ISSN 2307-8960 (online)

World Journal of *Clinical Cases*

World J Clin Cases 2020 January 6; 8(1): 1-244

Published by Baishideng Publishing Group Inc

World Journal of Clinical Cases

Contents

Semimonthly Volume 8 Number 1 January 6, 2020

REVIEW

ORIGINAL ARTICLE

Case Control Study

Retrospective Study

Observational Study

Prospective Study

CASE REPORT

LETTER TO THE EDITOR

World Journal of Clinical Cases
Volume 8 Number 1 January 6, 2020

Contents

NAME OF JOURNAL
World Journal of Clinical Cases

ISSN
ISSN 2307-8960 (online)

LAUNCH DATE
April 16, 2013

FREQUENCY
Semimonthly

EDITORS-IN-CHIEF
Dennis A Bloomfield, Bao-Gan Peng, Sandro Vento

EDITORIAL BOARD MEMBERS
https://www.wjgnet.com/2307-8960/editorialboard.htm

EDITORIAL OFFICE
Jin-Lei Wang, Director

PUBLICATION DATE
January 6, 2020

INSTRUCTIONS TO AUTHORS
https://www.wjgnet.com/bpg/gerinfo/204

GUIDELINES FOR ETHICS DOCUMENTS
https://www.wjgnet.com/bpg/GerInfo/287

GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH
https://www.wjgnet.com/bpg/gerinfo/240

PUBLICATION MISCONDUCT
https://www.wjgnet.com/bpg/gerinfo/208

ARTICLE PROCESSING CHARGE
https://www.wjgnet.com/bpg/gerinfo/242

STEPS FOR SUBMITTING MANUSCRIPTS
https://www.wjgnet.com/bpg/GerInfo/239

ONLINE SUBMISSION
https://www.f6publishing.com

World Journal of Clinical Cases

Submit a Manuscript: https://www.f6publishing.com

World J Clin Cases 2020 January 6; 8(1): 76-87

DOI: 10.12998/wjcc.v8.i1.76

ISSN 2307-8960 (online)

ORIGINAL ARTICLE

Observational Study

Relationship between β-amyloid protein 1-42, thyroid hormone levels and the risk of cognitive impairment after ischemic stroke

Lei Mao, Xiao-Han Chen, Jian-Hua Zhuang, Peng Li, Yi-Xin Xu, Yu-Chen Zhao, Yue-Jin Ma, Bin He, You Yin

ORCID number: Lei Mao (0000-0003-1202-2250); Xiao-Han Chen (0000-0003-3018-8924); Jian-Hua Zhuang (0000-0001-2281-1173); Peng Li (0000-0003-2284-2848); Yi-Xin Xu (0000-0002-2274-1934); Yu-Chen Zhao (0000-0002-3777-3872); Yue-Jin Ma (0000-0001-9372-3384); Bin He (0000-0001-8365-2849); You Yin (0000-0003-3514-5712).

Author contributions: Mao L and Chen XH contributed equally to this study; Mao L, Chen XH, Zhuang JH and Yin Y designed the research; Mao L, Chen XH, Li P, Xu YX, Zhao YC, Ma YJ and He B performed the research; Zhuang JH, Li P and Xu YX contributed new analytic tools; Mao L, Chen XH, Ma YJ and He B analyzed the data; Mao L, Chen XH, Zhuang JH, Li P, Xu YX, Zhao YC, Ma YJ, He B and Yin Y wrote the paper.

Supported by Science and Technology Support Projects in Biomedicine Field of Shanghai Science and Technology Commission, No. 19441907500; Naval Medical University Military Medical Innovation, No. 2017JS07; Science and Technology Action Innovation Program by Science and Technology Commission of Shanghai, No. 17411950104.

Institutional review board statement: The study was approved by the Ethics Committee of Changzheng Hospital, the PLA Naval Medical University.

Informed consent statement: All patients gave informed consent.

Conflict-of-interest statement: The authors declare that they have no

Lei Mao, Xiao-Han Chen, Jian-Hua Zhuang, Peng Li, Yi-Xin Xu, Yu-Chen Zhao, Yue-Jin Ma, Bin He, You Yin, Department of Neurology, Changzheng Hospital, the PLA Naval Medical University, Shanghai 200003, China

Lei Mao, Department of Neurology, Shanghai First People's Hospital Baoshan Branch, Shanghai 200003, China

Corresponding author: You Yin, MD, PhD, Chief Doctor, Chief Physician, Department of Neurology, Changzheng Hospital, the PLA Naval Medical University, NO. 415 Fengyang Road, Huangpu District, Shanghai 200003, China. yinyou179@163.com

Abstract

BACKGROUND

Post-stroke cognitive impairment (PSCI) is not only a common consequence of stroke but also an important factor for adverse prognosis of patients. Biochemical indicators such as blood lipids and blood pressure are affected by many factors, and the ability of evaluating the progress of patients with PSCI is insufficient. Therefore, it is necessary to find sensitive markers for predicting the progress of patients and avoiding PSCI. Recent studies have shown that β-amyloid protein 1-42 (Aβ1-42) and thyroid hormone levels are closely related to PSCI, which may be the influencing factors of PSCI, but there are few related studies.

AIM

To investigate the relationship between serum levels of Aβ and thyroid hormones in acute stage and PSCI and its predicted value.

METHODS

A total of 195 patients with acute cerebral infarction confirmed from June 2016 to January 2018 were enrolled in this study. Baseline data and serological indicators were recorded to assess cognitive function of patients. All patients were followed up for 1 year. Their cognitive functions were evaluated within 1 wk, 3 mo, 6 mo and 1 yr after stroke. At the end of follow-up, the patients were divided into PSCI and non-PSCI according to Montreal cognitive assessment score, and the relationship between biochemical indexes and the progression of PSCI was explored.

RESULTS

Compared with patients with non-PSCI, the levels of Aβ1-42, triiodothyronine (T_3) and free thyroxin were lower in the patients with PSCI. Repeated measures analysis of variance showed that the overall content of Aβ1-42 and T_3 in PSCI was

competing interests.

Data sharing statement: No additional data are available.

STROBE statement: The authors have read the STROBE statement, and the manuscript was prepared and revised according to the STROBE statement.

