

## Original Article

# The progressive supranuclear palsy patients exhibited lower levels of serum cholesterol and protein levels: a retrospective study

Guihong Wang<sup>1</sup>, Qing Huo<sup>2</sup>, Jiong Zhan<sup>3</sup>, Binbin Nie<sup>4,5,6</sup>, Baoci Shan<sup>4,5,6</sup>, Tau Feng<sup>1,7,8</sup>

<sup>1</sup>Department of Neurology, Center for Neurodegenerative Diseases, Beijing Tiantan Hospital, Capital Medical University, Beijing 100050, China; <sup>2</sup>Department of Biomedical, Biochemical Engineering College of Beijing Union University, Fatouxili 3 region 18<sup>#</sup>, Chaoyang District, Beijing 100023, China; <sup>3</sup>Neuroscience Imaging Center, Beijing Tiantan Hospital, 6 TiantanXili, Dongcheng District, Beijing 100050, China; <sup>4</sup>Division of Nuclear Technology and Applications, Institute of High Energy Physics, Chinese Academy of Sciences, Beijing 100049, China; <sup>5</sup>Beijing Engineering Research Center of Radiographic Techniques and Equipment, Beijing 100049, China; <sup>6</sup>CAS Center for Excellence in Brain Science, 320 Yue Yang Road, Shanghai 200031, China; <sup>7</sup>Parkinson's Disease Center, Beijing Institute for Brain Disorders, Capital Medical University, Beijing 100050, China; <sup>8</sup>China National Clinical Research Center for Neurological Diseases, Beijing, China

Received February 16, 2016; Accepted June 7, 2016; Epub August 15, 2016; Published August 30, 2016

**Abstract:** Many studies have showed that the serum cholesterol levels existed significant difference between Parkinson's disease (PD) patients and health controls. However, the serum cholesterol level in progressive supranuclear palsy (PSP) has not been studied. The object of this paper was to examine the levels of serum cholesterol and protein of PSP and their change in the disease progression. 57 possible PSP patients were collected in Beijing Tiantan Hospital from 2002 to 2014. The serum cholesterol and protein level of 57 patients were compared with 89 age- and sex-matched controls. In the 57 PSP patients, 12 patients have been in hospital two or more times. The data of these 12 patients were further analyzed to explore the changes of serum total cholesterol (TC) or total protein (TP) with the course of disease. Our findings showed that the serum TC and TP levels in patients were significantly lower than control. Multivariate logistics regression analysis showed that both TP and TC were independently associated with PSP. The serum protein and cholesterol levels further reduced from first hospitalization to the last time. The results implied that the serum protein and serum cholesterol might played a critical role in the development of PSP.

**Keywords:** Serum cholesterol, serum protein, parkinson disease, progressive supranuclear palsy

## Introduction

Progressive supranuclear palsy (PSP) is a rare neurodegenerative disease with movement disorder [1]. Many patients with PSP have Parkinson's disease (PD) symptoms, especially in its initial stage. So, PSP is also defined as a Parkinsonism plus syndromes. Considerable evidences suggest that genetic factors and environmental factors were associated with neurodegenerative diseases [2, 3]. Environment-gene interactions played a critical role in the development of disease [2, 4]. The environmental factors might act as triggers for genetic factors. If we can determine which environmental factor is the risk factor, which could then be

used as targets for the prevention or intervention, at least partly possible. The nutrition factors, such as serum cholesterol and protein, are the important environmental factors. Some studies have found that the serum cholesterol might be a possible risk factor for PD [5]. However, the association between serum cholesterol and PD is highly debated [6]. Some studies have reported that no significant association between the serum cholesterol and PD [7-10]. However, one large prospective study from Finland suggests that high total cholesterol is associated with an increased risk of PD [5]. Another prospective study from Netherland suggests that high total cholesterol level is associated with a decreased risk of PD [10].

