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Association of Ubiquitin C-Terminal Hydrolase-L1 (Uch-L1) serum levels with cognition and brain energy metabolism

M. ZHANG, M.-Y. CHEN, S.-L. WANG, X.-M. DING, R. YANG, J. LI, G.-H. JIANG

Department of Neurology, Affiliated Hospital of North Sichuan Medical College, Nanchong, China; Institute of Neurological Diseases, North Sichuan Medical College, Nanchong, Sichuan, China

Abstract. – OBJECTIVE: In recent years, many researchers have taken serum ubiquitin c-terminal hydrolase (Uch-L1) as an indicator of post-traumatic brain injury and associated it with cognitive impairment. Alzheimer's disease is characterized by cognitive impairment and energy metabolism disorders. The purpose of this study was to detect whether serum Uch-L1 is related to cognition and brain energy metabolism in healthy people, and to explore whether it can be used as an early blood marker of Alzheimer's disease.

PATIENTS AND METHODS: In this prospective cohort study, adult outpatients from a Grade 3A hospital were recruited. They completed the ^{18}F-FDG-PET/CT examination in the nuclear medicine department and were screened by the Mini Mental State scale (MMSE) and the Montreal Cognitive Assessment scale (MoCA). Blood samples were collected from all outpatients to detect the concentration of serum Uch-L1, and the mean standard uptake value (SUV_{mean}) of energy metabolism in the hippocampus during PET/CT examination was collected.

RESULTS: A total of 37 participants, 14 participants with cognitive impairment (MMSE score < 27) and 23 controls (MMSE score 27-30) were included. There was a significant difference in the SUV_{mean} of the hippocampus between the cognitive impairment group and the normal control group ($p < 0.05$). There was a significant correlation between the SUVmean of the hippocampus and the total score of MMSE in all participants [r = 0.439, 95% CI: (0.139-0.668), $p = 0.007$]. There were also significant correlations between serum Uch-L1 and MMSE. Based on the significant differences of demographic variables between groups, we conducted a multivariate linear regression analysis of MMSE cognitive scores based on age (X_1), length of education (X_2) and SUV_{mean} of hippocampus (X_3). The regression equation is as follows: $Y = 25.709-0.072\ X_1 + 0.422\ X_2 + 0.232\ X_3$.

CONCLUSIONS: Brain cognitive ability is closely related to energy metabolism and serum Uch-L1 concentration, so serum Uch-L1 may become a blood marker for extensive screening of dementia in the future. We look forward to the introduction of a more accurate and low-cost method for detecting serum Uch-L1 concentration.

Key Words:
PET-CT, Uch-L1, Cognition, Energy metabolism, Blood markers.

Introduction

Aging is the most important biomedical challenge facing mankind in the 21st century. The incidence of ageing-related diseases, such as Alzheimer's disease (AD), is expected to significantly increase in the next few decades. AD is the most prevalent neurodegenerative disease in the world, affecting more than 10% of the older people population worldwide[1]. Its pathological feature is that amyloid protein accumulates in the form of extracellular plaque and intracellular nerve fiber tangles[2]. In general, the early symptoms of AD are often ignored by patients and their families, and only obvious cognitive and behavioral changes in the middle and late stages attract their attention. However, at this time, the process of injury is irreversible. At present, all kinds of treatments can only improve the symptoms but cannot be cured[3]. Therefore, early AD screening in the older people has an important social epidemiological significance for prevention and treatment. At present, the common screening methods include detection of cerebrospinal fluid (CSF) biomarker: $A\beta_{42}/A\beta_{40}$ ratio, phosphorylated tau, total tau protein, head PET/CT detection of amyloid protein[4], and apolipoprotein E ε 4 (APOE ε 4) gene screening[5,6]. However, CSF biomarkers, PET and genetic

Corresponding Author: Guohui Jiang, MD; e-mail: neurodoctor@163.com

screening have high risks, strict operation requirements and high costs. Therefore, more economical and convenient blood tests have more realistic significance for community screenings with a large sample size and have been widely concerned and explored all over the world[7].

