scores hypertension compliance group (CT-HT) and lack of compliance group (NCT-HT)

Characteristic	CT-HT (Mean ± SD) (n=102)	NCT-HT (Mean ± SD) (n=63)
Gender (male), n (%)	67 (65.7%)	30 (47.6%)
Information	13.65 ± 2.48	12.96 ± 2.81
Comprehension	12.89 ± 2.41	12.44 ± 2.62
Arithmetic	9.33 ± 1.98a	8.51 ± 2.06
Similarities	11.37 ± 1.68a	10.91 ± 1.79
Digit span	10.04 ± 2.15	9.90 ± 1.93
Vocabulary	12.06 ± 2.87	11.21 ± 2.79
Language score	67.93 ± 9.06a	62.38 ± 9.12
Verbal intelligence (VI)	110.23 ± 9.27	107.62 ± 10.34
Digit Symbol	8.71 ± 2.73	7.92 ± 2.25
Picture Completion	9.61 ± 3.27	9.77 ± 3.46
Block Design	8.25 ± 1.91	8.17 ± 1.88
Picture Arrangement	7.91 ± 2.24	7.43 ± 2.83
Object Assembly	6.04 ± 2.39	6.52 ± 2.08
Working score	44.89 ± 7.13	41.33 ± 7.69
Performance IQ (PIQ)	98.64 ± 10.75	97.65 ± 9.41
Total score	109.72 ± 12.95a	104.22 ± 14.02
IQ	105.31 ± 9.02	102.77 ± 9.85

WAIS-RC, Wechsler Adult Intelligence Scale-Revised Chinese; "a" donates *P*<0.05, compliance group versus lack of compliance group.

these findings. Comparison of the NCT-HT group and CT-HT groupsreveled that cognitive function, memory, and intelligence are all affected if BP is not controlled.

The mechanisms underlyingClin hypertensive individuals are unclear. The early effects may be caused bya reduced cerebral perfusion reserve, abnormal energy metabolism, or other forms of pathophysiology dysfunction. Chronic hypertension reduces the flexibility of the arteries in the brain, leading to arteriosclerosis, intimal thickening, and stenosis, thereby reducing the blood supply and (ultimately) causing brain damage [25]. Sustained high systolic BP damages cerebral vascular endothelial cells and disrupts the structure of intimal and medial vessels. Increased cerebral vascular permeability reduces tolerance for BP fluctuations and increases edema and exudation, leading to proliferation of glial cells and neuronal inflammation. Damage to vascular endothelial cells increases the incidence of arteriosclerosis and *in situ* thrombosis [26]. Among the signaling pathways related to learning and memory, the hippocampal circuit plays a critical role. Pyramidal cells in the CA1 region are the most sensitive to ischemia. Insufficient blood supply due to chronic hypertension leads to apoptosis of hippocampal neurons and altered neuronal transmission, and changes the pathology of the cholinergic system [27, 28]. Mufson and colleagues found that the cholinergic system was closely related to memory dysfunction [29]. An insufficient cerebral blood supply either directly or indirectly reducesneurotransmitterexpression in the hippocampus, temporal lobe cortex, and thalamus, leading to memory and cognitive dysfunction. Hypertension results in subclinical morphological changes, such as silent cerebral infarction, cerebral white matter damage, atro-

phy, neurofibrillary tangles, and damage to the capillary structure, all of which are related to declining cognitive function and dementia [30].

In summary, hypertension is an important risk factor for middle-aged patients with essential hypertension. If untreated, this can lead toloss of cognitive function, memory, and intelligence. Positive antihypertensive intervention delays these impairments and prevents progression to dementia, leading to an improved quality of life.

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Disclosure of conflict of interest

None.

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