Manuscript source: Unsolicited manuscript

Received: September 8, 2019
Peer-review started: September 8, 2019
First decision: November 12, 2019
Revised: November 24, 2019
Accepted: November 27, 2019
Article in press: November 27, 2019
Published online: January 6, 2020

P-Reviewer: Dik VK, Guerin A
S-Editor: Wang JL
L-Editor: Filipodia
E-Editor: Liu JH

also lower than that of the non-PSCI patients. Further analysis revealed that Aβ1-42 (r = 0.348), T_3 (r = 0.273) and free thyroxin (r = 0.214) were positively correlated with disease progression ($P < 0.05$), suggesting that these indicators have the potential to predict disease progression and outcome. Cox regression analysis showed that Aβ1-42 and T_3 were important factors of PSCI. Then stratified analysis showed that the lower the Aβ1-42 and T_3, the higher risk of PSCI in patients who were aged over 70, female and illiterate.

CONCLUSION
Aβ1-42 and T3 have the ability to predict the progression of PSCI, which is expected to be applied clinically to reduce the incidence of PSCI and improve the quality of life of patients.

Key words: Post-stroke cognitive impairment; Triiodothyronine; β-amyloid protein; Prognosis; Montreal cognitive assessment; Free thyroxin

Core tip: Post-stroke cognitive impairment (PSCI) has become a deepening public health problem. PSCI diagnosis is mostly based on clinical manifestations, neuroimaging and a series of neuropsychological tests. However, early diagnosis is difficult because the implementation of the above-mentioned scheme depends on the cooperation of patients. Therefore, it is necessary to identify early biomarkers. Our study found that β-amyloid protein 1-42 and triiodothyronine can dynamically monitor the patient's clinical status and correlates with progression of the disease. It is suggested that β-amyloid protein 1-42 and triiodothyronine have the ability to predict the progress of PSCI and can be broadly applied.

Citation: Mao L, Chen XH, Zhuang JH, Li P, Xu YX, Zhao YC, Ma YJ, He B, Yin Y. Relationship between β-amyloid protein 1-42, thyroid hormone levels and the risk of cognitive impairment after ischemic stroke. *World J Clin Cases* 2020; 8(1): 76-87
URL: https://www.wjgnet.com/2307-8960/full/v8/i1/76.htm
DOI: https://dx.doi.org/10.12998/wjcc.v8.i1.76

INTRODUCTION

With its high morbidity, disability and mortality, stroke is one of the major health-threatening diseases[1-3]. Besides causing motor and sensory disorders, stroke can also result in cognitive impairment, including mild post-stroke cognitive impairment (PSCI) and dementia, which seriously affects the daily activities of patients and brings great burden to society[4,5]. Epidemiological data show that more than half of stroke patients have different degrees of PSCI, and about one-third of patients develop severe PSCI or even dementia at 3 mo after onset of the disease, but there is no specific treatment for this disease[6-8]. Thus, early detection and intervention of PSCI has become an important and urgent social need. Extensive experimental data show that the main factors affecting PSCI include hypertension, diabetes mellitus, hyperlipidemia and other vascular risk factors as well as demographic factors such as age and education level[9-11]. These high-risk factors suggest the occurrence of PSCI, but the relevant biochemical indicators are interfered by many factors and have low specificity, which is not suitable for early assessment and prediction of prognosis[12,13]. The Montreal Cognitive Assessment (MoCA) and Mini-Mental State Examination are the common neuropsychological scales of early screening and evaluating for PSCI and widely used in long-term follow-up of patients because of their good reliability and validity in PSCI large sample epidemiological studies and clinical trials[14,15]. However, different scales have their own limitations. It is difficult to perform accurate screening with a single application, and the combination of multiple scales will increase the burden on patients. Additionally, the neuropsychology scale has certain subjectivity and requires other clinical diagnostic indicators.

Recent research found that PSCI is closely related to the core pathological changes of Alzheimer's disease, suggesting that both may have common diagnostic biomarkers[16,17]. β-amyloid protein (Aβ) is the main component of senile plaques

characterized by Alzheimer's disease[18]. Previous studies have suggested that serum Aβ may be an independent cerebrovascular risk factor, which can indicate vascular injury during dementia[19,20]. Yu *et al*[21] found that Aβ not only exists in Alzheimer's disease but also has a close relationship with the progress of stroke. It shows a good application prospect in early diagnosis and judgment of the severity of dementia. Furthermore, the influence of metabolic factors such as thyroid hormone levels on PSCI has been observed[22]. Wang *et al*[23] confirmed that thyroid function may affect the cognitive level of patients by regulating brain energy metabolism and signal transduction. Nevertheless, little research has been done on the relationship between Aβ, thyroid hormone levels and PSCI, and further studies are needed to identify the value of these indicators assessing the risk of cognitive disorders after acute ischemic stroke.

Therefore, this study intends to analyze the relevant indicators of patients with acute cerebral infarction and to clarify the correlation between each index and PSCI.

MATERIALS AND METHODS

Participants

A total of 195 patients with acute cerebral infarction confirmed from June 2016 to January 2018 were enrolled in this study. There were 109 males and 86 females, aged from 60 to 80 years, and the average age was (69.38 ± 10.05) years. The diagnostic criteria were in line with the "Diagnostic Points for Various Cerebrovascular Diseases" formulated by the Fourth National Cerebral Vascular Disease Conference in 1995, and all patients were diagnosed by cranial magnetic resonance imaging or computed tomography. The inclusion criteria were: (1) Acute ischemic stroke occurring within 7 d before admission; (2) right-handed; and (3) new cases. The exclusion criteria were: (1) Aphasia, severe hearing or visual impairment; (2) thyroid disease and other endocrine diseases; (3) severe condition after cerebral infarction and unconsciousness unable to cooperate with examination and cognitive assessment; (4) with consciousness obstacle prior to the illness onset [the National Institutes of Health Stroke Scale (NIHSS) > 10] or other diseases associated with cognitive impairment in patients; (5) suffering from abnormal function of the heart, lungs, liver or systemic disease, estimated survival < 1 year; and (6) have a history of mental illness or behavioral disorders.

The patients and their guardians participated in the study voluntarily and provided written informed consent. The study was approved by the Ethics Committee of Changzheng Hospital, the PLA Naval Medical University.

