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Research Paper

The association between urinary Alzheimer-associated neuronal thread protein and cognitive impairment in late-life depression: a controlled pilot study

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Abstract

Accumulation of tau protein is associated with both Alzheimer's disease (AD) and late-life depression (LLD). Alzheimer-associated neuronal thread protein (AD7c-NTP), which is closely linked with the tau protein, is elevated in the cerebrospinal fluid and urine of AD patients. This study examined the association between urinary AD7c-NTP and late-life depression with cognitive impairment. One hundred and thirty-eight subjects were recruited into late-life depression with cognitive impairment (LLD-CI, n=52), late-life depression without cognitive impairment (LLD-NCI, n=29), AD (n=27), and healthy control (HC, n=30) groups. The level of urinary AD7c-NTP was measured using the enzyme-linked immunosorbent assay method. The Montreal Cognitive Assessment scale (MoCA), Hamilton Rating Scale for Depression (HRSD) and Hamilton Anxiety Rating Scale (HAMA) were used to assess cognitive functions and depressive and anxiety symptoms in the AD and LLD groups. Urinary levels of AD7c-NTP in the LLD-CI group (1.0 ± 0.7 ng/ml) were significantly higher than both the LLD-NCI (0.5 ± 0.3 ng/ml) and HC groups (0.5 ± 0.3 ng/ml), but lower than in the AD group (1.6 ± 1.7 ng/ml). No significant associations were found in the level of urinary AD7c-NTP in relation to age, gender, education and MoCA in the LLD-CI group. The level of urinary AD7c-NTP appears to be associated with cognitive impairment in late-life depression and may be a potential biomarker for early identification of cognitive impairment in LLD.

Key words: AD7c-NTP, Alzheimer's disease, late-life depression, cognitive impairment

Introduction

Late-life depression (LLD), defined as major depression occurring in older adults regardless of the age of onset [1], is common (10%-38%) among older people [2-4], and is associated with an increased risk of disability, suicide, high mortality and poor quality of life [5, 6]. Cognitive impairment, such as in episodic memory, speed of information processing, executive functioning, and visuospatial ability [7-9] often occurs in LLD [10], which is associated with increased relapse rate, functional impairment and poor

treatment adherence [1]. It was once thought that cognitive impairment could improve after the recovery of depression, thus the term "pseudo-dementia" was used to describe cognitive impairment in LLD [11]. However, it became evident that cognitive impairment persisted in a significant number of LLD patients even after the depressive symptoms improved [12].

In recent years the association between LLD and Alzheimer's disease (AD) has gained much attention.

The differential diagnosis of LLD and AD can be difficult to tease out in clinical practice. On one hand, cognitive impairment in LLD could be prominent resulting in the misdiagnosis of early stage AD, and on the other hand, patients with incipient AD may often present with somatic and mood symptoms including depression. LLD may be an early manifestation or a risk factor of AD [4, 13, 14], which is supported by epidemiological studies that found an increased risk of LLD converting to dementia compared to healthy controls [15] and possible progressive dementia within 2-4 years following depressive episodes of LLD [16, 17].

There appears to be similarities between LLD and AD in terms of neuropathology and brain structure [18, 19]. For example, there are neuronal loss, β -amyloid plaques and neurofibrillary tangles (NFTs) in AD patients, especially in the hippocampus [20, 21]. Similarly, there are also significant deposition of beta amyloid and accumulation of tau protein in the brain of LLD patients [22-24], which suggests a potential link between LLD and AD.

Early identification and treatment of cognitive impairment in LLD could have important clinical implications for dementia prevention [25, 26]. However, assessing cognitive function in LLD patients can be challenging because it is difficult to differentiate cognitive impairment from depressive symptoms, and some severely depressed older patients are unable to complete cognitive assessments. There is currently no biomarker available to accurately identify cognitive impairment in LLD [27].

Alzheimer-associated neuronal thread protein (AD7c-NTP), a transmembrane phosphoprotein, is found in central nervous system cells. Over-expression of AD7c-NTP could lead to neuritic sprouting and cell death, which is associated with pathological changes in AD [28, 29]. AD7c-NTP accumulation co-localizes with NFTs and malnutrition axons [30]. In addition, AD7c-NTP is positively associated with phosphorylated tau accumulation in central neurons and cerebrospinal fluid (CSF) in AD patients [31, 32]. Urinary AD7c-NTP level has been shown to have high sensitivity and specificity in predicting amyloid- β deposition in AD and mild cognitive impairment (MCI) [33]. Moreover, some studies found increased AD7c-NTP concentration in cerebrospinal fluid and urine in the early course of neurodegeneration in AD, which is positively associated with AD severity [34-37]. A meta-analysis has suggested that urinary AD7c-NTP may be helpful in the early diagnosis of probable AD [38].