## Neurodegenerative diseases

Though the serum cholesterol has not been finally affirmed as a risk factor for PD, many studies have been carried out to validate the relationship between serum cholesterol and PD [7]. However, there was not any study on the association between serum cholesterol and PSP, though PSP is a Parkinsonism plus syndromes.

In this study, we will investigate the association between serum cholesterol level and PSP. In addition, protein is also an important nutritional index in blood examination, which has not been studied on PSP, too. So, this study will also investigate the association between serum protein level and PSP.

### Materials and methods

#### *Subjects*

In this study, 57 patients with PSP were recruited from the inpatients at the neurology department of Beijing TianTan Hospital, Capital Medical University, Beijing, China. Two neurologists used a standard questionnaire to capture demographic and clinical characteristics from previous medical records from Sept. 2002 to Sept. 2014 in the Department of Neurology in Beijing Tiantan Hospital, including age, gender, disease duration; past medical history, such as hypertension, diabetes, hyperlipidemia, and medications, as well as personal history such as height, weight and smoking history. The PSP patients were diagnosed by the neurologists according to the standard of NINDS-SPSP (national institute of neurological disorders and the society for progressive supranuclear palsy) [11]. The patients taking lipid lowering drugs were excluded. The age and sex matched control subjects from outpatients were selected in the same hospital, which were excluded neurodegenerative disease, intracerebral infarction, severe demyelination lesions, severe heart, hepatic, renal function damage, and taking lipid lowering drugs. The above clinical information was collected using the same questionnaire. The protocol of this study was approved by the local ethics committee.

#### *Examination of serum lipid and protein profile*

Blood samples were drawn from the antecubital vein in the morning after overnight fast. Tubes were centrifuged at 3000 X g for 10 min at room temperature. After separation, plasma samples were frozen as rapidly as possible to

280 uC for storage until laboratory determinations were performed. For all participants, serum protein profile including total protein (TP) and albumin (ALB), serum lipid profile including total cholesterol (TC), high density lipoprotein cholesterol (HDL-C), low density lipoprotein cholesterol (LDL-C), triglycerides (TG) were assessed. All the blood variables were measured using an auto analyzer (LABOSPECT008; Hitachi, Japan) at the central laboratory of the Tiantan Hospital.

#### *MRI acquisition*

MR imaging for all subjects were performed on two MRI scanner (Siemens Trio 3 Tesla Erlangen, Germany; GE Signa HD 3-Tesla, USA) at the Neuroscience Imaging Center in the Beijing Tiantan Hospital. The parameters were as follow: repetition time (TR) = 2 s, echo time (TE) = 10 ms, inversion time = 860 ms, number of excitations (NEX) = 2, flip angle = 90°, matrix = 512 × 512, pixel size = 0.47 × 0.47 mm<sup>2</sup>, slice thickness = 6 mm, no slice gap, number of slices = 23. All scans were inspected by an neuroradiologist.

#### *Data collection (Supplementary Datas 1 and 2)*

The following data were collected on the patients and controls: (1) Demographic data: age and gender; (2) Conventional vascular risk factors: hypertension, diabetes and smoking history; (3) Hematology indexes: serum levels of TP, ALB and serum levels of TC, TG, HDL-C, LDL-C; (4) Body mass index (BMI): BMI = weight/height<sup>2</sup>.

#### *Statistical analysis*

The data were processed using SPSS 11.5 statistical software. The continuous variables were statistically analyzed using independent samples *t* test or paired *t* test to compare the difference between PSP and control group, and the count variables used chi square test. The multivariate logistic regression analysis was used to determine the correlation between PSP and serum cholesterol or protein levels. Significant level was  $P < 0.05$ .

