Journal of the Neurological Sciences 362 (2016) 258–262

Contents lists available at ScienceDirect

Journal of the Neurological Sciences

journal homepage: www.elsevier.com/locate/jns

Association between urine protein/creatinine ratio and cognitive dysfunction in Lewy body disorders

Yoon-Sang Oh [a], Joong-Seok Kim [a,*], Hyung-Eun Park [a], In-Uk Song [a], Jeong-Wook Park [a], Dong-Won Yang [a], Byung-chul Son [b], Si-Hoon Lee [a], Kwang-Soo Lee [a]

[a] Department of Neurology, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea
[b] Department of Neurosurgery, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea

ARTICLE INFO

Article history:
Received 26 July 2015
Received in revised form 27 January 2016
Accepted 28 January 2016
Available online 29 January 2016

Keywords:
Proteinuria
Dementia
Cognitive dysfunction
Lewy body disorders

ABSTRACT

Background: Impaired renal function and proteinuria have been associated with cognitive impairment and dementia. Chronic kidney disease is considered to be an independent risk factor for Lewy body spectrum disorders (LBD). However, few studies have mentioned an association between proteinuria and cognition in LBD. We investigated the relationship between proteinuria and cognitive dysfunction in patients with Parkinson's disease (PD) and dementia with Lewy bodies (DLB).
Methods: Among 186 patients with LBD, 53 had PD-normal cognition (PD-NC), 76 had PD-mild cognitive impairment (PD-MCI), 43 had PD-dementia (PDD) and 14 had DLB. The urine protein/creatinine ratio was calculated using the spot urine test and brain magnetic resonance scans was obtained in all patients.
Results: The urine protein/creatinine ratio was significantly higher in patients with PDD and DLB than in those with PD-MCI, PD-NC patients and healthy controls, and was correlated with white matter hyperintensities on magnetic resonance imaging. All abnormal neuropsychological test results were associated with increased urine protein/creatinine ratio. After controlling for age, education, symptom duration, diabetes mellitus, hypertension, and parkinsonian motor severity, the urine protein/creatinine ratio was significantly associated with decreased cognition.
Conclusion: The urine protein/creatinine ratio was associated with cognitive status in LBD. These finding suggests that increased protein excretion is associated with cognitive dysfunction in patients with LBD.

1. Introduction

Urinary protein is a strong marker of impaired renal function and kidney damage [1]. Proteinuria is an independent risk factor of renal disease and cardiovascular disease and is regarded as a predictor of end organ damage [2,3]. Reduced renal function and increased proteinuria are also independent risk factors of stroke [4]. Proteinuria is associated with increased hospitalization and death [5].

The relationship between kidney disease and cognitive function has been widely investigated [6–8]. Decreased glomerular filtration rate was related to cognitive impairment in community-based subjects [6]. A declining glomerular filtration rate and an increased serum creatinine were related to incident Alzheimer's dementia or vascular dementia [6]. Decreased glomerular filtration rate or increased serum creatinine reflect an impaired renal function and are predictors of renal disease. Decreased renal function was directly associated with rapid cognitive decline, and the rate of decline in renal function was also related to global cognitive decline and incident dementia [9,10].

Albuminuria was associated with dementia in a community-based study, and the odds of dementia were increased in the presence of albuminuria [11,12]. In healthy elderly individuals, albuminuria was associated with worse cognitive performance and decreased executive functions [13]. Mid-life proteinuria was also linked to late-life cognitive dysfunction and dementia in elderly Asian men [14].

Impaired renal function and chronic renal disease might be related to the incidence of Parkinsonism [15,16], although the mechanisms that lead to Parkinsonism in patients with uremia are not well understood. Uremia might induce metabolic derangements in the basal ganglia, and inadequate dialysis has been associated with basal ganglia injury [17]. Several studies have observed movement disorders in patients with chronic renal failure, who are particularly susceptible to aluminum and manganese toxicity [18,19].

This raises the question of whether impaired renal function, which is reflected as increased protein/creatinine ratio, relates to cognitive dysfunction in Lewy body spectrum disorders (LBD). We assessed whether cognitive status or white matter hyperintensities upon magnetic resonance imaging (MRI) were related to proteinuria in LBD.