There are few studies that have examined the level of AD7c-NTP in LLD. A longitudinal study

found that the urinary AD7c-NTP level in LLD was significantly increased at 24 months compared to baseline, which was higher than in a healthy control group [39]. However, the study lacked any comparison of AD7c-NTP levels with AD patients and between LLD patients with and without cognitive impairment. Further, the study did not control for potentially confounding effects of age, gender, and education.

Hence, this study aimed to compare urinary AD7c-NTP levels in four distinct groups, including LLD with cognitive impairment (LLD-CI), LLD without cognitive impairment (LLD-NCI), AD and healthy controls (HC), and to examine the association of urinary AD7c-NTP level in relation to age, gender, education, and cognitive function.

Methods

Participants and study setting

This case-control study was conducted between January 1, 2016 and August 31, 2017 in Beijing Anding Hospital of Capital Medical University in China.

Depressed subjects were consecutively invited to participate in the study if they fulfilled the following inclusion criteria: 1) a current episode of major depressive disorder according to the DSM-IV criteria [40] based on a clinical interview; 2) aged 55 years or older; 3) Hamilton Depression Rating Scale (HDRS-17) total score of ≥ 18 indicating moderate-severe depression; 4) ability to understand the contents of the interview. Exclusion criteria were: 1) any other psychiatric comorbidities and MCI; 2) major medical conditions; 3) use of psychotropic drugs or other medications that may affect cognition in the past two weeks. Eligible patients were further divided into two groups according to the Montreal Cognitive Assessment (MoCA) total score: (1) late-life depression with cognitive impairment group (LLD-CI; MoCA total score < 26); (2) late-life depression without cognitive impairment group (LLD-NCI; MoCA total score of ≥ 26) [41, 42].

The AD group was consecutively recruited during the study period if they fulfilled the following inclusion criteria: 1) diagnosis of AD according to the criteria devised by the United States National Institute of Neurology Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) [43]; 2) aged 55 years or older; 3) the Chinese version of the Mini Mental State Examination (MMSE) total score of ≤ 26 [44]; 4) HDRS-17 total score of ≤ 7 ; 5) Hachinski Ischemic Score (HIS) score of ≤ 4 [45]; 6) able to understand the contents of the interview. Exclusion criteria were: 1) cognitive dysfunction associated with neurologic

conditions such as cerebrovascular diseases, syphilis encephalopathy, traumatic brain injury, or alcohol or drug abuse; 2) use of psychotropic drugs or other medications that may affect cognition in the past two weeks.

Healthy controls (HC) matched in age (± 3 years) and education (± 3 years) were recruited by advertisements from the community. Inclusion criteria were: 1) aged 55 years or older; 2) MMSE total score of >26 . Exclusion criteria were: 1) past or current history of psychiatric disorder; 2) focal lesion(s) in the brain on CT or MRI scans.

The study protocol was approved by the Research and Ethics Committee of Beijing Anding Hospital. All participants provided written informed consent.

Measures and assessments

Detection of urine AD7c-NTP

Clean midstream urine specimens were collected from all subjects in the morning and immediately centrifuged, and then preserved in a refrigerator at 4°C. The levels of AD7c-NTP in urine specimens were measured using the enzyme-linked immunosorbent assay AD7c-NTP kit (Anqun Biological Technology Co. Ltd., Shenzhen, China), which is the only kit approved for such clinical test in China. A microplate reader at 450nm wavelength was used to measure absorbance (A value) and the AD7c-NTP concentration.

Measures

Demographic and clinical characteristics of all subjects were recorded on a data collection sheet via a review of medical records and confirmed in a clinical interview conducted by two attending psychiatrists. The Chinese version of the Montreal Cognitive Assessment scale (MoCA) [46, 47] was used to

evaluate cognitive functions in aspects of visuospatial, executive, naming, attention, language, abstraction, delayed recall and orientation. The MoCA is a short (5-10 minutes), user-friendly cognitive screening tool for AD and mild cognitive impairment [46, 48]. The contents of MoCA focus more on executive function and attention than other short cognitive measures, such as the MMSE, therefore it is more suitable in detecting non-AD cognitive impairment [49]. The severity of depressive and anxiety symptoms were assessed using the Chinese versions of the HRSD-17 [50, 51], and the Hamilton Anxiety Rating Scale (HAMA) [51, 52], respectively.

Statistical analysis

Data were analyzed by the Statistical Package for Social Sciences (SPSS), Version 21.0. Chi-square tests and analysis of variance were used to compare the demographic and clinical variables and neuropsychology performances, as appropriate. The MoCA, HAMA, HRSD-17 total scores and urine AD7c-NTP levels were compared between the four groups using analysis of covariance (ANCOVA) after controlling for age, education levels and gender. The associations between urinary AD7c-NTP levels and age, gender, education, and the MoCA total score were assessed with Spearman's rank correlations. The levels of significance were set at 0.05 (two-tailed).

