JCN Open Access ORIGINAL ARTICLE

pISSN 1738-6586 / eISSN 2005-5013 / J Clin Neurol 2023;19(4):344-357 / https://doi.org/10.3988/jcn.2022.0186

Risk of Cognitive Impairment in Patients With Parkinson's Disease With Visual Hallucinations and Subjective Cognitive Complaints

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Received May 7, 2022 **Revised** August 31, 2022 **Accepted** September 1, 2022

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Background and Purpose Visual hallucinations (VH) and subjective cognitive complaints (SCC) are associated with cognitive impairment (CI) in Parkinson's disease. Our aims were to determine the association between VH and SCC and the risk of CI development in a cohort of patients with Parkinson's disease and normal cognition (PD-NC).

Methods Patients with PD-NC (total score of >80 on the Parkinson's Disease Cognitive Rating Scale [PD-CRS]) recruited from the Spanish COPPADIS cohort from January 2016 to November 2017 were followed up after 2 years. Subjects with a score of ≥1 on domain 5 and item 13 of the Non-Motor Symptoms Scale at baseline (V0) were considered as "with SCC" and "with VH," respectively. CI at the 2-year follow-up (plus or minus 1 month) (V2) was defined as a PD-CRS total score of <81.

Results At V0 (n=376, 58.2% males, age 61.14±8.73 years [mean±SD]), the frequencies of VH and SCC were 13.6% and 62.2%, respectively. VH were more frequent in patients with SCC than in those without: 18.8% (44/234) vs 4.9% (7/142), p<0.0001. At V2, 15.2% (57/376) of the patients had developed CI. VH presenting at V0 was associated with a higher risk of CI at V2 (odds ratio [OR]=2.68, 95% confidence interval=1.05–6.83, p=0.039) after controlling for the effects of age, disease duration, education, medication, motor and nonmotor status, mood, and PD-CRS total score at V0. Although SCC were not associated with CI at V2, presenting both VH and SCC at V0 increased the probability of having CI at V2 (OR=3.71, 95% confidence interval=1.36–10.17, p=0.011).

Conclusions VH were associated with the development of SCC and CI at the 2-year follow-up in patients with PD-NC.

Key Words cognitive impairment; dementia; parkinson's disease; subjective cognitive complaints; visual hallucinations.

INTRODUCTION

Cognitive impairment (CI) is one of the most important nonmotor symptoms that can appear in patients with Parkinson's disease (PD).[1] The full spectrum of cognition appears in individuals with PD, ranging from normal cognition (NC) to mild cognitive impairment (MCI) to Parkinson's disease dementia (PDD).[2] About 50% of patients with Parkinson's disease and normal cognition (PD-NC) develop MCI within 6 years,[3] and almost 40% of patients with Parkinson's disease and mild cognitive impairment (PD-MCI) subsequently develop PDD.[4] Although findings vary among studies, the cumulative prevalence rates of PDD were found to be 17%, 46%, and 83% at 5, 10, and 20 years after diagnosis, respectively.[5] Since dementia is a frequent and highly disabling complication in patients with PD, it is important to identify predictive factors for CI development. The most-established risk factors for early dementia are old age, motor symptom severity (particularly postural and gait disturbances), MCI, and visual hallucinations (VH).[6]

VH are a common symptom in PD, affecting up to 45% of patients without dementia and 65% of those with PDD.[7] Importantly, the early presence of VH is a strong predictor of cognitive decline,[8] as well as increased mortality and reduced quality of life (QoL) for patients and their caregivers.[9] Subjective cognitive complaints (SCC) have more recently been suggested to be an independent predictor of MCI development in PD-NC.[10,11] SCC is the subjective identification of cognitive decline in people who may or may not have had impairment detected in neuropsychological tests.[12] The prevalence of SCC in PD reportedly varies from 30% to 60%,[10,13] and up to 70% of patients with PD-NC who develop CI over time have SCC at baseline.[14] However, the etiology of SCC can differ among patients, and they can be related to cognitive decline as well as to depression or other psychiatric symptoms.[13,15-17]

In this context, the relationships among SCC, VH, and CI are unknown, and it is unclear how VH and SCC contribute to CI development in patients with PD-NC. We hypothesized that the VH prevalence is higher in patients with PD-NC with SCC than in those without SCC and that both VH and SCC together could increase the risk of CI development in patients with PD-NC. Our aims were to determine the frequencies of VH and SCC in a PD-NC cohort, to perform comparison with a control group, and to determine the relationship between cognitive function and factors associated with VH and SCC and the risk of CI development at a 2-year follow-up. Moreover, we analyzed the values of different serum biomarkers (SB) regarding the presence of VH and SCC.

METHODS

Patients diagnosed with PD from January 2016 to November 2017 and controls were recruited from the COPPADIS cohort for inclusion in this study, and were evaluated again at a 2-year follow-up in 35 centers in Spain.[18] The methodology of the COPPADIS-2015 study can be found at https://bmcneurol.biomedcentral.com/articles/10.1186/s12883-016-0548-9.[19] This was a multicenter, observational, longitudinal-prospective, 5-year follow-up study designed to analyze disease progression in a Spanish population of patients with PD. All patients included were diagnosed according to the UK PD Brain Bank criteria.[20] The same inclusion (except PD diagnosis) and exclusion criteria were applied to patients and to the controls (subjects with a disabling neurological or nonneurological condition were excluded). Only subjects from the COPPADIS cohort without CI at baseline (i.e., PD-NC, corresponding to a total score on the Parkinson's Disease Cognitive Rating Scale [PD-CRS] of <81)[21] were analyzed in this study.

Information on sociodemographic aspects, and factors related to PD, comorbidities, and treatment were collected. The evaluations performed at V0 (baseline) and V2 (2-year follow-up, plus or minus 1 month) included motor assessments (Hoehn and Yahr, Unified Parkinson's Disease Rating Scale [UPDRS] part III and part IV, Freezing of Gait Questionnaire [FOGQ]), nonmotor symptoms (Non-Motor Symptoms Scale [NMSS], Parkinson's Disease Sleep Scale [PDSS], Visual Analog Scale–Pain [VAS-Pain], Visual Analog Scale–Fatigue [VASF]), cognition (PD-CRS), mood and neuropsychiatric symptoms (Beck Depression Inventory-II [BDI-II], Neuropsychiatric Inventory [NPI], Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease Rating Scale [QUIP-RS]), disability (Schwab and England Activities of Daily Living Scale [ADLS]), and QoL (39-item Parkinson's Disease Questionnaire Summary Index [PDQ-39SI], 8-item EUROHIS-QOL index [EUROHIS-QOL8]).[19] A higher score indicates a more-severe finding on each scale/questionnaire except for PD-CRS, PDSS, ADLS, and EUROHIS-QOL8, for which the opposite holds. In patients with motor fluctuations, motor assessments were performed during the Off state (without medication in the last 12 hours) and On state. On the other hand, the assessment was only performed without medication in patients without motor fluctuations. The same evaluations (except for the motor assessment) were performed on the control subjects at V0 and V2.[19]

Cognitive assessment and cognitive status classification

Cognitive statuses at V0 and V2 and the changes between these time points were assessed using the PD-CRS,[22] which is a cognitive screening battery validated to assess the cognitive status of patients with PD. The total score is the sum of the frontal-subcortical (FS) subscore (item 1, immediate free recall verbal memory; item 3, sustained attention; item 4, working memory; item 5, unprompted drawing of a clock; item 7, delayed free recall verbal memory; item 8, alternating verbal fluency; and item 9, action verbal fluency) and the posterior-cortical (PC) subscore (item 2, confrontation naming; item 6, copy drawing of a clock). According to the PD-CRS total score, each patient was classified as cognitively preserved (PD-NC; score of >80) or CI (score of <81).[23] All patients had PD-NC at baseline.