Clinical basic information

Patient data were collected within 3-5 d after admission, including demographic data (gender, age, body mass index and education level), lifestyle (smoking and drinking) and health status (systolic blood pressure; diastolic blood pressure, atrial fibrillation, hypertension, hyperlipidemia, diabetes, history of stroke/transient ischemic attack and myocardial infarction). Meanwhile, NIHSS scale was used to determine the neural function of patients (the higher the score, the more severe the neurologic impairment).

Imageology examination

Patients with acute cerebral infarction were tested by Siemens MAGNETOM Skyra, (Germany) and their infarct location (anterior circulation infarction or posterior circulation infarction) was recorded (Figure 1). Pulliino formula was used to calculate the size of the lesion, and TOAST classification was performed.

Biochemical tests

Blood samples of patients were collected within 24 h of admission. Three milliliters of venous blood was collected after fasting, centrifuged at 3000 r/min for 10 min to collect serum and then stored at -80 °C. Biochemical indexes including total cholesterol, triglyceride (TG), low-density lipoprotein (LDL), high-density lipoprotein, hypersensitive C-reactive protein and homocysteine were detected by AU-400 fall-automatic biochemical analyzer. ELISA was used to determine Aβ, and the kit was provided by Shanghai Hengfei Biotechnology Co., Ltd. Chemiluminescence immunoassay was applied to analyze the level of triiodothyronine (T_3), thyroxin (T_4), free triiodothyronine, free thyroxin (FT_4) and thyrotropin, and the kit was purchased from Beijing Baioleibo Technology Co., Ltd.

Scale measurement and definition of PSCI

The cognitive function scale was measured using the MoCA within 1 wk, 3 mo, 6 mo

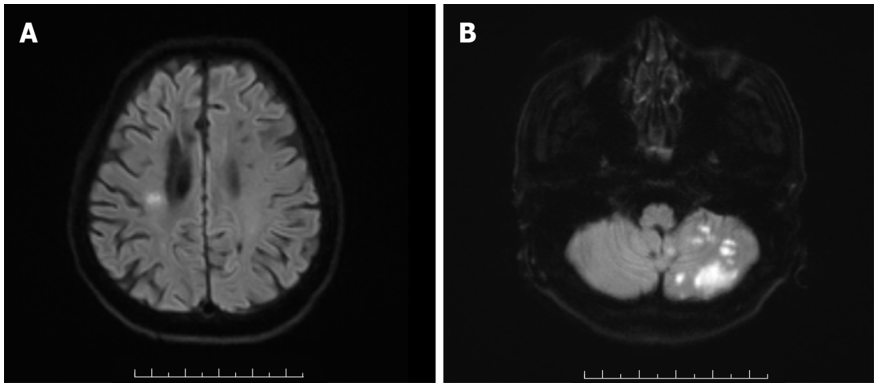

Figure 1 Magnetic resonance imaging images of the infarct location of the patient with cerebral infarction. A: Patient with anterior circulation infarction; B: Patient with posterior circulation infarction.

and 1 yr after the onset of the disease. The assessment areas included visual spatial ability, executive function, short-term memory and recall, attention, language and direction. The MoCA, with a total score of 30, showed high sensitivity in screening for mild cognitive impairment, and patients should take no more than 10 min to complete the assessment.

Follow-up and quality control

The patients were treated routinely and followed up for 1 year, starting at 14 d after treatment and then followed monthly. All investigators were trained uniformly, and pre-survey was conducted before formal investigation. The data records were independently conducted by two individuals. The endpoint was defined as the patient with a MoCA score < 26 were the PSCI group), and the patients with a MoCA score < 26 were the non-PSCI group (+ 1 was added to the patient's for an education level below 12 years).

The progress of the patient's condition was evaluated compared with the baseline. If the MoCA score decreased by more than 4 points, then progress was noted as aggravation. If the MoCA score decreased by less than 3 points, then progress was noted as stable. If the MoCA score increased by more than 4 points, then progress was noted as improvement. All ischemic stroke outcomes were assessed by a professional neurologist.

Statistical analysis

The data were analyzed by SPSS16.0 statistical software. Continuous variables conforming to normal distribution and homogeneity of variance were tested by independent sample *t* test, and the composition ratio was analyzed by Chi-square test/Fisher exact probability method. Repeated measures analysis of variance was used to compare the biochemical indicators in the two groups within 1 wk, 3 mo, 6 mo and 1 yr after stroke. The relationship between the biochemical indicators and the progression of the disease was evaluated by Spearman correlation analysis. Cox regression analysis was used to calculate the relative risk of each influencing factor.

RESULTS

Baseline data analysis of two groups

At the end of follow-up, a total of seven cases were lost to follow-up. According to the MoCA score, 72 cases with mild cognitive impairment were regarded as the PSCI group, while the remaining 116 cases were regarded as the non-PSCI group. Analysis of baseline data of admission between the two groups showed that there were more patients who were female, had a history of stroke/transient ischemic attack and had atrial fibrillation in the PSCI group than in the non-PSCI group ($P < 0.05$). In addition, compared with the non-PSCI group, age, TG, LDL and the NIHSS score at admission were higher in the PSCI group, while the education level, Aβ1-42, T_3 and FT_4 were lower in the PSCI group than in the non-PSCI group. The difference was significant ($P < 0.05$, Table 1).

Changes of biochemical indexes in two groups at different time points

The follow-up results showed that 15 out of 188 patients had PSCI at the 14th day after treatment, and the highest incidence was observed at 3 mo. In the PSCI group, 48

Table 1 Baseline clinical characteristics in non-post stroke cognitive impairment and post stroke cognitive impairment patients, *n* (%)

