Increased Serum Cystatin C in Early Parkinson's Disease with Objective Sleep Disturbances

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Abstract

Background: Sleep disturbance is one of the major non-motor symptoms which cause the disability of Parkinson's disease (PD) patients. Cystatin C (CysC) is a more sensitive biomarker than serum creatinine or estimated glomerular filtration rate. Previous studies have reported altered CysC levels in neurodegenerative disorders and sleep disorders. This study aimed to explore the correlations of serum CysC levels and objective sleep disturbances in early PD.

Methods: We recruited 106 early PD patients and 146 age- and sex-matched controls. All participants underwent clinical investigation and video-polysomnography. Sleep parameters and serum levels of CysC were measured. Then, we investigated the relationships between CysC and clinical variables and objective sleep disturbances in early PD patients.

Results: The mean serum level of CysC was significantly higher in patients with early PD (1.03 ± 0.19 mg/L) compared to controls (0.96 ± 0.15 mg/L, $P = 0.009$). There were significantly positive correlations between serum CysC levels and age ($r = 0.334$, $P < 0.001$), gender ($r = 0.264$, $P = 0.013$), and creatinine levels ($r = 0.302$, $P = 0.018$) in early PD patients. Increased serum CysC levels in early PD patients were significantly associated with higher apnea and hypopnea index (AHI) ($r = 0.231$, $P = 0.017$), especially hypopnea index ($r = 0.333$, $P < 0.001$). In early PD patients, elevated serum CysC levels were positively correlated with oxygen desaturation index ($r = 0.223$, $P = 0.021$), percentage of time spent at oxygen saturation (SaO_2) <90% ($r = 0.644$, $P < 0.001$), arousal with respiratory event during sleep ($r = 0.247$, $P = 0.013$). On the contrary, the elevated serum CysC levels were negatively correlated with mean and minimal SaO_2 ($r = -0.323$, -0.315, both $P = 0.001$) in PD patients.

Conclusions: The level of serum CysC was higher in early PD patients. PD patients with elevated serum CysC levels had more respiratory events and more severe oxygen desaturation. Therefore, the serum CysC levels may predict the severities of sleep-disordered breathing problems in early PD patients.

Key words: Cystatin C; Early Parkinson's Disease; Objective Sleep Disturbance

INTRODUCTION

Parkinson's disease (PD) is a common neurodegenerative disease which is identified by typical motor symptoms such as resting tremor, rigidity, bradykinesia, and postural instability.[1] It has been recognized recently that a variety of non-motor symptoms accompanied with PD such as sleep disorders, olfactory dysfunction, depression, autonomic changes, and dementia. Sleep disturbances, a major non-motor symptom of PD, particularly degrades PD patients' quality of life and even cause the disability of PD patients.[2]

Although the authentic pathophysiology of PD is still unknown, the pathogenesis of PD has been linked to several mechanisms, including inflammation, oxidative stress, mitochondrial dysfunction, abnormal protein aggregation, and hyperactivation of N-methyl-D-aspartic

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acid receptors.[3,4] Recent studies which focused on the mechanisms of neurodegenerative diseases have involved homocysteine, uric acid, cystatin C (CysC), and C-reactive protein.[5-7]

CysC, an inhibitor of cysteine proteases, belongs to the cystatin type 2 superfamily. As a biomarker of kidney dysfunction, it is more sensitive than serum creatinine or estimated glomerular filtration rate.[8] CysC shows a broad spectrum of biological activities in numerous cellular systems, including effects on growth promotion, inhibition of inflammation, and antimicrobial activity.[9] Even though previous studies have demonstrated that CysC has been got involved in neurodegenerative disease, its potential pathologic role is not completely understood and remains controversial. CysC induces autophagy *in vivo* as a protective mechanism in brain injury and in neurodegenerative disorders.[10] Enhanced CysC gene expression and higher CysC protein levels were also shown in dopaminergic-depleted rat striatum following a 6-hydroxydopamine (6-OHDA)-induced lesion in nigrostriatal neurons, astrocytes, and microglia cells.[11] Several studies have confirmed an association between CysC and sleep disorders especially obstructive sleep apnea (OSA).[12-14] In the study presented here, we compared CysC levels between early PD patients and healthy controls and explored the correlations between CysC levels and clinical variables in early PD patients. Moreover, we demonstrated the correlations between CysC and objective sleep disturbances in early PD patients. We seek to clarify whether CysC could predict objective sleep disturbances especially sleep-disordered breathing (SDB) problems in early PD patients.