VH and SCC definition

Subjects were classified as with or without VH according to item 13 of the NMSS at baseline (V0).[24] This is 1 of 30 items in this scale and is included in domain 4 (perception problems/hallucinations). The symptoms refer to the those that occur during the 4 weeks prior to the assessment. The question asking about VH was "Does the patient indicate that he/she sees things that are not there?" The score ranges from 0 (without symptoms) to 12 (most frequent and severe symptoms). Subjects with a score of 0 on item 13 of the NMSS were considered as "without VH" whereas subjects with a score of 1–12 were considered as "with VH." The same method was used at V2, and persistent VH were defined as having VH at both V0 and V2.

Regarding SCC, subjects were classified as with or without SCC according to domain 5 (attention/memory) of the NMSS at baseline. This domain includes three questions about cognition perception: "Does the patient have problems sustaining concentration during activities?" (item 16), and "Does the patient forget things that he/she has been told a short time ago or events that happened in the last few years?" (item 17), and "Does the patient forget to do things?" (item 18). The score for each item ranges from 0 (without symptoms) to 12 (most frequent and severe symptoms), with the total score of domain 5 ranging from 0 (without symptoms) to 36 (score of 12 [most frequent and severe symptoms] in all items). Subjects with a score of 0 in domain 5 of the NMSS were considered as "without SCC" whereas subjects with a score of 1–36 were considered as "with SCC." The same method was used at V2, and persistent SCC was defined as having SCC at both V0 and V2.

SB determination

SB were analyzed among a subgroup of the COPPADIS cohort.[19] Collected blood samples were used to determine different SB, and included S100B protein, tumor necrosis factor (TNF)-α, interleukin (IL)-1, IL-2, IL-6, vitamin B12, methyl-

malonic acid, homocysteine, uric acid, ultrasensitive CRP (US-CRP), ferritin, and iron. SB levels were determined from frozen blood samples obtained from subjects who participated in the COPPADIS-2015 study from nine centers in Spain. Sampling was carried out no longer than 3 months after the first clinical assessment (V0) in the absence of infections and/or fever. All analyses were conducted at the same laboratory: REFERENCE LABORATORY (www.reference-laboratory.es).[19] Different methods were used: visible spectrophotometry (iron), immunoluminescence (S100B protein, ferritin, vitamin B12, and homocysteine), enzyme immunoassay (IL-1, IL-2, and TNF-α), immunoassay (US-CRP), mass spectrometry (methylmalonic acid), and an enzymatic technique (uric acid). Outliers were excluded from the analysis.

Data analysis

Data were processed using SPSS software (version 20.0 for Windows, IBM Corp, Armonk, NY, USA). Comparisons between patients and controls and between patients with and without VH and/or SCC were performed using Student's t-test, the Mann-Whitney U test, the chi-square test, or Fisher's test as appropriate (distributions of variables were verified using the one-sample Kolmogorov-Smirnov test).

The general linear model repeated-measures procedure was used to test whether the PD-CRS total score, subscores, and items differed significantly between the two visits (V0 and V2) in patients with PD regarding the presence of VH and SCC. The Bonferroni method was used as a post-hoc test after ANOVA. Interactions for visit and group were then tested before testing for group differences over time. Cohen's d formula was applied to measure the effect size (in patients with PD), which was categorized into a small effect (=0.2), medium effect (=0.5), or large effect (=0.8). Age, disease duration, education, and levodopa equivalent daily dose (LEDD)[25] at V0 were included as covariates.

To explore the association between VH and/or SCC and the risk of CI, binary regression models were used with the presence of CI (PD-CRS score <81) as a dependent variable. The effect was controlled for age, sex, disease duration, education, LEDD, motor (UPDRS-III and UPDRS-IV) and nonmotor (NMSS) status, mood (BDI-II), cognitive function (PD-CRS total score), REM behavior disorder (RBD), and taking a dopamine agonist at V0, which were included as covariates in the model. Our analysis was based on a clearly specified a-priori hypothesis and a well-planned regression model, as recommended by best-practice methods.[26]

All values were quoted to two decimal places, with the exception of percentage values for which a single decimal place was used (in the case of zero, it was omitted). A probability value of $p<0.05$ was considered significant.

Standard protocol approvals, registrations, and patient consents

We received approval for this study from the Comité de Ética de la Investigación Clínica de Galicia in Spain (2014/534; December 2, 2014). Written informed consents were obtained from all participants in this study. COPPADIS-2015 was classified by the Agencia Española del Medicamento y Productos Sanitarios (AEMPS) as a postauthorization prospective follow-up study with the code COH-PAK-2014-01.

Data availability

The protocol and statistical analysis plan are available on request. Deidentified participant data are not available for legal and ethical reasons.

RESULTS

VH and SCC in patients with PD vs controls

At V0, VH and SCC were more frequent in patients with PD (n=376, 58.2% males, age 61.14±8.73 years) than in the controls (n=116, 48.3% males, age 62.40±8.46 years): 13.6% (51/376) vs 0% (0/116) ($p<0.001$) and 62.2% (234/376) vs. 50.9% (59/116) ($p=0.019$), respectively. SCC were significantly more frequent in patients with PD than in controls according to NMSS item 16 (44.4% vs. 21.6%, $p<0.001$) and item 17 (39.6% vs. 29.3%, $p=0.028$), but not in item 18 (29.5% vs. 25%, $p=0.205$).

No VH cases were detected in the control group. In the PD-NC group, SCC were present in 86.3% (44/51) of patients with VH compared with 58.5% (190/325) of patients without VH ($p<0.001$) (Fig. 1A). In the PD-NC subgroup with SCC, VH were more frequent than in the PD-NC group without SCC (18.8% [44/234] vs. 4.9% [7/142], $p<0.001$) (Fig. 1B).

At the 2-year follow-up, 66 out of 376 patients with PD-NC (17.6%) presented VH, of which 35 were new cases (10.8% of the patients without VH at V0). Only four cases (3.4%) with VH at V2 were found in the control group. SCC were detected at V2 in 65.7% and 44% of the patients and controls, respectively. The frequencies of SCC at V2 in the PD-NC and control groups that did not report SCC at V0 were 42.3% (60/142) and 15.8% (9/57), respectively.

Patients with PD-NC with vs without VH at baseline

VH presenting at baseline were associated with a higher LEDD (661.49±390.14 vs. 529.51±395.02, $p=0.011$), higher scores on the UPDRS-III (24.57±11.45 vs. 20.51±9.78, $p=0.022$), UPDRS-IV (2.63±2.67 vs. 1.74±2.26, $p=0.009$), FOGQ (4.41±4.45 vs. 3.14±4.41, $p=0.005$), NMSS (73.55±46.58 vs. 36.55±29.28, $p<0.001$), NPI (7.95±9.01 vs. 4.70±6.88, $p=0.010$), VASF–mental (2.82±2.43 vs. 1.87±2.4, p=0.004), and PDQ-