Variable	PSCI, *n* = 72	Non-PSCI, *n* = 116	*P* value
Age in yr	73 (66-80)	65 (60-74)	< 0.001
Gender, male/female	38/34	79/37	0.027
BMI as kg/m^2	24.5 ± 2.6	23.8 ± 2.7	0.081
Education levels			0.011
Illiterate	26 (36.1)	24 (20.7)	
Primary school	32 (44.4)	48 (41.4)	
Postsecondary school	14 (19.4)	44 (37.9)	
Smoking	13 (18.1)	26 (22.4)	0.449
Drinking	8 (11.1)	17 (14.7)	0.448
SBP as mmHg	152 ± 24	147 ± 26	0.189
DBP as mmHg	85 ± 12	83 ± 10	0.219
TC as mmol/L	4.54 ± 0.78	4.58 ± 0.72	0.720
TG as mmol/L	1.48 ± 0.57	1.31 ± 0.41	0.019
HDL as mmol/L	1.19 ± 0.17	1.12 ± 0.22	0.204
LDL as mmol/L	2.85 ± 0.71	2.34 ± 0.76	< 0.001
Aβ1-42 as pg/mL	363.0 ± 37.8	402.2 ± 35.3	< 0.001
hs-CRP as mg/L	4.8 ± 4.6	6.2 ± 7.1	0.138
Hcy as μmol/L	15.8 ± 8.2	15.0 ± 8.6	0.529
T_3 as nmol/L	1.23 ± 0.59	1.47 ± 0.77	0.025
T_4 as nmol/L	117.2 ± 26.4	110.5 ± 21.4	0.058
FT_3 as pmol/L	4.68 ± 0.85	4.42 ± 0.93	0.056
FT_4 as pmol/L	13.03 ± 2.26	16.47 ± 3.84	<0.001
TSH as mU/L	1.22 ± 0.64	1.41 ± 0.75	0.076
History of disease			
Hypertension	25 (34.7)	37 (31.9)	0.674
Hyperlipidemia	3 (4.2)	9 (7.8)	0.284
Diabetes	16 (22.2)	28 (24.1)	0.750
Stroke/TIA	19 (26.4)	17 (14.7)	0.041
Myocardial infarction	2 (2.8)	3 (2.6)	0.930
Atrial fibrillation	9 (12.5)	5 (4.3)	0.037
NIHSS score on admission	7.2 ± 3.7	5.1 ± 2.9	< 0.001
Cerebral infarction volume in cm^3	11.14 ± 2.25	10.86 ± 1.98	0.372
Lesion location			
Posterior circulation	16 (22.2)	33 (28.4)	0.313
TOAST			0.890
Large-artery atherosclerosis	39 (54.2)	58 (50)	
Cardioembolism	6 (8.3)	8 (6.9)	
Small-artery occlusion Lacunar	21 (29.2)	37 (31.9)	
Other determined etiology	5 (6.9)	9 (7.8)	
Undetermined etiology	1 (1.4)	4 (3.4)	
Medications during hospitalization			
Hypoglycemic	13 (18.1)	23 (19.8)	0.759
Antihypertensive	35 (48.6)	53 (45.7)	0.681
Lipid-lowering drugs	54 (75.0)	81 (69.8)	0.411
Antiplatelet	65 (90.3)	104 (89.7)	0.888

Data are presented as mean ± SD or median (interquartile range). PSCI: Post stroke cognitive impairment; BMI: Body mass index; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; TC: Total cholesterol; TG: Triglyceride; HDL: High-density lipoprotein; LDL: Low-density lipoprotein; Aβ1-42: β-amyloid protein1-42; hs-CRP: Hypersensitive C-reactive protein; Hcy: Homocysteine; T_3: Triiodothyronine; T_4: Thyroxin; FT_3: Free triiodothyronine; FT_4: Free thyroxin; TSH: Thyrotropin; TIA: Transient ischemic attack; NIHSS: National Institutes of Health Stroke Scale.

patients suffered from PSCI, which was significantly relieved at 6 mo and continued to recover at the end of the follow-up.

The results of repeated measures analysis of variance showed that the levels of Aβ1-42 and T_3 in the PSCI group decreased first and then increased at different time points, reaching a low level at 3 mo, stabilizing at 6 mo after stroke and then slowly increasing. By contrast, the levels of Aβ1-42 and T_3 in the non-PSCI group continuously, steadily and slowly increased. Aβ1-42 and T_3 reached the highest level within 1 wk of onset, and then decreased slightly, showing a steady trend. The level of Aβ1-42 and T_3 in the PSCI group were lower in the 3rd and 6th month after onset. The overall levels of Aβ1-42 (*FBetween groups* = 4.782, *PBetween groups* = 0.011) and T_3 (*FBetween groups* = 6.069, *PBetween groups* < 0.001) in the PSCI group was also lower than those in the non-PSCI group. The changes of FT_4 level in the two groups were analyzed, and the results revealed that the FT_4 content of both groups increased continuously with time, but there was no significant difference between the two groups as a whole (*FBetween groups* = 1.724, *PBetween groups* = 0.195, Table 2).

Relationship between Aβ1-42, thyroxine levels and disease progression

During the follow-up period, the progression of the disease was aggravated in 77, stable in 65 patients and improved in 46 patients. The relationships between Aβ1-42, T_3, FT_4 and disease progression (improvement, stabilization, and aggravation) were analyzed by Spearman rank correlation analysis, and the results are shown in Table 3. Aβ1-42, T_3 and FT_4 were positively correlated with disease progression ($P < 0.05$). Patient's condition improved with the increase of Aβ1-42, T_3 and FT_4 levels ($P < 0.05$).

Comparing the correlation degree of the above indicators, the correlation between Aβ1-42 and disease progression was better ($r = 0.348$), followed by T_3 ($r = 0.273$).

Cox analysis of the effect of Aβ1-42 and thyroxine levels on PSCI

Whether the patient has PSCI or not was taken as a dependent variable (MoCA score < 26 points = 1, ≥ 26 = 0), and Aβ1-42, T_3 and FT_4 levels were included in the Cox regression equation. The degree of influence of the above indicators on the risk of PSCI in univariate Cox (unadjusted), Model I (adjusted for age and gender), Model II (adjusted for age, gender, body mass index, education levels, smoking, drinking and history of disease) and Model III (adjusted for NIHSS, LDL and TG in addition to the confounders that were adjusted for in Model II) was calculated.

Univariate Cox regression analysis showed that Aβ1-42, T_3 and FT_4 had an effect on the occurrence of PSCI in patients and that they were protective factors. After adjusting age and gender, these above indicators were still important as influencing factors for the occurrence of diseases ($P < 0.05$). There was a regression relationship between Aβ1-42, T_3 and cognitive function of patients in Model III ($P < 0.05$). After further adjustment for NIHSS score, LDL, TG and other factors, we found that the increase of Aβ1-42 and T_3 could reduce the risk of PSCI ($P < 0.05$, Table 4).