### Results

This research was a retrospective analysis of 57 possible PSP patients, which included 46

## Neurodegenerative diseases

**Table 1.** Baseline data and statistical analysis result between the two groups

Variables	PSP group (n = 57)	Control group (n = 89)	P
Age: years	67.58 ± 8.84	66.71 ± 7.59	0.527
Gender: Male (%)	46 (80.7)	65 (73.0)	0.326
TP (mean ± SD, mmol/L)	64.58 ± 6.62	74.18 ± 5.34	< 0.001
ALB (mean ± SD, mmol/L)	39.84 ± 7.82	45.10 ± 3.67	< 0.001
TG (mean ± SD, mmol/L)	1.32 ± 0.75	1.62 ± 1.05	0.066
TC (mean ± SD, mmol/L)	4.20 ± 0.92	5.12 ± 0.88	< 0.001
HDL-C (mean ± SD, mmol/L)	1.17 ± 0.28	1.33 ± 0.29	0.001
LDL-C (mean ± SD, mmol/L)	2.51 ± 0.71	3.28 ± 0.80	< 0.001
BMI (mean ± SD)	24.78 ± 2.93	24.41 ± 3.24	0.496
Hypertension: n (%)	28 (49.1)	53 (59.6)	0.236
Diabetes: n (%)	8 (14.0)	9 (10.1)	0.598
Smoking: n (%)	20 (35.1)	40 (44.9)	0.301

All data from the first hospitalization.

**Table 2.** The association analysis results between the serum cholesterol and protein levels and PSP in the multivariate logistic regression model after correcting age, gender, HT, DM, smoking and BMI

Variables	Regression Coefficient	Corrected OR	95% CI	P
TP	-0.242	0.785	0.714-0.863	< 0.001
TC	-0.832	0.435	0.232-0.815	0.009

All data from the first hospitalization.

**Table 3.** Comparison of serum proteins and cholesterol levels of PSP patients in different stages (time interval of two measurement, median duration (four quartile) 1.5 (1.0, 2.0) years)

Variables	PSP1 (n = 12)	PSP2 (n = 12)	P
TP	67.87 ± 5.23	61.87 ± 3.45	0.015
ALB	41.29 ± 4.08	38.03 ± 1.47	0.04
TC	4.42 ± 0.82	3.65 ± 0.61	0.006
HDL	1.39 ± 0.23	1.17 ± 0.31	0.022
LDL	2.56 ± 0.67	2.09 ± 0.55	0.008

males and 11 females, the age was 67.58 ± 8.84 years old. The median disease duration (four quartile) was 3 (1.75, 4) years, ranging from 1 year to 11 years. Total 89 control subjects were selected, male 65 cases, female 24 cases, the average age was 66.71 ± 7.59 years old. The statistical analysis result between the two groups was shown in **Table 1**, the two groups were matched by age and sex (P > 0.05). Major vascular risk factors (hypertension, dia-

betes and smoking) also had no significant difference (P > 0.05 for all). However, the serum TP and ALB levels of PSP group were significantly lower than the control group (P < 0.01 for both). In blood lipid profile, serum TG level had no significant difference (P > 0.05) in two groups; serum cholesterol levels (TC, HDL-C and LDL-C) were significantly lower than the control group (P < 0.01 for all).

In order to further determine the independent risk factors of PSP, the multivariate logistic regression analysis was carried out for the variables of **Table 1**. The results showed that the lower levels of serum TP and TC were independently associated with the PSP (OR value 0.785 for TP, P < 0.001; OR value 0.435 for TC, P = 0.009), after correcting age, gender, HT, DM, smoking and BMI (**Table 2**). In order to explore to the influence of sub-variables in serum protein profile to PSP, TP removed and ALB moved into in the regression model, the result showed that the lower level of ALB was also associated with PSP (OR value 0.851 for ALB, P = 0.001). Using the same method, in the lipid profile, TC removed and TG, HDL-C and LDL-C moved into the model, the result displayed that the lower levels of HDL-C and LDL-C were associated with PSP (OR value 0.129 for HDL-C, P = 0.026; OR value 0.416 for LDL-C, P = 0.020).