Results

Altogether, 138 subjects were recruited into 4 groups: LLD-CI (n=52), LLD-NCI (n=29), AD (n=30) and HC groups (n=27). The comparisons of basic demographic and clinical characteristics between groups are shown in Table 1. There were significant group differences in MoCA total scores and all its domains (all p values <0.05).

Table 1. Comparison of demographic and clinical variables between groups

Variables	LLD-CI (n=52)		LLD-NCI (n=29)		AD (n=30)		HC (n=27)		Statistics		
	N	%	N	%	N	%	N	%	χ^2	df	p
Male sex	17	32.7	15	51.7	15	50.0	17	63.0	7.3	3	0.06
Formal education ≤ 9 years	26	50.0	15	51.7	19	63.3	13	48.1	1.7	3	0.63
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	F	df	p
Age (years)	64.2	6.2	63.1	5.7	66.5	6.1	64.5	5.4	1.7	3	0.16
HAMA total	24.7	8.8	23.0	6.3					0.6	1	0.41
HRSD-17 total	27.4	7.9	24.1	7.2					2.7	1	0.10
MoCA total	21.5	3.1	27.3	1.1	13.8	4.7	27.5	1.3	133.0	3	<0.001
Visuospatial/Executive	3.4	1.2	4.4	0.6	2.5	1.2	4.5	0.6	24.3	3	<0.001
Naming	7.2	0.5	3.0	0.0	2.0	0.7	3.0	0.1	4.7	3	<0.001
Attention	4.8	1.1	5.8	0.4	2.2	1.3	5.7	0.4	89.4	3	<0.001
Language	1.9	0.8	2.8	0.3	1.3	0.9	2.7	0.5	29.0	3	<0.001
Abstraction	1.3	0.6	1.7	0.4	1.3	0.8	1.9	0.2	8.1	3	<0.001
Delayed recall	1.7	1.4	3.4	0.9	0.2	0.3	3.4	1.0	58.6	3	<0.001
Orientation	5.4	1.0	5.9	0.2	4.2	1.0	6.0	0.0	29.2	3	<0.001

Bold values: p <0.05 ; LLD-CI=late-life depression with cognitive impairment; LLD-NCI=late-life depression without cognitive impairment; AD=Alzheimer's disease; HC=healthy control; MoCA=Montreal Cognitive Assessment scale; HRSD-17=17-item Hamilton Rating Scale for Depression; HAMA=Hamilton Anxiety Rating Scale

Urinary level of AD7c-NTP

After controlling for the potentially confounding effects of age, education level, and gender, there were significant group differences in urinary AD7c-NTP levels (Table 2). Specifically, urinary AD7c-NTP levels in the LLD-CI group were significantly higher than those in the HC and LLD-NCI groups, but lower than found in the AD group (all p values < 0.05).

Table 2. Comparisons of urinary AD7c-NTP levels between the LLD-CI, LLD-NCI, AD, and HC groups

	LLD-CI (n=52)	LLD-NCI (n=29)	AD (n=30)	HC (n=27)	ANCOVA*		Pairwise comparison
					F	p	p
Urinary AD7c-NTP (ng/ml)	1.0±0.7	0.5±0.3	1.6± 1.7	0.5± 0.3	12.9	<0.001	LLD-CI vs. LLD-NCI <0.001 LLD-CI vs. HC 0.03 LLD-CI vs. AD 0.66 LLD-NCI vs. HC <0.001 LLD-NCI vs. AD <0.001 HC vs. AD <0.001

* The level of AD7c-NTP was not normally distributed. A log transformation has been used in ANCOVA. Bold values: $p < 0.05$; AD7c-NTP=Alzheimer-associated neuronal thread protein. LLD-CI=late-life depression with cognitive impairment; LLD-NCI=late-life depression without cognitive impairment; AD=Alzheimer's disease; HC=healthy control

Comparison of MoCA domain between LLD-CI and AD groups

Compared to the AD group, subjects in the LLD-CI group had significantly lower scores in visuospatial, executive, naming, attention, language, delayed recall and orientation, but not in the abstraction domains (Table 3).