The brain needs to continuously provide energy in the form of adenosine triphosphate (ATP). At present, the disorder of energy metabolism in AD brain has gradually become a consensus, and the regulation of brain energy metabolism is also an important target for researchers to pay attention to[8]. The cause of brain metabolic decline in AD is unclear, but it may include impaired brain glucose transport, interrupted glycolysis and/or impaired mitochondrial function[9]. ^{18}F-FDG is a radionuclide labelled compound similar to glucose. After intravenous injection, ^{18}F-FDG enters the cell by glucose transporter on the cell membrane, which can reflect the level of glucose utilization and uptake in the body. Thus, it is used to detect high metabolic cancer cells[10]. In addition, because ^{18}F-FDG-PET/CT can detect the level of brain energy metabolism, it has been used by many researchers to predict and diagnose cognitive impairment and AD[11,12].

Ubiquitin c-terminal hydrolase (Uch-L1) is a specific deubiquitin enzyme that is highly expressed in neurons (accounting for 1-5% of the total brain proteins)[13]. It involved in the body's ubiquitin regulatory system. The protein was previously used as a histological marker for neurons. In terms of energy metabolism, Uch-L1 (C) has recently been found to regulate brain energy metabolism by regulating mitochondrial fusion protein Mitofusin-2 (Mfn2). In this way, it can regulate brain energy metabolism by altering mitochondrial volume, Ca^{2+} uptake, oxygen consumption, and connectivity to the endoplasmic reticulum[14]. Uch-L1 is promising to become a biomarker derived from neurons[15]. The level of the protein was found to be significantly decreased in the frontal cortex of AD donors[16]. It indicates the important intervention effect of Uch-L1 on AD. Some researchers have shown that the concentration of Uch-L1 in rats cerebrospinal fluid and serum, as biomarkers of spinal cord injury protein, is positively correlated with the severity of injury[17]. It has been proved that serum Uch-L1 can be used to diagnose whether there is immediate memory and delayed memory after intracranial injury[18,19]. Therefore, can serum Uch-1 be used to diagnose cognitive levels in healthy people without cranial injury? If the test samples come from easily available and economically safe blood samples, it will greatly reduce the physical pain and financial pressure of patients and make it feasible to carry out large-scale community AD screening and prevention. Since Uch-L1 is highly specific to neurons, the highest concentration is expected to appear in cerebrospinal fluid (CSF) and lower in serum. In order to get reliable screening results, we use sandwich enzyme-linked immunosorbent assay (ELISA) to quantitatively measure serum Uch-L1[20].

For the first time, our study assessed serum Uch-L1 levels in patients with cognitive impairment who underwent ^{18}F-FDG-PET/CT testing. The objectives are: (1) to observe the correlation between serum Uch-L1 and the changes of brain cognitive function and energy metabolism; (2) to explore whether Uch-L1 can be used as an early blood marker of AD.

Patients and Methods

Design

This study adopts prospective, cross-sectional and qualitative analysis.

Participants

The outpatients of the Department of Nuclear Medicine of the affiliated Hospital of North Sichuan Medical College, who had completed the examination of ^{18}F-FDG-PET/CT.

Steps

The researchers performed cognitive assessments of Mini Mental State examination (MMSE) and the Montreal Cognitive Assessment scale (MoCA), and venous blood collection on each fasting participant. Among the physical examiners who had been collected as samples, those who tested negative cancer for ^{18}F-FDG-PET/CT were finally included in the sample.

The hippocampus is recognized as a brain area related to cognitive function[21]. Therefore, we collected the standard uptake value (SUV) of hippocampal energy metabolism measured by ^{18F}FDG-PET/CT from participants eventually included in the study. The specific reference area is shown in Figure 2. The serum Uch-L1 of the participants was measured with double antibody sandwich ELISA kit (RayBiotech)[20]. The collected blood was placed in a stationary state and then centrifuged (3000 r/min, 10 min). Then the

serum was extracted and stored in a refrigerator at -80°C until analysis.

Ethical Consideration

This study was approved by the Medical Ethics Committee of the affiliated Hospital of North Sichuan Medical College in China (batch number: 2021ER130-1). Informed consent of participants has been obtained and privacy principles have been observed. It is in full compliance with all the principles established in the Helsinki Declaration (1975) and the Belmont report (1983).