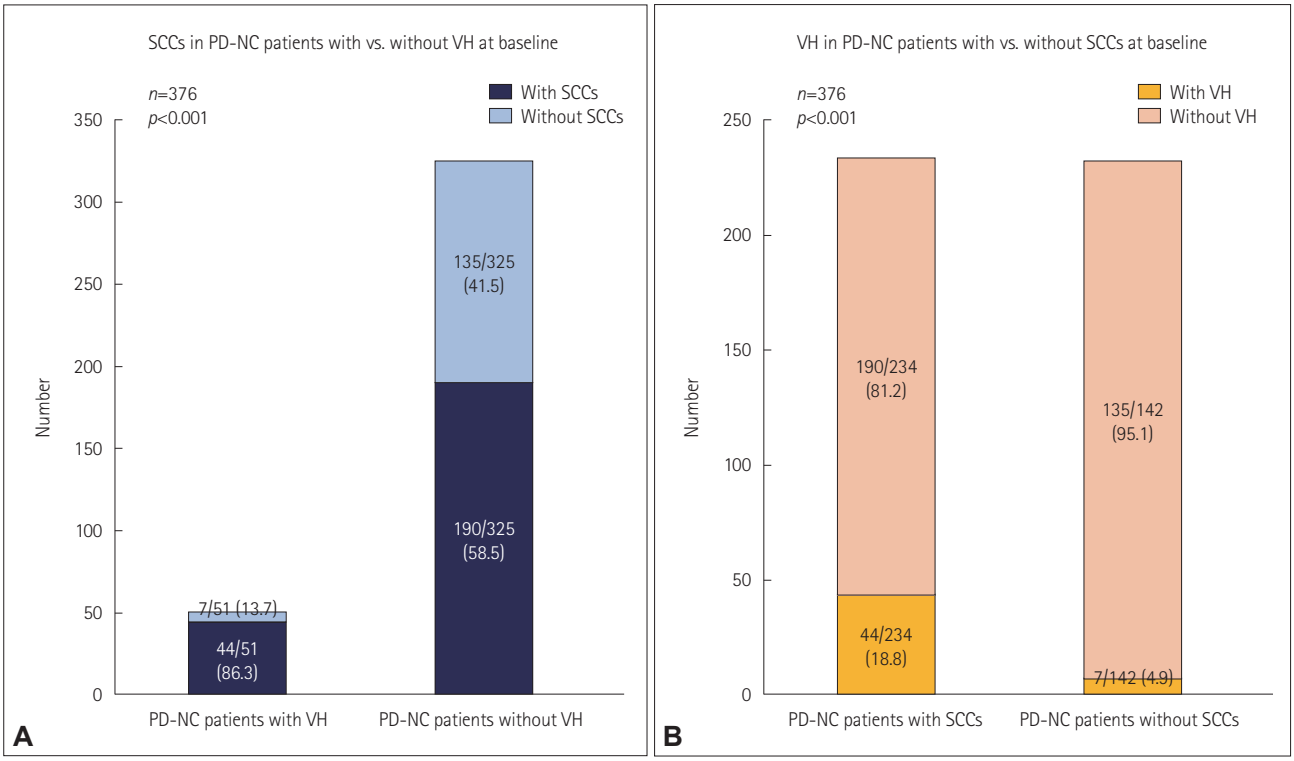

Fig. 1. SCCs and VH at baseline. A: Frequency at baseline (V0) of subjective cognitive complaints (SCC) in patients with Parkinson's disease with normal cognition (PD-NC, defined as total score on the Parkinson's Disease Cognitive Rating Scale [PD-CRS] of >80) with visual hallucinations (VH) (*n*=51) vs. without VH (*n*=325). B: Frequency at V0 of VH in patients with PD-NC with SCC (*n*=234) vs without SCC (*n*=142).

39SI (26.92±15.87 vs. 13.72±10.75, *p*<0.001), and lower scores on the PDSS (110.76±29.91 vs. 119.67±23.42, *p*=0.035), ADLS (86.86±9.05 vs. 90.31±8.49, *p*=0.004), and EUROHIS-QOL8 (3.67±0.55 vs. 3.86±0.52, *p*=0.026) (Table 1). Specifically, motor fluctuations (49.0% vs. 28.3%, *p*=0.003), FOGQ (41.2% vs. 28.1%, *p*=0.044), falls (21.6% vs. 8.0%, *p*=0.005), severe or very severe nonmotor symptoms burden (66.7% vs. 33.8%, *p*<0.001), and major depression (21.6% vs. 10.8%, *p*=0.031) were more frequent in patients with PD-NC with VH than in those without VH (Table 1). No differences were observed between patients with vs without VH in global cognition (PD-CRS total score) or FS functions (PD-CRS FS subscore), but the PD-CRS PC subscores were significantly lower in the subgroup with VH (26.16±4.58 vs. 28.97±1.46, *p*=0.001). There were no differences between patients with and without VH in the drugs that they were taking: levodopa (72.5% vs. 67.4%, *p*=0.286), dopamine agonist (76.5% vs. 71.1%, *p*=0.269), MAO-B inhibitor (86.3% vs. 74.5%, *p*=0.053), COMT inhibitor (23.5% vs. 16.6%, *p*=0.156), amantadine (5.9% vs. 8%, *p*=0.426), or anticholinergic drugs (2% vs. 3.1%, *p*=0.547).

Patients with PD-NC with vs without SCC at baseline

SCC presenting at baseline were associated with higher scores on the UPDRS-III (22.25±10.57 vs. 19.2±9.05, *p*=0.008), UPDRS-IV (2.08±2.47 vs. 1.5±2.05, *p*=0.006), FOGQ (3.77±4.6 vs. 2.54±4.02, *p*=0.002), NMSS (51.94±37.05 vs. 24.49±20.64, *p*<0.001), BDI-II (9.00±6.92 vs. 4.85±4.42, *p*<0.001), NPI (5.93±7.81 vs. 3.68±5.94, *p*=0.002), QUIP-RS (5.55±9.80 vs. 2.79±6.99, *p*<0.001), VAS-Pain (2.72±2.86 vs. 2.12±2.79, *p*=0.019), VASF–physical (3.19±2.67 vs. 2.00±2.45, *p*<0.001), VASF–mental (2.44±2.50 vs. 1.27±2.09, *p*<0.001), and PDQ-39SI (18.80±13.36 vs. 10.09±8.18, *p*<0.001), and lower scores on the PD-CRS (97.44±11.15 vs. 99.92±11.45, *p*=0.026), PD-CRS CP subscale (28.30±2.79 vs. 29.07±1.25, *p*=0.029), PDSS (113.38±27.12 vs. 126.85±16.54, *p*<0.001), ADLS (86.76±9.20 vs. 91.62±7.30, *p*=0.004), and EUROHIS-QOL8 (3.74±0.54 vs. 3.98±0.45, *p*<0.001) (Table 2). Specifically, FOGQ (34.6% vs. 22.0%, *p*=0.006), falls (12.8% vs. 4.9%, *p*=0.008), severe or very severe nonmotor symptoms burden (51.7% vs. 16.2%, *p*<0.001), major depression (17.1% vs 4.2%, *p*<0.001), pain (63.7% vs 47.9%, *p*=0.002), and functional dependency (6.8% vs 2.1%, *p*=0.032) were more frequent in patients with PD-NC with SCC than in those without SCC (Table 2).

SB related to VH and SCC

No significant differences were detected in SB levels between patients with PD-NC with (*n*=64) and without (*n*=68) SCC (data not shown). There were also no differences in SB levels

between patients with PD-NC with VH (n=14) and without VH (n=118) (data not shown).

VH and SCC development at the 2-year follow-up related to baseline symptoms

In the subgroup of patients with PD-NC without VH at base-

Table 1. Disease-related characteristics, motor and nonmotor symptoms, autonomy in performing the activities of daily living, and quality of life in patients with PD-NC (defined as total score on the PD-CRS of >80) with and without VH at baseline (n=376)