METHODS

Ethical approval

This study was approved by the Ethics Committee of the Second Affiliated Hospital of Soochow University, and each participant provided written informed consent.

Participants

We recruited 106 early PD patients from the Department of Neurology, The Second Affiliated Hospital of Soochow University from July 2011 to May 2016. All the PD patients met the United Kingdom PD Brain Bank diagnosis criteria.[15] We had excluded individuals with atypical parkinsonism (e.g., multiple system atrophy or progressive supranuclear palsy), serious heart disease, renal disease, liver disease, hematologic system disorders, cancer, and infective or inflammatory disorders. During the same enrollment period, we assessed 146 age- and sex-matched controls that we screened from the medical healthy examination system of our hospital.

Clinical assessment and video-polysomnography

All PD patients underwent comprehensive clinical investigation including general characters, disease history, and comorbid diseases. The Hoehn and Yahr (H-Y) stage of all PD patients were lower than or equal

to 2.5.[16] Each PD patient was performed an overnight video-polysomnography (vPSG) (Compumedics-E series, Australia) in the sleep center. The basic recordings included electroencephalogram (F3A2, F4A1, C3A2, C4A1, O1A2, and O2A1), electrooculogram (LOCA2, and ROCA1), chin EMG, electrocardiogram, nasaloral pressure transducer airflow, thermal oronasal airflow, thoracic and abdominal respiratory efforts, oxyhemoglobin saturation, snoring sound, body position, and leg movement. Sleep architecture such as awakenings (n); total sleep time (TST)(min); sleep efficiency (SE)(%); sleep latency (SL)(min); percentage of time spent in non rapid eye movement sleep stage (NREM) 1(%), NREM2(%), NREM3(%), and rapid eye movement sleep stage (REM)(%), the index of periodic leg movements during sleep (PLMSI)(/h), and sleep apnea parameters including apnea hypopnea index (AHI)(/h), apnea index (AI), hypopnea index (HI)(/h), oxygen desaturation index (ODI)(/h), and minimal oxygen saturation (SaO_2)(%), the percentage of time spent at SaO_2 <90% (%), mean SaO_2(%), and arousal with respiratory events (ARO RES)(/h) during sleep were assessed. The scoring of vPSG was determined by experienced PSG technologists and clinicians, according to the American Academy of Sleep Medicine (AASM).[17,18]

Laboratory measurements

All patients and controls underwent routine laboratory tests in our clinical laboratory center after they fasted overnight. The blood samples were drawn from a peripheral vein and centrifuged for up to one hour. Serum levels of CysC were measured using an immunoturbidimetry assay (Cystatin C Kit, Shanghai Jingyuan Company, China). Concentrations of serum creatinine, urea, and uric acid were determined using an enzymatic assay and different diagnostic reagents (Kyowa Medex Company, Japan). All laboratory tests were performed with an AU5400 random access analyzer (Olympus Corporation, Japan).

Statistical analysis

SPSS software 17.0 (Chicago, IL, USA) was used for the statistical analysis. Continuous variables were expressed as mean ± standard deviation (SD). Categorical variables are expressed as frequency (percent). Comparisons of continuous variables between two groups were conducted using independent Student's *t*-test. Relationships between CysC and clinical variables and sleep parameters in PD patients were assessed by Pearson's correlations. Statistical significance was defined as $P < 0.05$.

RESULTS

Demographics and clinical characteristics

Demographic and clinical characteristics of individuals are presented in Table 1. Among the 106 early PD patients, 70 were male. For the PD group, the mean age was 65.5 ± 9.6 years, mean body mass index was 23.06 ± 3.28 kg/m², mean disease duration was 4.4 ± 3.2 years, and mean H-Y stage was 2.07 ± 0.36. We found OSA in 47 (44.9%) PD patients, with 25 (53.19%) demonstrating mild OSA (5< AHI ≤15),

12 (25.53%) demonstrating moderate OSA (15< AHI ≤30), and 10 (21.28%) demonstrating severe OSA (AHI >30).[19]

As shown in Table 1, the PD patients and controls were similar in age and gender, but the PD group had a slightly higher percentage of men which is consistent with the male predominance of PD.[20] The mean serum level of CysC was significantly higher in patients with early PD (1.03 ± 0.19 mg/L) compared to controls (0.96 ± 0.15 mg/L, $P = 0.009$), while the creatinine, urea, and uric acid levels were very approximate of two groups.