Neuropsychological Assessment

Before the PET examination, the researchers assessed each participant's cognition with MMSE and MoCA. MMSE is widely used worldwide, and it is the preferred scale for dementia screening[22]. In Chinese population, the efficiency of MoCA in screening mild cognitive impairment (MCI) is higher than that of dementia, while the efficiency of MMSE in screening dementia is higher than that of MCI[23].

Serum ELISA Analysis

The collected blood was centrifuged (3000 r/min, 10 min) to extract serum and immediately stored in a -80°C refrigerator until analysis time. The 96-well plate of double antibody sandwich ELISA kit (RayBiotech) was coated with human Uch-L1 specific antibody. The 100 μl standard or sample was delivered to the orifice plate, and the Uch-L1 present in the sample was bound to the hole by fixed antibodies. After washing the hole for 3 times, biotin-labeled anti-human Uch-L1 antibody was added. After washing off the free biotin antibody, HRP-coupled streptavidin was transported into the pore. The orifice plates were cleaned again, the TMB substrate solution was added to the pores, and the color was proportional to the amount of Uch-L1 combined. Stop solution changed the color from blue to yellow, and the color intensity was measured at 450 nm. All serum samples were analyzed in duplicate, and the average value was collected.

Statistical Data Processing

Through the SPSS 23 Statistics Software (IBM Inc., Armonk, NY, USA), the demographic variables between the cognitive impairment group and the control group were analyzed by *t*-test, and the rest of the data were analyzed by correlation analysis. Results $p < 0.05$ indicated that the difference was statistically significant, and the measurement data were represented by mean ± standard deviation ($\bar{x} \pm s$).

Results

The inclusion criteria of the final sample in this study were as follows: the outpatients of the Department of Nuclear Medicine of the affiliated Hospital of North Sichuan Medical College, who have completed ^{18}F-FDG-PET/CT for cancer screening, ranging in age from 43 to 85 years old. The exclusion criteria were: (1) patients who were diagnosed with cancer as a result of the final test (cancer patients have high metabolic levels and high Uch-L1 levels[24,25]), (2) physical examinations with brain diseases, (3) those who did not want to take part in the study, (4) and patients with any type of speech disorder that prevented them from answering the test. The specific process of inclusion and exclusion is shown in Figure 1.

According to the score of MMSE scale, 37 cases of physical examination were divided into two groups: cognitive impairment group and control group. Demographic information for each subset of the queue is provided in Table I. Although the MoCA scale for early cognitive impairment may be more appropriate than the MMSE scale, it is more complex and takes more time than the MMSE scale. The older people with lack of energy have a lower acceptance of MoCA than MMSE. When measuring the two scales at the same time, they chose to answer only the MMSE with simple questions and refused to answer MoCA. Therefore, in the final inclusion of 37 samples, all were scored by MMSE, but only 24 cases were scored by MoCA scale. We recorded the total score of MMSE and MoCA and the score of each cognitive aspect. The higher the score, the better the cognitive function. Cognitive scale statistics for each subset of the queue are provided in Table II.

There is a Positive Correlation Between Brain Energy Metabolism and Overall Cognitive Level

The data of mean SUV value (SUV_{mean}) of hippocampal energy metabolism in the two groups are shown in Figure 2. The energy metabolism in the hippocampus of the cognitive impairment group was significantly lower than that of the control group ($p < 0.05$, Figure 2A-C). There was a significant correlation between the SUV_{mean} of the hippocampus of all participants and the total score of MMSE [r = 0.439, 95% CI: (0.139, 0.668),