	Entire sample (n=376)	Patients with PD-NC with VH (n=51)	Patients with PD-NC without VH (n=325)	p
Age (yr)	61.14±8.73	62.16±8.26	60.98±8.8	0.396
Sex, male (%)	58.2	56.9	58.5	0.473
Disease duration (yr)	5.29±3.9	5.86±3.74	5.19±3.92	0.176
Levodopa equivalent daily dose (mg)	547.61±396.44	661.49±390.14	529.51±395.02	0.011
Motor phenotype (%)				0.129
Tremor dominant	49.5	58.8	48.0	
PIGD	34.0	21.6	36.0	
Indeterminate	16.5	19.6	16.0	
Hoehn and Yahr stage	2 [1.5–2]	2 [1.5–2]	2 [1.5–2]	0.680
From 3 to 5 (%)	7.8	4.7	8.2	0.323
UPDRS-III score	21.09±10.11	24.57±11.45	20.51±9.78	0.022
UPDRS-IV score	1.86±2.33	2.63±2.67	1.74±2.26	0.009
Motor fluctuations (%)	31.1	49.0	28.3	0.003
Dyskinesia (%)	17.4	21.6	16.7	0.253
FOGQ score	3.31±4.34	4.41±4.45	3.14±4.41	0.005
Patients with freezing of gait (%)	29.9	41.2	28.1	0.044
Patients with falls (%)	9.8	21.6	8.0	0.005
PD-CRS total score	98.38±11.33	96.82±10.76	98.62±11.41	0.268
PD-CRS FS subscore	69.79±10.83	70.67±9.07	69.65±11.09	0.319
PD-CRS PC subscore	28.59±2.36	26.16±4.58	28.97±1.46	0.001
SCC (%)	62.2	86.3	58.5	<0.001
NMSS score	41.57±34.51	73.55±46.58	36.55±29.28	<0.001
Severe or very severe nonmotor symptoms burden (NMSS score >40) (%)	38.3	66.7	33.8	<0.001
BDI-II score	7.43±6.41	8.71±7.17	7.23±6.28	0.148
Major depression (%)	12.2	21.6	10.8	0.031
NPI score	5.14±7.28	7.95±9.01	4.7±6.88	0.010
QUIP-RS score	4.3±8.1	4.5±8	3.47±6.88	0.119
PDSS score	118.46±24.55	110.76±29.91	119.67±23.42	0.035
VAS-Pain score	2.49±2.84	2.64±2.9	2.47±2.84	0.791
Patients with pain (%)	57.7	60.8	57.2	0.375
VASF–physical score	2.74±2.65	3.35±2.57	2.65±2.65	0.072
VASF–mental score	2±2.42	2.82±2.43	1.87±2.4	0.004
ADLS score	89.84±8.64	86.86±9.05	90.31±8.49	0.004
Patients with functional dependency (%)	5.1	9.8	4.3	0.099
PDQ-39SI score	15.51±12.41	26.92±15.87	13.72±10.75	<0.001
EUROHIS-QOL8 score	3.83±0.53	3.67±0.55	3.86±0.52	0.026

Data are percentage, mean±SD, or median [interquartile range] values. Chi-square and Mann-Whitney-Wilcoxon tests were used to compare patients with and without SCC at baseline. Data on Hoehn and Yahr stages and UPDRS scores were obtained during the Off state (first hour in the morning without taking medication in the previous 12 hours).

ADLS, Schwab and England Activities of Daily Living Scale; BDI-II, Beck Depression Inventory-II; EUROHIS-QOL8, 8-item EUROHIS-QOL index; FS, frontal-subcortical; NMSS, Non-Motor Symptoms Scale; NPI, Neuropsychiatric Inventory; PC, posterior-cortical; PD-CRS, Parkinson's Disease Cognitive Rating Scale; PD-NC, Parkinson's disease with normal cognition; PDQ-39SI, 39-item Parkinson's Disease Quality of Life Questionnaire Summary Index; PDSS, Parkinson's Disease Sleep Scale; PIGD, Postural Instability Gait Difficulty; QUIP-RS, Questionnaire for Impulsive Compulsive Disorders in Parkinson's Disease Rating Scale; SCC, subjective cognitive complaints; UPDRS, Unified Parkinson's Disease Rating Scale; VASF, Visual Analog Scale–Fatigue; VAS-Pain, Visual Analog Scale–Pain; VH, visual hallucinations.

line (*n*=325), 13.7% of the group with SCC at baseline (26/190) and 6.7% of the group without SCC at baseline (9/135) had developed VH at V2 (*p*=0.032). In contrast, in the subgroup of patients without SCC at baseline (*n*=142), 42.7% of the group with VH at baseline (3/7) and 42.2% of the group without VH at baseline (57/135) had developed SCC at V2 (*p*=0.632). Like

Table 2. Disease-related characteristics, motor and nonmotor symptoms, autonomy in performing the activities of daily living, and quality of life in patients with PD with and without SCC at baseline (*n*=499)

	Entire sample (*n*=376)	Patients with PD-NC with SCC (*n*=234)	Patients with PD-NC without SCC (*n*=142)	*p*
Age (yr)	61.14±8.73	62.31±8.40	60.86±9.26	0.791
Sex, male (%)	58.2	60.3	54.9	0.182
Disease duration (yr)	5.29±3.9	5.53±3.99	4.91±3.72	0.144
Levodopa equivalent daily dose (mg)	547.61±396.44	569.35±390.69	512.39±404.5	0.099
Motor phenotype (%)				0.363
Tremor dominant	49.5	47.4	52.8	
PIGD	34.0	36.8	29.6	
Indeterminate	16.5	15.8	17.6	
Hoehn and Yahr stage	2 [1.5–2]	2 [1.5–2]	2 [1.5–2]	0.412
From 3 to 5 (%)	7.8	8.6	6 .5	0.319
UPDRS-III score	21.09±10.11	22.25±10.57	19.2±9.05	0.008
UPDRS-IV score	1.86±2.33	2.08±2.47	1.5±2.05	0.006
Motor fluctuations (%)	31.1	33.3	27.5	0.141
Dyskinesia (%)	17.4	18.1	16.3	0.391
FOGQ score	3.31±4.34	3.77±4.6	2.54±4.02	0.002
Patients with FOG (%)	29.9	34.6	22.0	0.006
Patients with falls (%)	9.8	12.8	4.9	0.008
PD-CRS total score	98.38±11.33	97.44±11.15	99.92±11.45	0.026
PD-CRS FS subscore	69.79±10.83	69.15±10.6	70.85±11.16	0.112
PD-CRS PC subscore	28.59±2.36	28.3±2.79	29.07±1.25	0.029
VH (%)	13.6	18.8	4.9	<0.001
NMSS score	41.57±34.51	51.94±37.05	24.49±20.64	<0.001
Severe or very severe nonmotor symptoms burden (NMSS score >40) (%)	38.3	51.7	16.2	<0.001
BDI-II score	7.43±6.41	9±6.92	4.85±4.42	<0.001
Major depression (%)	12.2	17.1	4.2	<0.001
NPI score	5.14±7.28	5.93±7.81	3.68±5.94	0.002
QUIP-RS score	4.30±8.10	5.55±9.80	2.79±6.99	<0.001
PDSS score	118.46±24.55	113.38±27.12	126.85±16.54	<0.001
VAS-Pain score	2.49±2.84	2.72±2.86	2.12±2.79	0.019
Patients with pain (%)	57.7	63.7	47.9	0.002
VASF–physical score	2.74±2.65	3.19±2.67	2.00±2.45	<0.001
VASF–mental score	2.00±2.42	2.44±2.50	1.27±2.09	<0.001
ADLS score	89.84±8.64	86.76±9.20	91.62±7.30	0.004
Patients with functional dependency (%)	5.1	6.8	2.1	0.032
PDQ-39SI score	15.51±12.41	18.8±13.36	10.09±8.18	<0.001
EUROHIS-QOL8 score	3.83±0.53	3.74±0.54	3.98±0.45	<0.001

Data are percentage, mean±SD or median [interquartile range] values. Chi-square and Mann-Whitney-Wilcoxon tests were applied to compare patients with and without SCC at baseline. Data on Hoehn and Yahr stages and UPDRS-III scores were obtained from during the Off state.
ADLS, Schwab and England Activities of Daily Living Scale; BDI-II, Beck Depression Inventory-II; EUROHIS-QOL8, 8-item EUROHIS-QOL index; FS, frontal-subcortical; NMSS, Non-Motor Symptoms Scale; NPI, Neuropsychiatric Inventory; PC, posterior-cortical; PD-CRS, Parkinson's Disease Cognitive Rating Scale; PD-NC, Parkinson's disease with normal cognition; PDQ-39SI, 39-item Parkinson's Disease Quality of Life Questionnaire Summary Index; PDSS, Parkinson's Disease Sleep Scale; PIGD, Postural Instability Gait Difficulty; QUIP-RS, Questionnaire for Impulsive Compulsive Disorders in Parkinson's Disease Rating Scale; SCC, subjective cognitive complaints; UPDRS, Unified Parkinson's Disease Rating Scale; VASF, Visual Analog Scale–Fatigue; VAS-Pain, Visual Analog Scale–Pain; VH, visual hallucinations.

at baseline, no relationship was observed between drug treatment and VH at V2 in patients with and without VH: levodopa (89.4% vs. 87.4%, p=0.378), dopamine agonist (71.2% vs. 75.8%, p=0.393), MAO-B inhibitor (78.8% vs. 77.1%, p=0.432), COMT inhibitor (33.3% vs. 26.8%, p=0.253), amantadine (12.1% vs. 10%, p=0.668), or anticholinergic drugs (4.5% vs. 2.6%, p=0.328).