Stratified analysis of Aβ1-42, T_3 and risk of PSCI

As shown in Table 5, the relationship between Aβ1-42, T_3 and PSCI were further analyzed in different age, gender and educational level groups. After adjustment for age, gender, education level, body mass index, smoking, drinking, history of disease, NIHSS, LDL and TG, the results showed that the lower the Aβ1-42 and T_3 levels, the higher the risk of PSCI in patients who were aged over 70, female and illiterate.

DISCUSSION

Currently, comprehensive treatment is the main treatment for PSCI in the clinic. Traditional rehabilitation training is suitable for patients with early and mild illness. Those with severe illness can be treated with adjuvant drugs. However, most drugs are aimed at people with Alzheimer's disease and vascular cognitive impairment, and there are few drugs that specifically target PSCI[24]. It is worth noting that PSCI itself has a high heterogeneity. The disease tends to develop dynamically, and the early symptoms are not obvious and easy to ignore. Therefore, the search for sensitive predictive markers and early detection of PSCI are essential for the improvement of PSCI patients.

In this study, we compared the baseline data of the PSCI patients with that of the non-PSCI patients and found that Aβ1-42, LDL, TG, T_3 and FT_4 levels were closely related to the risk of PSCI, which had the potential to evaluate the prognosis of stroke patients. Aβ1-42 is one of the important markers of the development of Alzheimer's disease and vascular dementia. A large accumulation of Aβ1-42 in the brain can cause apoptosis and cognitive impairment, leading to a cascade of neuron injury and death and amplifying inflammation[25]. An increasing amount of evidence indicates that Aβ

Table 2 Difference of biochemical indexes in two groups at different time points

Variable group	1st week	3rd month	6th month	1st year
Aβ1-42 in pg/mL				
PSCI, *n* = 72	363.0 ± 37.8	356.1 ± 37.5	360.7 ± 32.2	372.5 ± 38.6
Non-PSCI, *n* = 116	402.2 ± 35.3	404.8 ± 32.6	411.4 ± 36.5	428.1 ± 40.9
T_3 in nmol/L				
PSCI, *n* = 72	1.23 ± 0.59	1.17 ± 0.62	1.38 ± 0.55	1.45 ± 0.67
Non-PSCI, *n* = 116	1.47 ± 0.77	1.49 ± 0.85	1.46 ± 0.72	1.52 ± 0.64
FT_4 in pmol/L				
PSCI, *n* = 72	13.03 ± 2.26	13.15 ± 2.14	13.79 ± 1.57	14.28 ± 2.19
Non-PSCI, *n* = 116)	16.47 ± 3.84	16.23 ± 3.21	16.58 ± 4.04	17.67 ± 3.18

Data are presented as mean ± standard deviation. Aβ1-42: *FBetween groups* = 4.782, *PBetween groups* = 0.011; T3: *FBetween groups* = 6.069, *PBetween groups* < 0.001; FT_4: *FBetween groups* = 1.724, *PBetween groups* = 0.195. PSCI: Post stroke cognitive impairment; Aβ1-42: β-amyloid protein1-42; T_3: Triiodothyronine; FT_4: Free thyroxin.

is closely related not only to Alzheimer's disease but also to cerebral ischemia, suggesting that Aβ may be a risk factor for stroke and play an important role in the process of PSCI.

Previous studies have also reported that atrial fibrillation is associated with the degree of severity of stroke, poor prognosis and mortality during long-term follow-up of stroke patients[26-28]. Even in atrial fibrillation patients without a history of stroke, their cognitive function sharply declines. Therefore, appropriate cardiac assessment and anticoagulation therapy should be given priority to these patients. This study also showed that the location and cause of the lesion had no statistically significant effect on the occurrence of PSCI. It may be due to the disease subtype, the time of cognitive assessment and other factors, which affect the credibility of the index[29,30]. It is limiting to analyze the prognosis of stroke patients only by the location of stroke, and comprehensive analysis should be made in combination with factors such as stroke volume and number.

A longitudinal study showed that the prevalence of severe cognitive impairment at 2 wk, 3 mo and 6 mo after stroke was 16.3%, 32.0%, and 13.6%-31.8%, respectively[31]. Studies from Britain and France found that the incidence of cognitive impairment 3 mo after stroke was 39% and 47.3%, respectively[32,33]. After a 1-year follow-up of stroke patients in this study, we also found that the incidence rate was the highest at 3 mo after onset of the disease and gradually recovered at 6 mo, which accorded with the above conclusion. This suggests that the management of patients should be strengthened 3 to 6 mo after stroke in order to identify and prevent the occurrence of PSCI as soon as possible. Moreover, the results of repeated measurements of variance analysis suggested that the overall content of Aβ1-42 and T_3 in the PSCI group was lower than that in non-PSCI group, suggesting that the changes in Aβ1-42 and T_3 after stroke may be related to disease progression, and both of them can dynamically monitor and evaluate the risk of disease for a long time. However, due to the impact of subsequent changes in indicators, there is a need to expand the analysis.

After further evaluation of the relationship between Aβ1-42, T_3, FT_4 and the disease progression, Spearman analysis showed that each index correlated with the patient's disease progression and had a certain clinical value in indicating the severity of the disease and prognosis. Then, we performed a regression analysis of the relationship between each indicator and the risk of PSCI. Because of the high correlation among independent variables, multiple models were used to correct the related factors. The results show that both Aβ1-42 and T_3 were important influencing factors for the occurrence of the disease, regardless of whether the confounding factors were adjusted or not. This indicates that Aβ1-42 and T_3 had a good application prospect in evaluating the occurrence and development of PSCI.

According to the conclusion of Chen *et al*[34], the mechanism of T_3 changes after stroke may be that the decrease of cerebral perfusion damages the blood-brain barrier and affects the level of organic anion transporting polypeptide in epithelial cells, causing the decline of peripheral thyroid hormone responsible for transporting, which changes the content of T_3 in brain[34]. Conversely, the decrease of thyroid hormone level will also affect cerebral blood flow perfusion, energy metabolism and so on, leading to diffuse neurological dysfunction and cognitive decline[35]. A stratified analysis of the level Aβ1-42, T_3 and risk of PSCI found that the lower the Aβ1-42 and

Table 3 Analysis of the correlation between indicators and disease progression

	Montreal Cognitive Assessment			*r*	*P* value
	Aggravation, *n* = 77	Stable condition, *n* = 65	Improvement, *n* = 44		
Aβ1-42 in pg/mL	358.6 ± 38.7	364.7 ± 33.9	392.5 ± 36.4	0.348	< 0.001
T_3 in nmol/L	1.19 ± 0.75	1.42 ± 0.66	1.48 ± 0.61	0.273	< 0.001
FT_4 in pmol/L	14.03 ± 2.86	15.15 ± 3.04	16.58 ± 2.42	0.214	0.005

Data are presented as mean ± standard deviation. Aβ1-42: β-amyloid protein1-42; T_3: Triiodothyronine; FT_4: Free thyroxin.