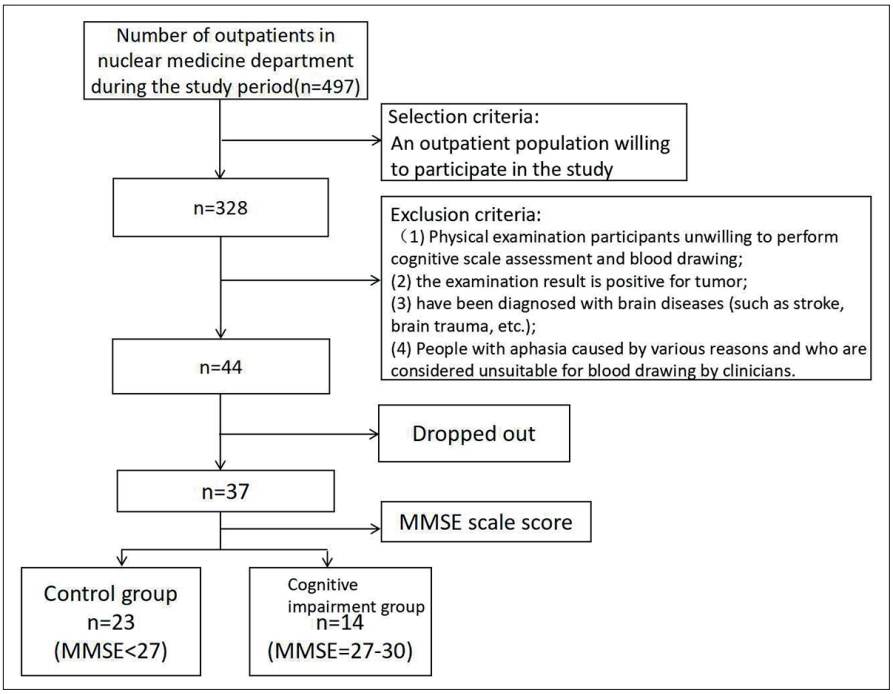

Figure 1. Sample is included in the process.

Table I. Cohort demographics.

	Cognitive impairment group	Control group	*p*-value
Hippocampal SUV_{mean}	5.06 (1.05)	6.05 (1.38)	0.0313
Age (SD)	67.4 (12.1)	50.9 (9.6)	0.0003
BMI (SD)	23.35 (4.23)	22.67 (2.98)	0.5889
Length of Education (SD)	2.71 (3.79)	10.17 (4.08)	< 0.0001
Male/female	4/10	14/9	0.0589

SUV_{mean}: mean standard uptake value; BMI: Body Mass Index.

p = 0.007, Figure 2D]. In order to examine the specific effects of brain energy metabolism on cognition, we completed an intergroup difference test of demographic variables, and the results are shown in Table I. Considering the significant differences between groups, we used age (X_1) and length of education (X_2) plus the SUV_{mean} of hippocampal area (X_3) to analyze the MMSE

Table II. Scores of participants' cognitive function tests.

	MMSE (n = 37) mean (SE)/Total	MoCA (n = 24) mean (SE)/Total
Total score	26 (4)/30	22.9 (4.6)/30
Orientation	8.76 (1.6)/10	5.7 (0.7)/6
Registration	1.8 (1)/3	1.7 (1.5)/5
Attention and calculation	4.1 (1.5)/5	5.4 (1)/6
Language	7.6 (0.6)/8	2.4 (0.7)/3
Visual space	0.7 (0.5)/1	3 (1.7)/5
Instant memory	3/3	——
Abstract thinking and naming	——	4.1 (1)/5

The total score of the two scales was 30, including the following five aspects: time, place orientation, memory, attention and calculation, language and visual space. The MMSE scale also has immediate memory, and the MoCA scale also includes abstract thinking and naming. When the level of education is lower than 12 years, the score of the MoCA scale should be increased by 1 point in the total score.

Table III. Correlation between Cognition (MMSE score) and age, length of education and energy metabolism (SUV_{mean}).

Variable	B	Std. Error	95% CI of B		N	*p*-value	Tolerance
			LL	UL			
Age	-0.072	0.047	-0.167	0.024	37	0.135	0.588
Length of education	0.422	0.108	0.203	0.641	37	0.000	0.629
SUV_{mean}	0.232	0.401	-0.584	1.049	37	0.566	0.716

B, Unstandardized Coefficients; CI, confidence interval; LL, lower limit; UL, upper limit; SUVmean: standard mean intake value of hippocampus.

cognitive score by multi-factor linear regression analysis. The results are shown in Table III. The regression equation is as follows: $Y = 25.709 - 0.072\ X_1 + 0.422\ X_2 + 0.232\ X_3$.

The Relationship Between Brain Energy Metabolism and Serum Uch-L1 Levels

One case of abnormally high serum Uch-L1 due to increased tumor markers was excluded from the sample. No clear correlation was found between the SUV_{mean} of energy metabolism in the hippocampus and serum Uch-L1 levels in all participants. The reason for this result may be that the energy metabolism of the brain not only has glucose metabolism, but also ketone body metabolism is an important energy source. Therefore, if ketone metabolism can be included in the later research, more accurate results can be obtained.