Change in cognition related to VH and SCC

At the 2-year follow-up, the PD-CRS total score had significantly decreased in both patients with PD-NC with VH (n=51, from 96.82±10.76 to 91.08±17.85, Cohen's d=-0.71, p=0.001) and with PD-NC but without VH (n=325, from 98.62±11.41 to 96.26±14.6, Cohen's d=-0.31, p<0.001). The FS and PC subscores of PD-CRS also decreased significantly in both groups (Table 3). Comparing both groups, in patients with PD-NC with VH, the score on the PD-CRS PC subscale decreased significantly more than that in patients with PD-NC without VH (Cohen's d=-0.41 vs. -0.23, p<0.001). A significant trend was observed in the reduction of the PD-CRS total score in the group with VH compared with the group without VH (Cohen's d=-0.71 vs. -0.31, p=0.061), but no differences were detected in the PD-CRS FS subscore (Table 3). At V2, the frequency of CI was significantly higher in patients with than without VH at V0: 33.3% (17/51) vs. 12.3% (40/325), p< 0.001 (Fig. 2A). Moreover, CI was significantly more frequent at V2 in patients with PD with VH at V2 compared with those without VH at V2 (38.6% vs. 13.8%, p<0.001), and in those patients with persistent VH (i.e., at both V0 and V2) than in those with no VH or with VH at only one of the two visits (24.6% vs. 5.3%, p<0.001).

Regarding SCC, global cognitive function (PD-CRS total score, Cohen's d=-0.43 vs. -0.27, p=0.008) and FS function (PD-CRS FS subscore, Cohen's d=-0.53 vs. -0.23, p=0.035) were significantly impaired in patients with PD-NC with SCC compared with those without SCC (Table 4). However, patients with PD-NC without SCC exhibited a significantly larger decrease in PD-CRS PC subscore compared with patients with PD-NC and SCC (Cohen's d=-0.31 vs. -0.23, p=0.003). A significant trend (p=0.066) was observed in the higher frequency of CI at V2 in patients with PD-NC with SCC compared with those without SCC (17.5% [41/234] vs. 11.3% [16/142]) (Fig. 2B). Similar results were observed when SCC at V2 were considered (17.4% [43/247] vs. 10.9% [14/129], p=0.061). When patients with persistent SCC (at V0 and V2) were compared with patients without persistent SCC, CI was more frequent in the former (19.3% [36/187] vs. 11.1% [21/189], p=0.020).

VH and SCC as predictors of CI at the 2-year follow-up

In patients with PD-NC (n=376), VH presenting at V0 was associated with CI at the 2-year follow-up (odds ratio [OR]= 3.56, 95% confidence interval=1.82–6.96, p<0.001). After ad-

Table 3. Changes in cognition in patients with PD-NC with vs without VH at V0 (baseline) from V0 to V2 (2-year follow-up, plus or minus 1 month)

	Patients with PD with VH at V0 (n=51)	Patients with PD with VH at V2 (n=51)	Cohen's d	p^*	Patients with PD without VH V0 (n=325)	Patients with PD without VH V2 (n=325)	Cohen's d	$p^\dagger$	$p^\ddagger$	$p^\S$
PD-CRS total score	96.82±10.76	91.08±17.85	-0.71	0.001	98.62±11.41	96.26±14.6	-0.31	<0.001	0.100	0.061
PD-CRS FS subscore	70.67±9.07	66.61±14.32	-0.69	0.001	69.65±11.09	67.67±13.8	-0.28	<0.001	0.114	0.927
Immediate verbal memory	8.96±1.80	8.53±1.94	-0.32	0.103	8.45±1.86	8.64±2.75	0.10	0.179	0.153	0.324
Sustained attention	9.33±1.03	8.65±1.36	-0.69	0.001	9.03±1.21	8.66±1.70	-0.29	<0.001	0.310	0.218
Working memory	8.41±1.75	7.57±1.70	-0.62	0.003	7.65±1.90	7.24±1.93	-0.29	<0.001	0.180	0.013
Clock drawing	9.65±0.62	8.86±1.45	-0.79	<0.001	9.33±1.51	9.18±1.32	-0.11	0.154	0.022	N.A.
Delayed verbal memory	7.06±2.90	6.69±2.50	-0.25	0.210	5.97±2.63	6.3±2.88	0.17	0.026	0.105	0.016
Alternating verbal fluency	11.41±4.45	11.08±4.06	-0.43	0.032	12.9±3.96	12.1±4.47	-0.27	0.001	0.857	0.148
Action verbal fluency	12.2±3.17	14.24±7.04	0.28	0.160	16.33±5.18	15.56±5.50	-0.22	0.004	0.698	0.054
PD-CRS PC subscore	26.16±4.58	25.47±5.23	-0.41	0.046	28.97±1.46	28.59±2.19	-0.23	0.003	0.412	<0.001
Confrontation naming	16.27±4.57	16.12±4.81	-0.13	0.485	19.19±1.20	18.95±1.96	-0.17	0.030	0.787	<0.001
Clock copying	9.59±1.19	9.35±1.38	-0.60	0.004	9.78±0.81	9.64±0.95	-0.16	0.033	0.041	N.A.

Data are mean±SD values. p values were computed using the GLM repeated-measures procedure.
*p, change over time (V2 vs. V0) in patients with PD-NC with VH at V0; †p, change over time (V2 vs. V0) in patients with PD-NC without VH at V0; ‡p, group–visit interaction; §p, patients with PD-NC with VH vs patients with PD-NC without VH. Age, disease duration, education, and LEDD at V0 were included as covariates. Patients with PD-NC with VH vs. patients with PD-NC without VH were not applicable if the interaction test was significant (indicating that the rates of change over time differ between the two groups).
GLM; general linear model; LEDD, levodopa equivalent daily dose; N.A., not applicable; PC, posterior-cortical; PD, Parkinson's disease; PD-CRS, Parkinson's Disease Cognitive Rating Scale; PD-NC, Parkinson's disease with normal cognition; PIGD, Postural Instability Gait Difficulty; VH, visual hallucinations.