In the 57 cases of PSP patients, 12 patients have been in hospital two or more times. The first and the last hospitalization data of these 12 patients were further analyzed to explore the correlation between the course of diseases and the level of serum cholesterol or protein. PSP1 stand for first hospitalization data, the median duration (four quartile) was 2.5 (1.25, 3.75) years; PSP2 stand for the last hospitalization data, the median duration (four quartile) was 3.75 (3, 7.5) years. As shown in (**Table 3**), compared with PSP1 group, the serum levels of TP, ALB, TC, HDL and LDL in the PSP2 group

further reduced, and these differences were significant (see **Table 3**).

### Discussion

PSP is a rare chronic progressive neurodegenerative disease, which is characterized clinically by the presence of symmetrical akinetic-rigid parkinsonian syndrome, vertical supranuclear palsy, postural instability with falls, pyramidal symptoms and cognitive changes. PSP belongs to the family of tauopathies like Alzheimer's disease (AD), Pick's disease, corticobasal degeneration (CBD), and frontotemporal dementias [12]. But, the clinical character of PSP is more similar to PD. Compared with PD, the incidence of PSP is low [13]. Many aspects of PSP, such as the prevalence, neuropathology, brain structure and function, have been studied [1]. But the nutrition factors, such as serum cholesterol and protein, have not been reported on PSP yet. In other hand, it has been reported that the serum cholesterol and protein might be associated with AD and PD [3]. So, the relationship between serum protein and cholesterol levels and PSP should be explored.

For the relationship between serum protein levels and PSP, our study found that serum levels of TP or ALB were significantly lower in PSP patients compared with the control group. After adjusting for age, sex, common vascular risk factors and serum TC, Logistics regression analysis showed that low level of serum TP or ALB were the independent risk factor for the PSP. And with the illness duration extended, the levels of serum TP and ALB further decreased ( $P < 0.05$ ) in 12 PSP patients. This result suggested the low levels of TP or ALB were associated with PSP. Up to now, we have not found any report on the relationship between serum protein levels and PSP, and also not found any report on the relationship between serum protein levels and PD.

For the relationship between serum cholesterol levels and PSP, our study found that serum TC, HDL-C and LDL-C levels of PSP were lower than the control group, which was similar with PD research [10, 14]. Logistics regression analysis supported that low levels of TC, HDL-C and LDL-C were independent risk factors for the PSP. With the illness duration extended, the levels of TC, HDL-C and LDL-C were further reduced. This result implied that low levels of cholesterol not only might be a risk factor of

PSP, but also related to the progression of PSP. Though the results on the serum cholesterol and protein of PSP have not been found, the results of PD have been reported in many studies. Recent studies in China have shown that TC, HDL-C and LDL-C in PD group are significantly lower than the control group, and throughout the different stages of the disease [15, 16].

Our results suggest that the nutrition aspects, serum protein and cholesterol might be associated with PSP, and the low levels of serum protein and cholesterol may be the risk factors of the PSP and may aggravate the disease. It should be pay attention to nutritional problems to avoid the development and progression of PSP. In addition, our results might provide a prevention target for PSP. In the future, study with large sample size or cohort study should be carried out to clarify the effect of serum protein and cholesterol levels on PSP.

### Acknowledgements

This study was sponsored by grants from National Natural Science Foundation of China, Grant No. 81571226 and No. 11475020; 2014 Beijing Natural Science Foundation - Beijing Institute of Science and Technology jointly funded projects L140006; the biological marker study of alpha - the synaptic core protein in lip gland at the early stage Parkinson's disease.

### Disclosure of conflict of interest

None.