Relationships between cystatin C level and clinical variables

Correlation analysis between CysC and clinical variables in early PD patients was presented in Table 2. There were significant positive correlations between serum CysC levels and age ($r = 0.334$, $P < 0.001$), gender ($r = 0.264$, $P = 0.013$), and creatinine levels ($r = 0.302$, $P = 0.018$) in early PD patients. No correlation was observed between CysC levels and urea ($r = 0.224$, $P = 0.083$) or uric acid ($r = 0.000$, $P = 0.998$) in PD cohort.

Relationships between cystatin C level and objective sleep disturbances

The objective sleep parameters of this early PD cohort were similar to our studies before[21,22] as TST was 352.6 ± 108.3 min, SE was 60.9% ± 18.3%, SL was 30.6 ± 52.0 min, awakenings (n) was 20.5 ± 9.4, NREM1 was 29.6% ± 18.5%, NREM2 was 42.9% ± 16.0%, NREM3 was 13.1% ± 11.6%, REM was 14.4% ± 9.1%, PLMSI was 31.5 ± 50.1/h, AHI was 9.2 ± 13.5/h, AI was 6.2 ± 11.1/h, HI was 3.0 ± 5.4/h, ODI was 8.6 ± 12.5/h, minimal SaO_2 (%) was 89.3% ± 3.9%, the percentage of time spent at SaO_2 <90% (%) was 1.7% ± 4.2%, and arousal with respiratory events during sleep was 2.5 ± 6.3/h.

The relationships between CysC level and objective sleep parameters were displayed in Table 3. Increased serum CysC levels in early PD patients were significantly associated with higher AHI ($r = 0.231$, $P = 0.017$) especially HI ($r = 0.333$, $P < 0.001$). Therefore, elevated serum CysC levels were positively correlated with ODI ($r = 0.223$, $P = 0.021$), percentage of time spent at SaO_2 <90% ($r = 0.644$, $P < 0.001$), arousal with respiratory event during sleep ($r = 0.247$, $P = 0.013$). On the contrary, the elevated serum CysC levels were negatively correlated with mean and minimal SaO_2 ($r = -0.323$, -0.315, both $P = 0.001$). There were no significant relationships among serum CysC levels and sleep architecture parameters including TST, SL, SE, awakenings, percentage of NREM1, percentage of NREM2, percentage of NREM3, percentage of REM, and PLMSI ($r = 0.047$, 0.060, -0.066, 0.149, 0.138, -0.157, -0.063, 0.077, 0.016, all $P > 0.05$).

DISCUSSION

This study was to investigate the relationships between CysC and objective sleep disturbances in early PD patients. We

Table 1: Comparison between CysC and clinical variables in PD patients and controls

Characteristics	PD	Control	P
Number of subjects	106	146	
Demographics			
Age (years)	65.5 ± 9.6	65.7 ± 8.4	0.964
Male gender	70 (66.0)	84 (57.5)	0.204
CysC (mg/L)	1.03 ± 0.19	0.96 ± 0.15	0.009*
Creatinine (μmol/L)	64.5 ± 11.5	65.5 ± 12.3	0.591
Urea (mmol/L)	5.3 ± 1.5	5.4 ± 1.4	0.594
Uric acid (μmol/L)	291.5 ± 64.9	303.5 ± 75.7	0.277

Continuous variables are expressed as mean ± SD. Categorical variables are expressed as n (%). $P<0.05$ was considered statistically significant. *$P<0.05$. SD: Standard deviation; CysC: Cystatin C; PD: Parkinson's disease.

Table 2: Correlation analysis between CysC and clinical variables in PD patients

Variables	r	P
Age	0.334	<0.001†
Gender	0.264	0.013*
BMI	0.139	0.161
Creatinine	0.302	0.018*
Urea	0.224	0.083
Uric acid	0.000	0.998

$P<0.05$ was considered statistically significant. *$P<0.05$; †$P<0.01$. BMI: Body mass index.