* Corresponding author at: Department of Neurology, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, 222, Banpo-daero, Seocho-gu, Seoul 06591, Republic of Korea.
E-mail address: neuronet@catholic.ac.kr (J.-S. Kim).

http://dx.doi.org/10.1016/j.jns.2016.01.061
0022-510X/

2. Methods

2.1. Patients

This study was approved by the ethics committee of Seoul St. Mary's Hospital, and a waiver of consent was obtained for this Health Insurance Portability and Accountability Act-compliant retrospective study.

Consecutive patients newly diagnosed with Parkinson's disease (PD) and dementia with Lewy bodies (DLB) who visited the movement disorder clinic of Seoul St. Mary's hospital and Yeouido St. Mary's Hospital in Seoul, Korea, between March 2013 and December 2014 were enrolled. The diagnosis was made at follow-up visit 6–18 months after initial tentative diagnosis according to the clinical diagnostic criteria for PD and DLB [20,21]. Twenty elderly subjects without any neurological or psychiatric history were included as controls (68.1 ± 5.0 years).

Clinical information was obtained including age, sex, disease duration, history of hypertension, diabetes mellitus, smoking status, and current medications. Data from complete physical and neurological examinations, and laboratory tests were also obtained. Patients with (1) a history of stroke or other neurological or psychiatric disorders, (2) other atypical PD or secondary Parkinsonism, (3) secondary causes of dementia, or (4) cardiovascular, kidney, or peripheral artery disease were excluded. None of the patients had ever taken anti-parkinsonian or anti-dementia medications. No patients had ever taken antipsychotics, antidepressants, or anxiolytics prior to the evaluation of cognitive status.

All patients were evaluated using the Unified Parkinson's Disease Rating Scale (UPDRS) part I–III and were classified according to modified Hoehn and Yahr stage.

Random spot urine was sampled for all patients. An automatic analyzer (7600-210; Hitachi Medical Corp., Tokyo, Japan) was used to measure urine protein and creatinine.

2.2. Cognitive evaluations

Information about memory problems and other subjective cognitive deficits was obtained from caregiver interviews. General cognitive status and dementia severity were evaluated using the Korean version of the Mini-Mental State Examination, Clinical Dementia Rating (CDR) scale, and the sum of box (SOB) of the CDR scale.

To assess cognitive domains, we used the Seoul Neuropsychological Screening Battery [22], which includes attention, language, praxis, four elements of Gerstmann syndrome, visuospatial function, verbal and visual memory, and frontal/executive functions. Quantifiable indices were digit span forward and backward, the Korean version of the Boston Naming Test, the Rey–Osterrieth Complex Figure Copy Test, the Seoul Verbal Learning Test for verbal memory, the Rey–Osterrieth Complex Figure Test for nonverbal and visuospatial memory, the Controlled Oral Word Association Test (semantic: animals, grocery items, and phonemic: Korean letters) for word fluency, and the Stroop color/word conflict test. Frontal motor functions were assessed based on motor impersistence, contrasting programs, the go–no go test, and fist–edge–palm, alternating squares and triangles, and Luria loop tests. Test scores were classified as abnormal when they were <16% of those of age-, sex-, and education-matched normal subjects [22]. Mild cognitive impairment (MCI) was diagnosed if at least 1 of 5 cognitive domains was abnormal [23]. PD-dementia (PDD) was diagnosed based on the Movement Disorder Society consensus criteria for dementia associated with PD [24] and DLB was diagnosed according to the revised consensus criteria for DLB [21].

2.3. MRI and cholinergic pathways hyperintensities scale (CHIPS)

All patients underwent 3.0-Tesla MRI (Magnetom Verio, 3 T, Siemens). White matter hyperintensities were quantified on axial sections of fluid-attenuated inversion recovery sequence images using the recently developed visual rating scale CHIPS [25–27], which quantifies the extent of white matter hyperintensities in the periventricular and subcortical white matter.