T_3 levels, the higher risk of PSCI in patients who were aged over 70, female and illiterate. Those studies at home and abroad have confirmed that the age, gender and education level are high risk factors for stroke, which is consistent with this result.

A prospective research method was applied in this study, and the collected data had good reliability and persuasiveness. However, the weaknesses of this study are a short follow-up time, small number of included research factors and insufficient extrapolation.

In conclusion, Aβ1-42 and T_3 have the ability to predict progression of PSCI and are expected to be applied clinically to reduce the incidence of PSCI and improve the quality of life of patients.

Table 4 Effects of indicators on patients with post stroke cognitive impairment

	Aβ1-42	T_3	FT_4
Unadjusted			
RR	0.658	0.741	0.582
95% CI	0.427-0.933	0.385-0.929	0.306-0.884
P value	0.022	0.036	0.017
Model I			
RR	0.932	0.895	0.918
95% CI	0.852-0.936	0.876-0.982	0.923-0.994
P value	0.033	0.028	0.019
Model II			
RR	0.684	0.673	0.825
95%CI	0.501-0.846	0.337-0.812	0.762-1.109
P value	0.009	0.017	0.092
Model III			
RR	0.282	0.430	0.748
95%CI	0.258-0.833	0.332-0.918	0.747-1.116
P value	0.012	0.038	0.116

Model I: Adjusted for age and gender; Model II: Adjusted for age, gender, body mass index, education levels, smoking, drinking and history of disease; Model III: Adjusted for National Institutes of Health Stroke Scale, low-density lipoprotein, triglyceride in addition to the confounders that were adjusted for in Model II. Aβ1-42: β-amyloid protein1-42; T_3: Triiodothyronine; FT_4: Free thyroxin; RR: Relative risk; CI: Confidence interval.

Table 5 Association between β-amyloid protein 1-42, triiodothyronine levels and post stroke cognitive impairment stratified by age, gender and education levels

Variable	Aβ1-42			T_3		
	RR[1]	95%CI	*P* value	RR[1]	95%CI	*P* value
Age in yr						
< 70	0.982	0.437-2.188	0.173	0.371	0.208-0.663	0.001
≥ 70	0.416	0.290-0.612	< 0.001	0.319	0.139-0.731	0.007
Gender						
Male	0.794	0.328-1.901	0.075	0.618	0.249-1.527	0.298
Female	0.537	0.352-0.846	0.028	0.472	0.270-0.794	0.005
Education levels						
Illiterate	0.682	0.511-0.853	0.034	0.151	0.056-0.403	< 0.001
Primary school	0.945	0.875-0.998	0.047	0.786	0.414-1.495	0.464
Postsecondary school	0.853	0.640-1.066	0.089	0.937	0.625-1.403	0.256

[1]These statistical results were adjusted for age, gender, body mass index, education levels, smoking, drinking, history of disease, National Institutes of Health Stroke Scale, low-density lipoprotein and triglyceride. Aβ1-42: β-amyloid protein1-42; T_3: Triiodothyronine; RR: Relative risk; CI: Confidence interval.

ARTICLE HIGHLIGHTS

Research background

Acute ischemic stroke is the second most common cause of cognitive impairment and dementia in recent years. According to statistics, more than 64% of the patients after stroke show different degrees of cognitive impairment, and about 25% of stroke survivors suffer from dementia within 12 mo after stroke. Early monitoring is very important for clinical assessment of the severity and prognosis of ischemic stroke. Recent studies and epidemiological investigations have shown that the deposition of β-amyloid protein (Aβ) is associated with vascular risk factors and plays an important role in the development of post-stroke cognitive impairment. In addition, it has the advantages of invasiveness, small variability and good stability and has a good application prospect. However, the conclusions of the relationship between Aβ and post-stroke cognitive impairment (PSCI) have not been unified, and there are few related studies.

Research motivation
The commonly used tools for detecting cognitive function include neuropsychological scales, related imaging and cerebrospinal fluid examinations. Neuropsychological scales are limited by their clinical application due to a variety of factors and the need for higher expertise. The cost of imaging examination is relatively high, and its accuracy is related to the level of medical facilities. Therefore, the discovery of effective biomarkers may increase the efficiency of diagnosis and treatment of PSCI. Aβ is considered to be the common pathway of vascular dementia induced by various causes, which can lead to a cascade reaction of neuron injury. More and more studies have shown that Aβ1-42 is associated with PSCI, but there is no direct correlation between the two.

Research objectives
The purpose of this study is to explore the relationship between serum Aβ1-42, thyroid hormone level and PSCI and its predictive effect on this disease and to understand the influence of other possible risk factors on PSCI.

Research methods
A total of 195 patients with acute cerebral infarction were followed up for 1 year and grouped according to the Montreal Cognitive Assessment score. We analyzed the difference of clinical data and Aβ1-42 and thyroid hormone between the two groups. The changes of Aβ1-42 and thyroid hormone with time after onset were analyzed by repeated measurement variance analysis, and the relationship between the above indicators and the progression of the disease was explored. COX regression and stratified analysis were used to evaluate the effects of Aβ1-42 and thyroid hormone on PSCI and other possible risk factors.

Research results
Our results showed that the prevalence of PSCI was highest at 3 mo after stroke and gradually decreased at 6 mo after stroke. We found that Aβ1-42, triiodothyronine (T_3) and free thyroxin in patients with PSCI were lower than those with non-PSCI, and the above indicators were correlated with disease progression. Furthermore, Cox regression analysis revealed that Aβ1-42 and T_3 were the factors influencing the development of disease, and the higher the Aβ1-42 and T_3 levels, the lower the risk of disease.