Table 3: Correlation analysis between CysC and sleep parameters in PD patients

Variables	r	P
TST (min)	0.047	0.634
SL (min)	0.060	0.539
SE (%)	−0.066	0.498
Awakenings (n)	0.149	0.125
NREM1 (%)	0.138	0.155
NREM2 (%)	−0.157	0.107
NREM3 (%)	−0.063	0.519
REM (%)	0.077	0.429
PLMSI (/h)	0.016	0.878
AHI (/h)	0.231	0.017*
AI (/h)	0.102	0.295
HI (/h)	0.333	<0.001†
ODI (/h)	0.223	0.021*
Mean SaO_2 (%)	−0.323	0.001†
Minimal SaO_2 (%)	−0.315	0.001†
Percentage of time spent at SaO_2 <90% (%)	0.644	<0.001†
ARO RES (/h)	0.247	0.013*

$P<0.05$ was considered statistically significant. *$P<0.05$; †$P<0.01$. TST: Total sleep time; SE: Sleep efficiency; SL: Sleep latency; NREM: Non rapid eye movement sleep stage; REM: Rapid eye movement sleep stage; PLMSI: Index of periodic leg movements during sleep; AHI: Apnea hypopnea index; AI: Apnea index; HI: Hypopnea index; ODI: Oxygen desaturation index; ARO RES: Arousal with respiratory events during sleep; SaO_2: Oxygen saturation.

found that patients with early PD had higher serum CysC levels than healthy controls. We found significant positive

correlations between CysC level and age, sex, and creatinine level in early PD patients. More importantly, elevated serum CysC levels in early PD patients were found in correlation with the severity of sleep apnea, hypopnea, and oxygen desaturation. These findings suggest that serum CysC level could predict the situation of OSA in early PD patients.

There were rare studies about the correlation of CysC and PD. In our previous study, Hu *et al*.[23] identified the elevated CysC levels and their positive correlations with age, sex, and creatinine in PD patients, which were consistent with our results. On the other hand, it demonstrated that the PD patients with higher CysC levels had lower scores on cognitive tests while we identified that increased CysC had a significant correlation with objective sleep disturbances especially OSA characters. Therefore, CysC may predict cognitive dysfunction and SDB in patients with PD. In addition, it showed PD patients with middle- and late-stage disease had significantly higher CysC levels than those in the early stage and CysC level correlated significantly with H-Y stage and with disease duration.[23] Since all the PD patients we enrolled in this cohort were at early stages with H-Y stage less than or equal to 2.5, we did not repeat the analysis of the relationship between serum CysC level and H-Y stage. The recruitment strategy of this study would be more critical for biomarker research in early PD patients even though we did not comprehensively enroll PD participants with all H-Y stages.

CysC, a 13-kD protein and a member of a family of competitive inhibitors of lysosomal cysteine protease, was originally identified in human cerebrospinal fluid and was later found to be expressed in most mammalian tissues as well as in blood.[24] CysC has an excellent ability to detect clinically latent chronic kidney disease (CKD) and to reflect cardiovascular diseases mortality.[25] Enhanced CysC expression in neurodegeneration diseases caused a debate as to whether CysC up-regulation facilitates neurodegeneration or it is an endogenous neuroprotective attempt to prevent the progression of the pathology. Nagai *et al*.[26] reported that direct injection of CysC caused the death of rat hippocampal neurons and that CysC released from toxin-injured rat dopaminergic neurons induced microglial activation and exacerbated neurotoxicity. However, recent *in vitro* and *in vivo* data have demonstrated that CysC played protective roles via pathways that were dependent on inhibition of cysteine proteases, such as cathepsin B, or by induction of autophagy, induction of proliferation, and inhibition of amyloid-beta aggregation.[9] For instance, Xu *et al*.[11] reported that loss of dopaminergic neurons in cultures of rat fetal mesencephalic cells exposed to 6-OHDA could be partially reversed by treatment with human CysC. This result suggested that the neuroprotective effect of CysC in PD might result from the regrowth of dopaminergic neurons.