The Relationship Between Serum Uch-L1 Level and Different Cognitive Aspects

The correlation between serum Uch-L1 level and cognitive domains such as MMSE total score, time and place orientation, memory, attention and calculation, language, visual space, immediate memory, abstract thinking and naming was analyzed in Table II. The result is shown in Figure 3: there were significant correlations between serum Uch-L1 and MMSE total score [r = 0.417, 95% CI: (0.092, 0.661), $p = 0.0115$, n = 36, Figure 3a], serum Uch-L1 and attention and calculation ability [r = 0.413, 95% CI: (0.087, 0.658), $p = 0.0124$, n = 36, Figure 3b], and serum Uch-L1 and language ability [r = 0.51, 95% CI: (0.208 ~ 0.723), $p = 0.0015$, n = 36, Figure 3c].

Discussion

The results of this study show that the level of serum Uch-L1 is related to various cognitive domains, and there is a statistically significant correlation between serum Uch-L1 and the total score of MMSE, attention and calculation ability, language ability, etc. The results of PET/CT show

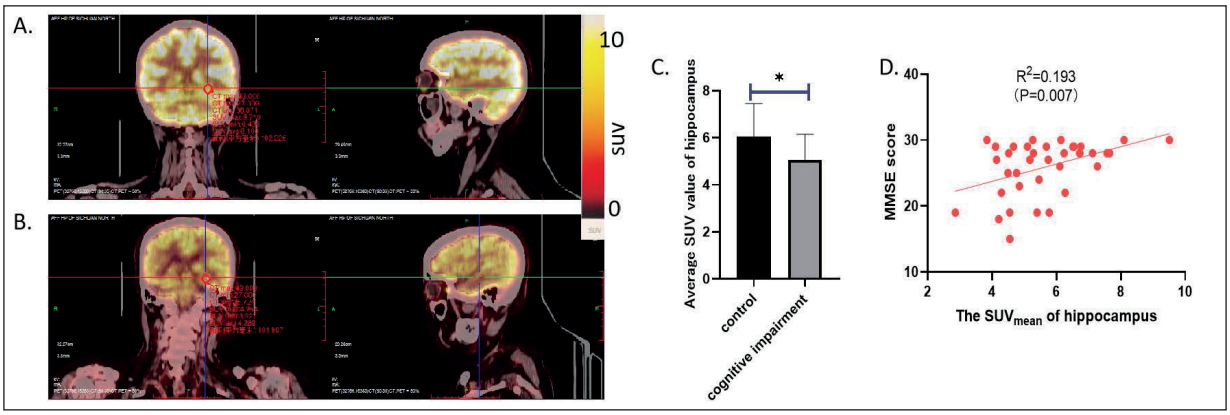

Figure 2. The relationship between brain energy metabolism and cognition. **A,** shows the brain ^{18}F-FDG-PET/CT test results of normal control group, as shown, the higher the color brightness is, the stronger the energy metabolism is; **B,** shows the test results' map of cognitive impairment group; **C,** shows the comparison of SUV_{mean} values of energy metabolism in the hippocampus of the two groups of participants; **D,** shows the correlation analysis scatter's map of the SUV_{mean} value of hippocampal region and the total score of MMSE of all participants.