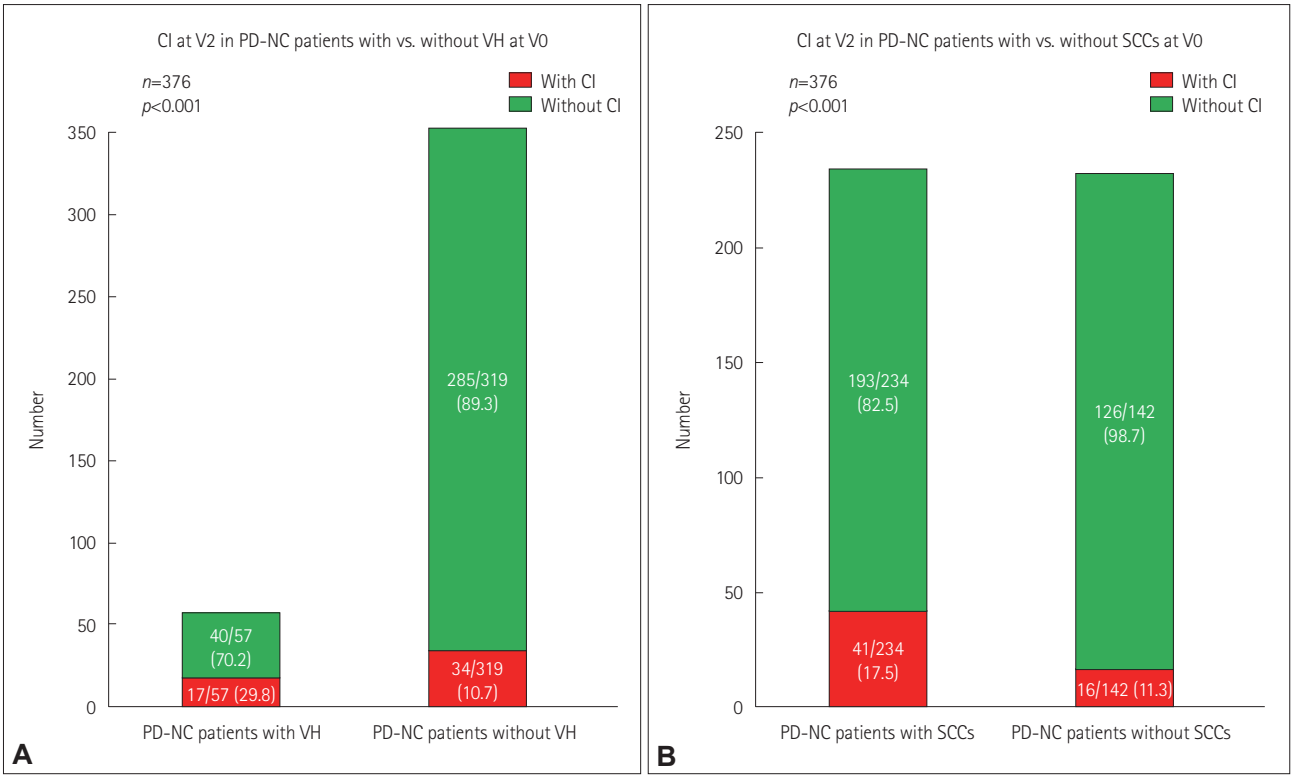

Fig. 2. CI at V2 regarding VH and SCCs. A: Frequency of cognitive impairment (CI, defined as Parkinson's Disease Cognitive Rating Scale [PD-CRS] total score of <81) in patients with Parkinson's disease with normal cognition (PD-NC) with vs without visual hallucinations (VH) at the 2-year follow-up (V2). B: Frequency of CI in patients with PD-NC with vs without subjective cognitive complaints (SCC) at V2.

Table 4. Changes in cognition in patients with PD-NC with vs without SCC at V0 from V0 to V2

	Patients with PD with SCC V0 (*n*=234)	Patients with PD with SCC V2 (*n*=234)	Cohen's d	*p**	Patients with PD without SCC V0 (*n*=142)	Patients with PD without SCC V2 (*n*=142)	Cohen's d	*p*†	*p*‡	*p*§
PD-CRS total score	97.44±11.15	94.18±15.39	-0.43	<0.001	99.92±11.45	97.83±14.52	-0.27	0.023	0.434	0.008
PD-CRS FS subscore	69.15±10.6	66.31±13.81	-0.53	<0.001	70.85±11.16	69.16±13.84	-0.23	0.050	0.391	0.035
Immediate verbal memory	8.44±1.91	8.41±2.23	-0.02	0.785	8.64±1.76	8.99±3.21	0.16	0.163	0.106	0.022
Sustained attention	9.14±1.17	8.57±1.72	-0.46	<0.001	8.96±1.22	8.81±1.55	-0.12	0.287	0.026	N.A.
Working memory	7.73±1.83	7.18±1.78	-0.42	<0.001	7.78±2.02	7.45±2.09	-0.22	0.064	0.305	0.645
Clock drawing	9.38±1.48	9.51±1.19	0.25	0.007	9.36±1.33	9.32±1.08	-0.03	0.754	0.111	0.432
Delayed verbal memory	6.06±2.80	6.22±2.82	0.09	0.310	6.21±2.50	6.56±2.86	0.17	0.149	0.729	0.233
Alternating verbal fluency	12.49±3.70	11.74±4.53	-0.26	0.004	13.32±4.08	12.31±4.26	-0.33	0.006	0.362	0.078
Action verbal fluency	15.90±5.57	15.16±5.81	-0.22	0.016	16.58±4.92	15.73±5.62	-0.24	0.045	0.718	0.177
PD-CRS PC subscore	28.30±2.79	27.86±3.44	-0.23	0.010	29.07±1.25	28.67±1.94	-0.31	0.010	0.976	0.003
Confrontation naming	18.50±2.69	18.35±3.12	-0.09	0.284	19.29±1.03	18.92±1.80	-0.30	0.010	0.199	0.007
Clock copying	9.80±0.88	9.51±1.19	-0.29	0.002	9.78±0.52	9.75±0.64	-0.06	0.571	0.041	N.A.

Data are mean±SD values.

p values were computed using a GLM repeated-measures procedure. **p*, change over time (V2 vs V0) in patients with PD-NC with SCC at V0; †*p*, change over time (V2 vs V0) in patients with PD-NC without SCC at V0; ‡*p*, group–visit interaction; §*p*, patients with PD-NC with SCC vs patients with PD-NC without SCC. Age, disease duration, education, and LEDD at V0 were included as covariates. Patients with PD-NC with SCC vs patients with PD-NC without SCC were not applicable if the interaction test was significant.

FS, frontal-subcortical; GLM; general linear model; LEDD, levodopa equivalent daily dose; N.A., not applicable; PD, Parkinson's disease; PD-CRS, Parkinson's Disease Cognitive Rating Scale; PD-NC, Parkinson's disease with normal cognition.

justing for age, sex, disease duration, education, LEDD, motor (UPDRS-III and UPDRS-IV) and nonmotor (NMSS) status, mood (BDI-II), cognitive function (PD-CRS total score), RBD, and taking a dopamine agonist at V0, VH at V0 were also associated with CI at V2 (OR=2.68, 95% confidence interval=1.05–6.83, p=0.039; adjusted R^2=0.39, Hosmer-Lemeshow test=0.87) (Table 5). Although SCC at V0 were not associated with CI at V2 after adjusting for the same covariates (OR=1.01, 95% confidence interval=0.45–2.27, p=0.965), having both VH and SCC at V0 markedly increased the probability of having CI at V2 (OR=3.71, 95% confidence interval=1.36–10.17, p=0.011). Finally, a higher risk of CI at V2 was observed in patients with PD-NC who suffered from persistent VH and from persistent SCC simultaneously (n=24) after adjusting for the same covariates in the model (OR=8.32, 95% confidence interval=2.17–31.85, p=0.002; adjusted R^2=0.41, Hosmer-Lemeshow test=0.31).

DISCUSSION

This study found that VH and SCC occurred frequently in patients with PD without CI, affecting about one in seven and more than half of patients, respectively, and were more common than in the controls. It was also observed that VH and SCC were interrelated and that together they contribute to increasing the risk of CI development over the short term. In contrast, no SB (e.g., inflammation, degeneration) from the COPPADIS study were associated with either VH or SCC in the analysis.

The frequencies of VH and SCC were generally high but have varied in previous studies according to the methodology used, including the characteristics of the sample. The reported prevalence of VH in PD was between 8.8% and 44% according to a previous study.[27] In a large retrospective study of 445 patients with pathologically confirmed PD diagnoses, half of the patients had a history of VH, indicating a lifetime prevalence of 50%.[28] VH were found in 82.7% of 513 patients with PD from the United Kingdom followed over 36 months.[29] VH may occur even earlier in the disease process, but are often minor.[30] A recent study found that 34 out of 154 (22%) newly diagnosed patients with PD reported VH, with minor VH being the most common.[31] The prevalence of VH in our cohort was 13.6% at baseline and 17.6% at the 2-year follow-up. Importantly and unlike other studies, all patients at baseline in our analysis had PD-NC, and the results suggested that VH is frequent even in PD without objective cognitive problems. However, 62.2% of these patients had SCC, and it was particularly interesting that VH were associated with SCC. Given that SCC could be a risk factor for CI development in PD,[10,11] we analyzed the relationship between VH and SCC, and found that VH were four times more frequent in patients with PD-NC and SCC compared with those without SCC. In line with our findings, Bejr-Kasem et al.[32] observed 131 de novo patients with PD from the Parkinson's Progression Marker Initiative, and found that 35.1% of the patients developed minor hallucinations during the first 5 years of follow-up, meaning an increased prevalence of subjective cognitive decline compared with those who did not develop hallucinations (44.1% vs. 13.9%, p<0.001).