Research conclusions
Aβ1-42 and T_3 play an important role in the development of PSCI. Low levels of Aβ1-42 and T_3 at the acute phase of ischemic stroke is the predictor of PSCI, and a higher education level may help to reduce the risk of PSCI.

Research perspectives
Currently, most of the studies on the biological markers of cognitive impairment are related to cerebrospinal fluid markers, and most of them are single predictive indicators. Therefore, there are some disadvantages in clinical practicability, sensitivity and specificity. This study analyzed the predictive ability of serum Aβ1-42 and thyroid hormone levels in cognitive impairment after ischemic stroke, improving the diagnostic rate of patients with PSCI. It provided reference for the prevention and treatment of PSCI and has potential clinical application value.

ACKNOWLEDGEMENTS
The authors acknowledge the invaluable participation of the patients.

REFERENCES
1 **Randolph SA**. Ischemic Stroke. *Workplace Health Saf* 2016; **64**: 444 [PMID: 27621261 DOI: 10.1177/2165079916665400]
2 **Meschia JF**, Brott T. Ischaemic stroke. *Eur J Neurol* 2018; **25**: 35-40 [PMID: 28800170 DOI: 10.1111/ene.13409]
3 **Hart RG**, Catanese L, Perera KS, Ntaios G, Connolly SJ. Embolic Stroke of Undetermined Source: A Systematic Review and Clinical Update. *Stroke* 2017; **48**: 867-872 [PMID: 28265016 DOI: 10.1161/STROKEAHA.116.016414]
4 **Robinson RG**, Jorge RE. Post-Stroke Depression: A Review. *Am J Psychiatry* 2016; **173**: 221-231 [PMID: 26684921 DOI: 10.1176/appi.ajp.2015.15030363]
5 **Kalaria RN**, Akinyemi R, Ihara M. Stroke injury, cognitive impairment and vascular dementia. *Biochim Biophys Acta* 2016; **1862**: 915-925 [PMID: 26806700 DOI: 10.1016/j.bbadis.2016.01.015]
6 **Rodríguez García PL**, Rodríguez García D. Diagnosis of vascular cognitive impairment and its main categories. *Neurologia* 2015; **30**: 223-239 [PMID: 22739039 DOI: 10.1016/j.nrl.2011.12.014]
7 **Harrison RA**, Field TS. Post stroke pain: identification, assessment, and therapy. *Cerebrovasc Dis* 2015; **39**: 190-201 [PMID: 25766121 DOI: 10.1159/000375397]
8 **Burton L**, Tyson SF. Screening for cognitive impairment after stroke: A systematic review of psychometric properties and clinical utility. *J Rehabil Med* 2015; **47**: 193-203 [PMID: 25590458 DOI: 10.2340/16501977-1930]
9 **Arba F**, Quinn T, Hankey GJ, Inzitari D, Ali M, Lees KR; VISTA Collaboration. Determinants of post-stroke cognitive impairment: analysis from VISTA. *Acta Neurol Scand* 2017; **135**: 603-607 [PMID:

27412470 DOI: 10.1111/ane.12637]
10 **Teng Z**, Dong Y, Zhang D, An J, Lv P. Cerebral small vessel disease and post-stroke cognitive impairment. *Int J Neurosci* 2017; **127**: 824-830 [PMID: 27838946 DOI: 10.1080/00207454.2016.1261291]
11 **Chander RJ**, Lam BYK, Lin X, Ng AYT, Wong APL, Mok VCT, Kandiah N. Development and validation of a risk score (CHANGE) for cognitive impairment after ischemic stroke. *Sci Rep* 2017; **7**: 12441 [PMID: 28963553 DOI: 10.1038/s41598-017-12755-z]
12 **Zhao L**, Biesbroek JM, Shi L, Liu W, Kuijf HJ, Chu WW, Abrigo JM, Lee RK, Leung TW, Lau AY, Biessels GJ, Mok V, Wong A. Strategic infarct location for post-stroke cognitive impairment: A multivariate lesion-symptom mapping study. *J Cereb Blood Flow Metab* 2018; **38**: 1299-1311 [PMID: 28895445 DOI: 10.1177/0271678X17728162]
13 **Bordet R**, Ihl R, Korczyn AD, Lanza G, Jansa J, Hoerr R, Guekht A. Towards the concept of disease-modifier in post-stroke or vascular cognitive impairment: a consensus report. *BMC Med* 2017; **15**: 107 [PMID: 28539119 DOI: 10.1186/s12916-017-0869-6]
14 **Chan E**, Altendorff S, Healy C, Werring DJ, Cipolotti L. The test accuracy of the Montreal Cognitive Assessment (MoCA) by stroke lateralisation. *J Neurol Sci* 2017; **373**: 100-104 [PMID: 28131163 DOI: 10.1016/j.jns.2016.12.028]
15 **Fu C**, Jin X, Chen B, Xue F, Niu H, Guo R, Chen Z, Zheng H, Wang L, Zhang Y. Comparison of the Mini-Mental State Examination and Montreal Cognitive Assessment executive subtests in detecting post-stroke cognitive impairment. *Geriatr Gerontol Int* 2017; **17**: 2329-2335 [PMID: 28675607 DOI: 10.1111/ggi.13069]
16 **Tong Z**, Wang W, Luo W, Lv J, Li H, Luo H, Jia J, He R. Urine Formaldehyde Predicts Cognitive Impairment in Post-Stroke Dementia and Alzheimer's Disease. *J Alzheimers Dis* 2017; **55**: 1031-1038 [PMID: 27802225 DOI: 10.3233/JAD-160357]
17 **Molad J**, Hallevi H, Korczyn AD, Kliper E, Auriel E, Bornstein NM, Ben Assayag E. Vascular and Neurodegenerative Markers for the Prediction of Post-Stroke Cognitive Impairment: Results from the TABASCO Study. *J Alzheimers Dis* 2019; **70**: 889-898 [PMID: 31282420 DOI: 10.3233/JAD-190339]
18 **Cheignon C**, Tomas M, Bonnefont-Rousselot D, Faller P, Hureau C, Collin F. Oxidative stress and the amyloid beta peptide in Alzheimer's disease. *Redox Biol* 2018; **14**: 450-464 [PMID: 29080524 DOI: 10.1016/j.redox.2017.10.014]
19 **Koizumi K**, Wang G, Park L. Endothelial Dysfunction and Amyloid-β-Induced Neurovascular Alterations. *Cell Mol Neurobiol* 2016; **36**: 155-165 [PMID: 26328781 DOI: 10.1007/s10571-015-0256-9]
20 **Van Nostrand WE**. The influence of the amyloid β-protein and its precursor in modulating cerebral hemostasis. *Biochim Biophys Acta* 2016; **1862**: 1018-1026 [PMID: 26519139 DOI: 10.1016/j.bbadis.2015.10.020]
21 **Yu CC**, Wang Y, Shen F, Kong LH, Wang YW, Zhou H, Tang L. High-frequency (50 Hz) electroacupuncture ameliorates cognitive impairment in rats with amyloid beta 1-42-induced Alzheimer's disease. *Neural Regen Res* 2018; **13**: 1833-1841 [PMID: 30136700 DOI: 10.4103/1673-5374.238620]
22 **Dhital R**, Poudel DR, Tachamo N, Gyawali B, Basnet S, Shrestha P, Karmacharya P. Ischemic Stroke and Impact of Thyroid Profile at Presentation: A Systematic Review and Meta-analysis of Observational Studies. *J Stroke Cerebrovasc Dis* 2017; **26**: 2926-2934 [PMID: 28821377 DOI: 10.1016/j.jstrokecerebrovasdis.2017.07.015]
23 **Wang Y**, Zhou S, Bao J, Pan S, Zhang X. Low T_3 levels as a predictor marker predict the prognosis of patients with acute ischemic stroke. *Int J Neurosci* 2017; **127**: 559-566 [PMID: 27401927 DOI: 10.1080/00207454.2016.1211649]
24 **Guekht A**, Skoog I, Edmundson S, Zakharov V, Korczyn AD. ARTEMIDA Trial (A Randomized Trial of Efficacy, 12 Months International Double-Blind Actovegin): A Randomized Controlled Trial to Assess the Efficacy of Actovegin in Poststroke Cognitive Impairment. *Stroke* 2017; **48**: 1262-1270 [PMID: 28432265 DOI: 10.1161/STROKEAHA.116.014321]
25 **Lauriola M**, Paroni G, Ciccone F, D Onofrio G, Cascavilla L, Paris F, Gravina C, Urbano M, Seripa D, Greco A. Erythrocyte Associated Amyloid-β as Potential Biomarker to Diagnose Dementia. *Curr Alzheimer Res* 2018; **15**: 381-385 [PMID: 29125073 DOI: 10.2174/1567205014666171110160556]
26 **Chander RJ**, Lim L, Handa S, Hiu S, Choong A, Lin X, Singh R, Oh D, Kandiah N. Atrial Fibrillation is Independently Associated with Cognitive Impairment after Ischemic Stroke. *J Alzheimers Dis* 2017; **60**: 867-875 [PMID: 28922154 DOI: 10.3233/JAD-170313]
27 **Banerjee G**, Chan E, Ambler G, Wilson D, Cipolotti L, Shakeshaft C, Cohen H, Yousry T, Lip GYH, Muir KW, Brown MM, Jäger HR, Werring DJ; CROMIS-2 collaborators. Effect of small-vessel disease on cognitive trajectory after atrial fibrillation-related ischaemic stroke or TIA. *J Neurol* 2019; **266**: 1250-1259 [PMID: 30847646 DOI: 10.1007/s00415-019-09256-6]
28 **Tang SC**, Yang KC, Hu CJ, Chiou HY, Wu CC, Jeng JS. Elevated Plasma Level of Soluble Form of RAGE in Ischemic Stroke Patients with Dementia. *Neuromolecular Med* 2017; **19**: 579-583 [PMID: 29098526 DOI: 10.1007/s12017-017-8471-9]
29 **Brainin M**, Tuomilehto J, Heiss WD, Bornstein NM, Bath PM, Teuschl Y, Richard E, Guekht A, Quinn T; Post Stroke Cognition Study Group. Post-stroke cognitive decline: an update and perspectives for clinical research. *Eur J Neurol* 2015; **22**: 229-238, e13-e16 [PMID: 25492161 DOI: 10.1111/ene.12626]
30 **Hewetson R**, Cornwell P, Shum D. Cognitive-communication disorder following right hemisphere stroke: exploring rehabilitation access and outcomes. *Top Stroke Rehabil* 2017; **24**: 330-336 [PMID: 28218007 DOI: 10.1080/10749357.2017.1289622]
31 **Babulal GM**, Huskey TN, Roe CM, Goette SA, Connor LT. Cognitive impairments and mood disruptions negatively impact instrumental activities of daily living performance in the first three months after a first stroke. *Top Stroke Rehabil* 2015; **22**: 144-151 [PMID: 25936546 DOI: 10.1179/1074935714Z.0000000012]
32 **Adamit T**, Maeir A, Ben Assayag E, Bornstein NM, Korczyn AD, Katz N. Impact of first-ever mild stroke on participation at 3 and 6 month post-event: the TABASCO study. *Disabil Rehabil* 2015; **37**: 667-673 [PMID: 24889677 DOI: 10.3109/09638288.2014.923523]
33 **Sundar U**, Adwani S. Post-stroke cognitive impairment at 3 months. *Ann Indian Acad Neurol* 2010; **13**: 42-46 [PMID: 20436746 DOI: 10.4103/0972-2327.61276]
34 **Chen X**, Duan L, Han Y, Tian L, Dai Q, Wang S, Lin Y, Xiong Y, Liu X. Predictors for vascular cognitive impairment in stroke patients. *BMC Neurol* 2016; **16**: 115 [PMID: 27461245 DOI: 10.1186/s12883-016-0638-8]
35 **Chen H**, Wu Y, Huang G, He W, Lin S, Zhang X, He J. Low Tri-iodothyronine Syndrome Is Associated With Cognitive Impairment in Patients With Acute Ischemic Stroke: A Prospective Cohort Study. *Am J*

Geriatr Psychiatry 2018; **26**: 1222-1230 [PMID: 30236902 DOI: 10.1016/j.jagp.2018.07.007]

Published By Baishideng Publishing Group Inc
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-2238242
E-mail: bpgoffice@wjgnet.com
Help Desk:https://www.f6publishing.com/helpdesk
https://www.wjgnet.com