2.4. Data analysis

Statistical analysis was performed with SPSS software version 15.0 (SPSS Inc., Chicago, IL). One-way analyses of variance (ANOVAs) or analyses of covariance (ANCOVAs) (with Bonferroni post-hoc testing) were used to compare groups, and Pearson's χ^2 tests were used to compare frequencies for categorical variables. The relationships between urine protein/creatinine ratio and cognitive variables and CHIPS scores were tested using the Spearman rank correlation coefficients. Linear regression analyses were performed with the MMSE, CDR, and SOB of CDR as the dependent variables and age, sex, education, symptom duration, hypertension, diabetes mellitus, current or former smoking, UPDRS part III, and urine protein/creatinine ratio as covariates. A p-value <0.05 was considered significant.

3. Results

Of the 186 LBD patients, 14 (7.5%) was DLB, 43 (23.1%) was PDD, 76 (40.9%) was PD-MCI, and 53 (28.5%) had PD-normal cognition (PD-NC). The mean age was higher in the PDD and DLB groups than in the PD-MCI

Table 1
Demographics, clinical characteristics, and general cognitive functions of patients with Lewy body spectrum disorders.

	PD-NC (n = 53)	PD-MCI (n = 76)	PDD (n = 43)	DLB (n = 14)	P-value	Post-hoc tests
Age (years)*	62.5 ± 9.4	68.8 ± 6.6	76.3 ± 6.8	77.6 ± 5.1	<0.001	PDD = DLB > PD-MCI > PD-NC
Sex, male (%)	27 (50.9%)	32 (42.1%)	8 (18.6%)	6 (42.9%)	0.011	
Education (years)*	10.9 ± 4.6	9.3 ± 5.2	5.3 ± 5.8	7.4 ± 5.6	<0.001	PDD < PD-MCI = PD-NC, PDD = DLB
Disease duration (years)*	1.9 ± 1.8	1.7 ± 1.6	2.4 ± 0.7	1.2 ± 0.7	0.025	
Hypertension (%)	19 (35.8%)	33 (43.4%)	19 (44.2%)	19 (44.2%)	0.625	
Diabetes mellitus (%)	6 (9.4%)	13 (17.1%)	11 (25.6%)	5 (35.7%)	0.775	
Current or ex-smoker (%)	21 (39.6%)	19 (25.0%)	4 (9.3%)	2 (14.3%)	0.005	
UPDRS score*	19.6 ± 17.9	21.2 ± 11.7	44.9 ± 19.3	34.0 ± 21.4	<0.001	PDD > PD-MCI = PD-NC, PDD = DLB
Hoehn and Yahr stage*	1.5 ± 0.7	1.7 ± 0.6	2.4 ± 0.7	2.3 ± 1.3	<0.001	PDD = DLB > PD-MCI = PD-NC
General cognitive function						
K-MMSE**	27.9 ± 2.3	25.3 ± 3.8	16.4 ± 6.6	18.8 ± 7.0	<0.001	PDD = DLB < PD-MCI = PD-NC
CDR**	0.2 ± 0.3	0.5 ± 0.2	1.1 ± 0.7	1.3 ± 0.9	<0.001	PDD = DLB > PD-MCI = PD-NC
Sum of Box of CDR**	0.5 ± 0.6	1.2 ± 1.0	5.7 ± 4.0	5.8 ± 3.9	<0.001	PDD = DLB > PD-MCI = PD-NC
CHIPS score**	13.2 ± 9.6	20.3 ± 14.9	31.7 ± 15.3	32.4 ± 15.0	<0.001	PDD = DLB > PD-MCI > PD-NC

The data represent the mean ± standard deviation or number of patients (percentage).
Abbreviations: UPDRS, Unified Parkinson's Disease Rating Scale; K-MMSE, Korean version of the Mini-Mental State Examination; CDR, Clinical Dementia Rating; CHIPS, Cholinergic pathways hyperintensities scale; PD-NC, Parkinson's disease normal cognition; PD-NC, Parkinson's disease normal cognition; PD-MCI, Parkinson's disease mild cognitive impairment; PDD, Parkinson's disease dementia; DLB, dementia with Lewy bodies.
Analyses were carried out using the χ^2-test or *one-way analysis of variance and **analysis of covariance with Bonferroni post-hoc tests.