OSA is a common condition characterized by repetitive obstruction episodes of the upper airway during sleep, resulting in oxygen desaturation and arousal from sleep. The associations are believed to be in part based on adverse effects of intermittent hypoxia[27] and sympathetic nervous system activity on oxidative stress, insulin resistance, and endothelial dysfunction.[28] Epidemiological studies suggested that OSA is not an uncommon disorder in PD as well.[29,30] Previous studies reported a frequency of OSA between 20% and 66% in PD.[19] Kato *et al*.[12] performed a cross-sectional study with 267 consecutive OSA patients without CKD who had an AHI ≥5 events per hour and demonstrated CysC was significantly correlated with AHI ($r = 0.17$), severe OSA defined by an AHI ≥30 events per hour was an independent variable for the highest quartiles of serum CysC levels (≥0.88 mg/L), indicated that severe OSA independently increases serum CysC levels in patients without CKD. Zhang *et al*.[13] detected that serum CysC levels were associated with the severity of OSA in younger men without comorbidities.

Strengths of our study include its enrollment of early PD patients with H-Y stage lower than or equal to 2.5, a relatively precise cohort in comparison with prior investigations, comprehensive measures of objective sleep disturbances, and concurrent identification of OSA using vPSG and AASM scoring manual. Nevertheless, our study has several limitations. The sample size was not sufficient, and all participants were recruited from a single center. This was a retrospective study, precluding any conclusions regarding causality. Furthermore, the challenge of identifying true associations between CysC and sleep disturbances in the early PD patients related to multiple comorbidities that may confound or modify hypothesized associations.

In conclusion, the level of serum CysC was higher in early PD patients than in controls. PD patients with elevated serum CysC levels had more respiratory events and more severe oxygen desaturation. Therefore, the serum CysC levels may predict the severities of SDB problems in early PD patients. Further studies which should be performed in multicenter with prospective and mechanic design are needed to clarify the predictive value of CysC in early PD and understand the pathologic mechanisms of altered CysC in early PD patients with SDB problems.

Conflicts of interest
There are no conflicts of interest.

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血清胱抑素C水平与早期帕金森病客观睡眠障碍的关系

摘要

背景： 帕金森病（PD）是常见的神经系统变性疾病，睡眠障碍是其主要的非运动症状之一，可导致PD患者的日常生活功能障碍。血清胱抑素C（Cys C）是一种半胱氨酸蛋白酶抑制剂，与血清肌酐或肾小球滤过率相比，对监测肾功能受损更灵敏。有研究报告Cys C水平的变化与许多神经系统疾病有关，此外亦有研究发现失眠、不宁腿综合征患者的Cys C水平较正常对照出现变化。我们的研究探讨PD患者Cys C水平的变化及其与客观睡眠障碍之间的关系。

方法： 连续纳入在苏州大学附属第二医院神经内科就诊的早期PD患者106例，选取年龄性别匹配的健康中老年人146名作为对照组。所有研究对象进行一般情况、运动功能（PD患者）、生物化学指标、多导睡眠监测及睡眠参数分析采集，胱抑素等血清指标采用生化分析仪进行分析，采用SPSS17.0软件分析PD组CysC水平的变化及其与临床参数和客观睡眠障碍指标之间的关系。

结果： PD组CysC平均水平（1.03 ± 0.19 mg/l）较健康对照组（0.96 ± 0.15 mg/l）显著升高（p =0.009）。斯皮尔曼相关分析提示PD组的CysC水平与年龄（r = 0.334，p <0.001）、性别（r = 0.264，p =0.013）、肌酐（r = 0.302，p =0.018）存在相关性。 PD患者CysC水平与睡眠呼吸暂停低通气指数（AHI）（r = 0.231，p =0.017）、低通气指数（HI）（r = 0.333，p <0.001）、氧减指数（ODI）（r = 0.223，p =0.021）、血氧饱和度<90%的比例（r = 0.644，p <0.001）、呼吸相关微觉醒指数（r = 0.247，p =0.013）均存在显著正相关。而与整夜平均血氧饱和度和最低血氧饱和度均呈显著负相关（r = -0.323，-0.315，both p =0.001）。

结论： 早期PD患者CysC水平升高，且CysC水平越高，PD患者的睡眠呼吸事件及缺氧情况越严重。CysC可能作为一个潜在的生物标记物用以评价早期PD患者的睡眠呼吸障碍。