One critical aspect of our analyses was that both VH and SCC were defined according to specific questions from the NMSS that ask for the symptoms, while a specific interview to try to identify type and phenomenology, differential diagnosis, and other visual symptoms was not specifically conducted. This type of post-hoc analysis was not initially considered in the COPPADIS study protocol.[19] However, as we reported previously, this methodology is not infrequent when scales are used (e.g., constipation,[33] freezing of gait,[34] motor fluctuations,[35] dysphagia,[36] and psychotic symptoms[32]), and a PD expert conducted face-to-face interviews with the subjects. More-

Table 5. Analysis of CI (defined as PD-CRS total score of <81) risk at the 2-year follow-up related to VH and/or SCC in patients with PD-NC (n=376)

	OR*	OR†	Hosmer–Lemeshow test	R^2	95% CI*	95% CI†	p*	p†
VH at V0	3.56	2.68	0.87	0.39	1.82–6.96	1.05–6.83	<0.001	0.039
SCC at V0	1.67	1.01	0.57	0.37	0.90–3.11	0.45–2.27	0.104	0.965
VH and SCC at V0	4.05	3.71	0.83	0.40	2.02–8.13	1.36–10.17	<0.001	0.011
Persistent VH	5.78	4.35	0.47	0.39	2.66–12.56	1.37–13.78	<0.001	0.012
Persistent SCC	1.91	1.19	0.48	0.37	1.06–3.41	0.54–2.61	0.029	0.654
Persistent VH and persistent SCC	8.27	8.32	0.31	0.41	3.49–19.6	2.17–31.85	<0.001	0.002

Dependent variable: CI at V2. Age, sex, disease duration, education, LEDD, motor (UPDRS-III and UPDRS-IV) and nonmotor (NMSS) status, mood (BDI-II), cognitive function (PC-CRS total score), REM behavior disorder, and taking a dopamine agonist at V0 were included as covariates in the model. Similar results were found when different drugs that patients were taking at V0 (levodopa, dopamine agonist, MAO-B inhibitor, COMT inhibitor, amantadine, and anticholinergic drugs) were included in the model.
*Univariate analysis; †Multivariate analysis.
BDI-II, Beck Depression Inventory-II; CI, cognitive impairment; LEDD, levodopa equivalent daily dose; NMSS, Non-Motor Symptoms Scale; SCC, subjective cognitive complaints; UPDRS, Unified Parkinson's Disease Rating Scale; VH, visual hallucinations.

over, we compared the prevalence of VH with a control group, and both VH and SCC were found to be more frequent in patients with PD. Cross-sectional data collected from 414 patients with PD using a questionnaire circulated via an online patient community indicated a VH prevalence of 15.5%.[37] Similar to our study, Martinez-Martin et al.[38] identified 72 out of 411 (17.5%) patients as patients with PD with VH using the NMSS. The sensitivity and specificity of detecting VH and SCC were partly influenced by the number of questions (one question for VH but three for SCC). The prevalence of SCC in our cohort was 62.2% at baseline and 65.7% at the 2-year follow-up, both of which were significantly higher than in controls; the complaints were specifically not only for subjective memory but also for concentration. Using only a single question ("Do you feel that your memory and thinking have gotten worse?"), Purri et al.[14] found that 81 out of 153 patients with PD (52.9%) with consensus process-determined NC at baseline reported SCC. The Parkinson's Disease Cognitive Impairment Study conducted recently in Italy found that SCC were present in 88 of 147 patients with PD (59.8%), 27.2% of those with NC, and 32.6% of those with MCI.[13] In that study, 26.1% of the patients with MCI did not have SCC, which was consistent with our finding of 28.1% (16/57) at the 2-year follow-up. SCC seemed to be frequent even in early PD. Pan et al.[16] very recently observed that up to 42.3% (42/108) of newly diagnosed nondemented patients with PD reported SCC. Unlike other studies,[15,17] they used the Cognitive Complaint Interview, which is a more-appropriate subjective measure that includes ten questions that explore the cognitive, memory, and behavioral domains. In summary, previous and new data suggest that VH and SCC are frequent even in patients with PD-NC and that these symptoms could be related.

The univariate analysis identified many factors that were associated with VH and SCC. Importantly, neither of these two variables were associated with age, sex, disease duration, or LEDD. However, patients with VH and with SCC generally had worse motor and nonmotor symptoms, QoL, and autonomy in performing the activities of daily living. Previous studies found that higher age, longer illness duration, more-severe motor symptoms, CI, and dementia, dopamine agonist use, depression, and sleep disturbances were strongly associated with VH.[27-31,39-41] All of the patients in this subgroup from the COPPADIS cohort had PD-NC at baseline, an age limit of 75 years at baseline, and the short mean time from symptom onset (5.3 years), which could explain why age and disease duration were not associated with VH in the present analysis. We detected that mood was associated with both VH and SCC, with major depression being up to four times more frequent in patients with PD-NC with SCC than in those without SCC. Some studies have similarly found SCC to be correlated with psychiatric symptoms including depression,[14,15,17] suggesting that SCC in PD have a different etiology according to the presence of MCI and/or depressive symptoms. Another interesting observation was that depressive symptoms as a comorbid factor could explain why SCC were perceived to be associated with impaired FS functions (PD-CRS FS subscore) in our cohort at the 2-year follow-up, whereas the presence of VH was associated with PC dysfunction (PD-CRS PC subscore). However, PC dysfunction was due to clock-copying impairment but not to confrontation naming, which was associated with greater worsening of symptoms in both patients without VH and without SCC. Confrontation naming is complex and involves the visual-perceptive, semantic, and phonological output stages, which might involve different areas of the brain. However, in clock copying but not in clock drawing, the function could be more specific to visuospatial areas. In particular, the frontostriatal syndrome does not predict PDD, whereas PC syndrome does.[42,43] In this context, some biomarkers could help us to understand the origin of these complications in patients with PD,[30,41,44-46] but we did not detect differences in the SB analysis. Although previous studies found that SCC were an independent predictor of MCI development in CN patients with PD,[10,11,47] only persistent SCC were associated with CI in our study when no other covariates were considered. On the contrary and as reported previously,[6,8] VH were an independent predictor for CI after adjusting for many other variables, even including cognitive function at baseline (PD-CRS total score). With respect to the previous literature, the novel and very interesting finding was that the presence of SCC increased the probability of developing CI compared with only suffering from VH (for persistent symptoms, 8.3% vs. 4.4%), making it an independent predictor after controlling for motor and nonmotor symptoms, medication (LEDD and dopamine agonist), and cognitive function. In clinical practice, it could be useful and very easy to firstly ask patients with PD-NC about VH and then SCC. If both symptoms are present, it is necessary to consider that a high short-term risk of CI development could exist independently of age, disease duration, or even objective cognitive function.

The present study had some limitations. First, as indicated above, a post-hoc analysis was performed in which VH and SCC were considered based on answers to questions from the NMSS (yes/no) referring to the 4 weeks prior to assessment, and a complete assessment about the symptoms and specific tools was not conducted.[48,49] Second, selection bias may have been present since this study involved a patient population that tended to have early-to-moderate PD. Third, the samples of some subgroups for some analyses were small. Finally, this study did not include pathological data. One strength of this study was that it performed the largest prospective lon-

gitudinal analysis of PD to identify relationships among VH, SCC, and CI. Other strengths were the comparison with a control group, the exhaustive assessments at both visits of many variables, the inclusion of SB, and consistent results in the binary model after adjusting for many covariates, even including the PD-CRS total score at baseline that explained about 40% of the variance.