**Address correspondence to:** Tau Feng, Department of Neurology, Center for Neurodegenerative Diseases, Beijing Tiantan Hospital, Capital Medical University, Beijing 100050, China. E-mail: happyft@sina.com; Qing Huo, Department of Biomedical, Biochemical Engineering College of Beijing Union University, Fatouxili 3 region 18#, Chaoyang District, Beijing 100023, China. Tel: +86 010 52072259; E-mail: huo\_q2002@aliyun.com

### References

- [1] Colosimo C, Bak TH, Bologna M and Berardelli A. Fifty years of progressive supranuclear palsy. *J Neurol Neurosurg Psychiatry* 2014; 85: 938-944.
- [2] Dauncey MJ. Recent advances in nutrition, genes and brain health. *Proc Nutr Soc* 2012; 71: 581-591.

## Neurodegenerative diseases

- [3] Campdelacreu J. Parkinson's disease and Alzheimer disease: environmental risk factors. *Neurología* 2014; 29: 541-549.
- [4] Tanner CM, Ottman R, Goldman SM, Ellenberg J, Chan P, Mayeux R and Langston JW. Parkinson disease in twins: an etiologic study. *JAMA* 1999; 281: 341-346.
- [5] Hu G, Antikainen R, Jousilahti P, Kivipelto M and Tuomilehto J. Total cholesterol and the risk of Parkinson disease. *Neurology* 2008; 70: 1972-1979.
- [6] Hu G. Total cholesterol and the risk of Parkinson's disease: a review for some new findings. *Parkinsons Dis* 2010; 2010: 836962.
- [7] Gudala K, Bansal D and Muthyala H. Role of Serum Cholesterol in Parkinson's Disease: A Meta-Analysis of Evidence. *J Parkinsons Dis* 2013; 3: 363-370.
- [8] Simon KC, Chen H, Schwarzschild M and Ascherio A. Hypertension, hypercholesterolemia, diabetes, and risk of Parkinson disease. *Neurology* 2007; 69: 1688-1695.
- [9] Scigliano G, Musicco M, Soliveri P, Piccolo I, Ronchetti G and Girotti F. Reduced risk factors for vascular disorders in Parkinson disease patients - A case-control study. *Stroke* 2006; 37: 1184-1188.
- [10] de Lau LM, Koudstaal PJ, Hofman A, Breteler MM. Serum cholesterol levels and the risk of Parkinson's disease. *Am J Epidemiol* 2006; 164: 998-1002.
- [11] Litvan I, Agid Y, Calne D, Campbell G, Dubois B, Duvoisin RC, Goetz CG, Golbe LI, Grafman J, Growdon JH, Hallett M, Jankovic J, Quinn NP, Tolosa E, Zee DS, Chase TN, FitzGibbon EJ, Hall Z, Juncos J, Nelson KB, Oliver E, Pramstaller P, Reich SG and Verny M. Clinical research criteria for the diagnosis of progressive supranuclear palsy (Steele-Richardson-Olszewski syndrome): Report of the NINDS-SPSP International Workshop. *Neurology* 1996; 47: 1-9.
- [12] Rampello L, Butta V, Raffaele R, Vecchio I, Battaglia G, Cormaci G and Alvano A. Progressive supranuclear palsy: A systematic review. *Neurobiol Dis* 2005; 20: 179-186.
- [13] Linder J, Stenlund H and Forsgren L. Incidence of Parkinson's Disease and Parkinsonism in Northern Sweden: A Population-Based Study. *Movement Mov Disord* 2010; 25: 341-348.
- [14] Wei Q, Wang HH, Tian YH, Xu FC, Chen XW and Wang K. Reduced Serum Levels of Triglyceride, Very Low Density Lipoprotein Cholesterol and Apolipoprotein B in Parkinson's Disease Patients. *PLoS One* 2013; 8: e75743.
- [15] Yang X, Liu H and Ma Y. The study on relationship between blood fat and Parkinson's disease. *Med J West China (in Chinese)* 2014; 26: 725-727.
- [16] Liu WP and Liao K. Serum lipid metabolism condition and cognitive impairments in Parkinson's disease. *J Trop Med (in Chinese)* 2014; 14: 1166-1169.