Table 3. Comparisons of MoCA scores between the LLD-CI and AD groups

Variables	LLD-CI (n=52)		AD (n=30)		Statistics		
	Mean	SD	Mean	SD	F	df	p
MoCA total	21.5	3.1	13.8	4.7	61.4	1	<0.001
Visuospatial/Executive (range: 0-5)	3.4	1.2	2.5	1.2	5.4	1	0.02
Naming (range: 0-3)	7.2	0.5	2.0	0.7	21.6	1	<0.001
Attention (range: 0-6)	4.8	1.1	2.2	1.3	82.1	1	<0.001
Language (range: 0-3)	1.9	0.8	1.3	0.9	7.0	1	0.01
Abstraction (range: 0-2)	1.3	0.6	1.3	0.8	0.2	1	0.64
Delayed recall (range: 0-4)	1.7	1.4	0.2	0.3	27.0	1	<0.001
Orientation (range: 0-6)	5.4	1.0	4.2	1.0	18.6	1	<0.001

Bold values: $p < 0.05$; LLD-CI=late-life depression with cognitive impairment; AD=Alzheimer's disease; MoCA=Montreal Cognitive Assessment scale

Associations between AD7c-NTP levels and age, gender, education and MoCA score

Spearman correlation analyses revealed that urinary AD7c-NTP level was significantly and positively associated with the MoCA score in the

LLD-NCI group ($r=0.40$, $P=0.02$). However, no significant associations were found in the level of urinary AD7c-NTP in relation to age, gender, education and MoCA score in the LLD-CI group.

Table 4. Associations of AD7c-NTP levels in study groups with age, gender, education, and MoCA

Groups	Age		Gender		Education		MoCA	
	r	p	r	p	r	p	r	p
LLD-CI (n=52)	0.08	0.57	0.02	0.88	0.13	0.33	0.16	0.25
LLD-NCI (n=29)	0.27	0.15	-0.25	0.17	0.09	0.62	0.40	0.02
AD (n=30)	-0.01	0.95	0.10	0.60	0.01	0.93	-0.09	0.63
HC (n=27)	0.03	0.87	0.07	0.67	0.29	0.11	0.17	0.36

Bolded values: $p < 0.05$; LLD-CI: late-life depression with cognitive impairment; LLD-NCI: late-life depression without cognitive impairment; AD: Alzheimer's disease; HC: healthy control; Bolded values are $p < 0.05$; AD7c-NTP=Alzheimer-associated neuronal thread protein.

Discussion

Urinary AD7c-NTP has been proposed as a sensitive and specific diagnostic marker in early identification of probable AD and MCI [33]. According to one study, the level of urinary AD7c-NTP was 1.9 $\mu\text{g/L}$ (1.9 ng/ml) in mild AD, 3.9 $\mu\text{g/L}$ (3.9 ng/ml) in moderate/severe AD and 0.6 $\mu\text{g/L}$ (0.6 ng/ml) in healthy control groups [53]. The optimal cutoff value of urinary AD7c-NTP level for early diagnosis of AD was set at 1.5 $\mu\text{g/L}$ (1.5 ng/ml), with 90.6% sensitivity and 91.8% specificity [37].

In this study the urinary AD7c-NTP levels in LLD-CI (1.0 ng/ml) were significantly higher than those in HC (0.5 ng/ml) and LLD-NCI (0.5 ng/ml), which may be related to similar pathological changes in AD, such as accumulation of tau protein and overexpression of AD7c-NTP [29, 54]. To date, the association between urine AD7c-NTP level and the severity of cognitive impairment has been inconclusive. Some studies found that AD7c-NTP levels were negatively related with the severity of AD as measured by the MMSE [32, 53]. Another study also found that urinary AD7c-NTP levels in advanced AD were significantly higher than in early stage AD [37]. However, other studies found that moderate AD had a lower urinary AD7c-NTP level than mild AD [55], and several studies also failed to find any relationships between urinary AD7c-NTP levels and the severity of cognitive impairment in AD [33, 53]. Our study found a positive association between urinary AD7c-NTP level and the severity of cognitive impairment in the LLD-NCI group. However, due to the small sample size, this finding needs to be confirmed in future studies. Similar to previous findings [56, 57], our study found no association between urinary AD7c NTP level with age, gender and education.

There are several limitations to this study. First,

the sample size was relatively small, which limits the power of the findings. In addition, due to the cross-sectional design, the dynamic changes of urinary AD7c-NTP level in the four groups could not be examined. Second, clean midstream urine specimens were collected in the morning. Instead, 24-hour urine samples should have been used because the concentration of AD7c-NTP might be influenced by diurnal fluctuations. Third, the confounding effects of depressive symptoms on cognitive performance could not be controlled for. Fourth, some variables that could influence urine AD7c-NTP levels, such as the duration of the illness and use of psychotropic medications, were not examined.

In conclusion, the level of urinary AD7c-NTP appears to be associated with cognitive impairment in LLD as it was found to be significantly higher in LLD-CI than LLD-NCI and HC subjects. Hence, urinary AD7c-NTP could serve as a potential biomarker for early identification of cognitive impairment in LLD. Prospective studies with a larger sample size are needed to confirm such findings.

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Competing Interests

The authors have declared that no competing interest exists.

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