In conclusion, VH and SCC were frequent in patients with PD with normal objective cognition, both symptoms were interrelated, and together they significantly increased the short-term CI risk. Asking about VH and SCC could be useful in clinical practice.

Supplementary Materials

The online-only Data Supplement is available with this article at https://doi.org/10.3988/jcn.2022.0186.

Availability of Data and Material

The datasets generated or analyzed during the study are available from the corresponding author on reasonable request.

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Conflicts of Interest

Santos-García D. has received honoraria for educational presentations and advice service by Abbvie, UCB Pharma, Lundbeck, KRKA, Zambon, Bial, Italfarmaco, and Teva.
Cores Bartolomé C. has received honoraria for educational presentations and advice service by Lundbeck and UCB Pharma.
Jesús S. has received honoraria from AbbVie, Bial, Merz, UCB, and Zambon and holds the competitive contract "Juan Rodés" supported by the Instituto de Salud Carlos III. She has received grants from the Spanish Ministry of Economy and Competitiveness (PI18/01898) and the Consejería de Salud de la Junta de Andalucía (PI-0459-2018).
Aguilar M.: UCB and Schwabe with assistance to a Congress; Nutricia with assistance to a Congress and payment of lecture.
García Caldentey J. has received honoraria for educational presentations and advice service by Qualigen, Nutricia, Abbvie, Italfarmaco, UCB Pharma, Lundbeck, Zambon, Bial, and Teva.
Caballol N. has received honoraria from Bial, Italfármaco, Qualigen, Zambon, UCB, Teva and KRKA and sponsorship from Zambon, TEVA and Abbvie for attending medical confer-ences.
Legarda I. has received honoraria for educational presentations and advice service by Abbvie, UCB Pharma, Zambon, Bial, and Teva.
Hernández Vara J. has received travel bursaries and educational grants from Abbvie and has received honoraria for educational presentations from Abbvie, Teva, Bial, Zambon, Italfar-maco, and Sanofi-Genzyme.
Cabo I. has received honoraria for educational presentations and advice service by Abbvie, Zambon, and Bial.
López Manzanares L.: Compensated advisory services, consulting, research grant support, or speaker honoraria: AbbVie, Acorda, Bial, Intec Pharma, Italfarmaco, Pfizer, Roche, Teva, UCB, and Zambon.
Ávila Rivera MA. has received honoraria from Zambon, UCB Pharma, Qualigen, Bial, and Teva, and sponsorship from Zambon and Teva for attending conferences.
Puente V. has served as consultant for Abbvie and Zambon; has received grant/research from Abbvie.
Dotor García-Soto J.: Compensated advisory services, consulting, research grant support, or speaker honoraria: Merck, Sanofi-Genzyme, Allergan, Biogen, Roche, UCB and Novartis.
Solano Vila B. has received honoraria for educational presentations and advice service by UCB, Zambon, Teva, Abbvie, Bial.
Álvarez Sauco M. has received honoraria for educational presentations and advice service by Abbvie, UCB Pharma, Zambon, Bial, and Teva.
Vela L. has received honoraria for educational presentations and advice service by Abbvie, UCB Pharma, Lundbeck, KRKA, Zambon, Bial, and Teva.
Escalante S. has received honoraria for educational presentations and advice service by Abbvie, Zambon, and Bial.
Cubo E.: Travel grants: Abbvie, Allergan, Boston; Lecturing honoraria: Abbvie, International Parkinson´s disease Movement Disorder Society.
Carrillo Padilla F. has received honoraria from Zambon (SEN Congress assistance).
Martínez Castrillo JC. has received research support from Lundbeck, Italfarmaco, Allergan, Zambon, Merz, and Abbvie. He has received speaking honoraria from AbbVie, Bial, Italfar-maco, Lundbeck, Krka, TEVA, UCB, Zambon, Allergan, Ipsen, and Merz.
Sánchez Alonso P. has received honoraria for educational presentations and advice service by Abbvie, UCB Pharma, Lundbeck, KRKA, Zambon, Bial, and Teva.
Alonso Losada M. G. has received honoraria for educational presentations and advice service by Zambon and Bial.
López Ariztegui N. has received honoraria for educational presentations and advice service by Abbvie, Italfarmaco, Zambon, and Bial.
Gastón I. has received research support from Abbvie and Zambon and has served as a con-sultant for Abbvie, Exelts, and Zambon.
Kulisevsky J.: (1) Consulting fees: Roche, Zambon; (2) Stock / allotment: No; (3) Patent roy-alties / licensing fees: No; (4) Honoraria (e.g. lecture fees): Zambon, Teva, Bial, UCB; (5) Fees for promotional materials: No; (6) Research funding: Roche, Zambon, Ciberned; Instituto de SaludCarlos III; FundacióLa Maratóde TV3; (7) Scholarship from corporation: No; (8) Corporate laboratory funding: No; (9) Others (e.g. trips, travel, or gifts): No.
Blázquez Estrada M. has received honoraria for educational presentations and advice service by Abbvie, Abbott, UCB Pharma, Allergan, Zambon, Bial, and Qualigen.
Seijo M. has received honoraria for educational services from KRKA, UCB, Zambon, Bial; travel grants from Daiichi and Roche.
Rúiz Martínez J. has received honoraria for educational presentations, attending medical con-ferences, and advice service by Abbvie, UCB Pharma, Zambon, Italfarmaco, Bial, and Teva.
Valero C. has received honoraria for educational services from Zambon, Abbvie and UCB.
Kurtis M. has received honoraria from Bial, the Spanish Neurology Society, and the Interna-tional and Movement Disorders Society.
de Fábregues O. has received honoraria for educational presentations and advice service by Bial, Zambon, Abbvie, KRKA, and Teva.
González Ardura J. has recieved honoraria for speking from italofarma, Krka, Genzyme, UCB, Esteve, Psyma iberica marketing research SL and Ferrer, course grant from Teva and travel grant from Merck.
López Díaz L. M. has received honoraria from UCB, Lundbeck, and KRKA.
Martinez-Martin P. has received honoraria from National School of Public Health (ISCIII), Editori-al Viguera and Takeda Pharmaceuticals for lecturing in courses, and from the Interna-tional Parkinson and Move-

ment Disorder Society (MDS) for management of the Program on Rating Scales.
Mir P. has received honoraria from AbbVie, Abbott, Allergan, Bial, Merz, UCB, and Zambon and have received grants from the Spanish Ministry of Economy and Competitiveness [PI16/01575] co-founded by ISCIII (Subdirección General de Evaluación y Fomento de la Investigación) and by Fondo Europeo de Desarrollo Regional (FEDER), the Consejería de Economía, Innovación, Ciencia y Empleo de la Junta de Andalucía [CVI-02526, CTS-7685], the Consejería de Salud y Bienestar Social de la Junta de Andalucía [PI-0437-2012, PI-0471-2013], the Sociedad Andaluza de Neurología, the Jacques and Gloria Gossweiler Foundation, the Fundación Alicia Koplowitz, the Fundación Mutua Madrileña..

Funding Statement

The resources obtained for the development of this project have been obtained by the Degen Foundation (https://fundaciondegen.org/). A part of the Project is financed with grants from the Spanish Ministry of Economy and Competitiveness [PI16/01575] co-founded by ISCIII (Concesión de subvenciones de Proyectos de Investigación en Salud de la convocatoria 2020 de la Acción Estratégica en Salud 2017-2020 por el proyecto "PROGRESIÓN NO MOTORA E IMPACTO EN LA CALIDAD DE VIDA EN LA ENFERMEDAD DE PARKINSON").

Acknowledgements

We would like to thank all patients and their caregivers who collaborated in this study. Many thanks also to Fundación Española de Ayuda a la Investigación en Parkinson y otras Enfermedades Neurodegenerativas (Curemos el Parkinson; www.curemoselparkinson.org), Alpha Bioresearch (www.alphabioresearch.com), and other institutions helping us.

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