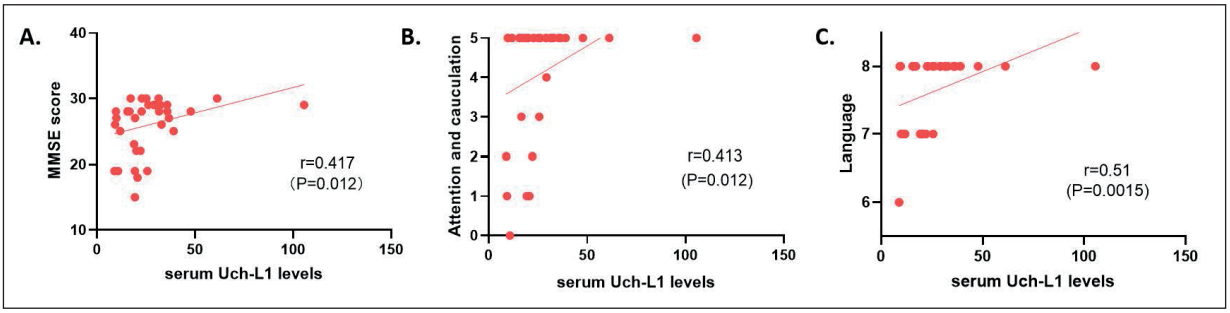

Figure 3. The relationship between serum Uch-L1 level and different cognitive aspects: **A,** shows the scatter plot of the correlation analysis between serum Uch-L1 and MMSE total score; **B,** shows the scatter plot of the correlation analysis between serum Uch-L1 and attention and computing ability; **C,** shows the scatter chart of the correlation analysis between serum Uch-L1 and language ability.

that the glucose metabolism in the hippocampus is related to the cognitive function represented by MMSE, which is consistent with the results of previous studies on the decrease of brain metabolism in patients with AD[12].

From the completion of the MMSE and MoCA cognitive scales in the sample, the simpler MMSE scale is more acceptable to the participants with poor physical condition. The level of education has a great influence on the two cognitive scales, especially MoCA[26,27]. Since illiteracy and primary school education account for a large proportion of the middle-aged and aged people in southwest China, MoCA cannot well judge whether they have cognitive impairment or dementia. In the study, we found that some illiterate older people flexible in thinking, had a low MoCA score, so they are classified as dementia, which is obviously not in line with the actual situation. So, investigators need to consult the actual clinical manifestations to judge these people.

Many design and analysis decisions affect our interpretation of the data and the resulting conclusions. First of all, during the cognitive scale test, it is found that the level of education of the participants had a great impact on their scores. However, there was a great difference in the level of education among these participants, so it might not be very objective to judge whether there was cognitive impairment by the score of the scale only. Secondly, it is evident that age is a direct factor affecting cognitive status, so it is not accurate if we only analyze the relationship between cognition and energy metabolism without the intervention of other factors. In order to detect the specific effects of brain energy metabolism factors on cognition, we completed a test of the differences between groups of demographic variables, as shown in Table I. Three factors (age, length of education and SUV_{mean} of hippocampal) were included in the multi-factor linear regression analysis of cognition, and the linear regression equation was obtained. From the results of the regression analysis in Table III, we can see that the collinearity between brain energy metabolism and the latter two is not strong. So, it is necessary to take brain energy metabolism as a separate factor to judge the cognitive situation. In addition, the optical density (OD) value of the sample diluted twice the concentration was multiplied by two times, which may be different from the actual concentration when converted to concentration. Fortunately, we only analyze the trend of concentration distribution among samples and the correlation of other factors, and do not need specific values, so the impact on the results of correlation analysis is still within the tolerable range. The current results are essentially cross-sectional and do not capture the process of longitudinal changes in cognitive state. If we want to carry out the next predictive study, follow-up and re-evaluation of the participants is a feasible method.

Because of the visible advantages of blood markers compared with other detection methods, many gratifying achievements have been made in exploring effective early blood markers of AD (such as Aβ, tau protein, APOE ε 4, etc.) in recent years. By means of supersensitive single molecular array (Simoa) method, it was found that the ratio of plasma $Aβ_{42}/Aβ_{40}$ was negatively correlated with AD, which was highly consistent with the results of brain Aβ load measured by PET, the gold standard for early diagnosis of AD[28]. Recently, it has been found that the performance of plasma P-tau217 as a marker of AD is not significantly different from that of key indicators based on CSF or

PET[29]. Thus, it can be seen that the sensitivity of blood markers of AD is similar to that of CSF or PET.

Our study shows for the first time that serum Uch-L1 concentration in healthy people is related to overall cognitive ability, attention and calculation ability, language ability, etc., which is also consistent with its performance in evaluating immediate and delayed memory of TBI patients after injuries[19]. With the continuous innovation and development of detection technology, the detection of serum Uch-L1 concentration may become one of the safe and convenient methods for community dementia screenings in the future.

Conflict of Interest

The Authors declare that they have no conflict of interests.

Acknowledgements

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Trial Number and the Name of the Registry

ChiCTR2100052371; Chinses Clinical Trial Registry.

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