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

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

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Abstract

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

- Gangguan kognitif (CI) adalah salah satu gejala non motor terpenting yang dapat muncul pada pasien dengan penyakit Parkinson (PD). Spektrum penuh kognisi muncul pada individu dengan PD, mulai dari kognisi normal (NC) hingga gangguan kognitif ringan (MCI) hingga demensia penyakit Parkinson (PDD).
- Visual halusinasi (VH) adalah gejala umum pada PD yang mempengaruhi hingga 45% pasien tanpa demensia dan 65% pasien parkinson. VH merupakan prediktor kuat penurunan kognitif, serta peningkatan mortalitas dan penurunan kualitas hidup (QoL) untuk pasien.
- Keluhan kognitif subyektif (SCC) baru-baru ini disarankan untuk menjadi prediktor independen perkembangan gangguan kognitif ringan pada pasien parkinson dengan kognisi normal. SCC adalah identifikasi subjektif dari penurunan kognitif pada orang yang mungkin atau mungkin tidak memiliki gangguan yang terdeteksi dalam tes neuropsikologis.
- Prevalensi Keluhan kognitif subyektif (SCC) pada penyakit parkinson dilaporkan bervarjasi dari 30% hingga 60%, dan hingga 70%

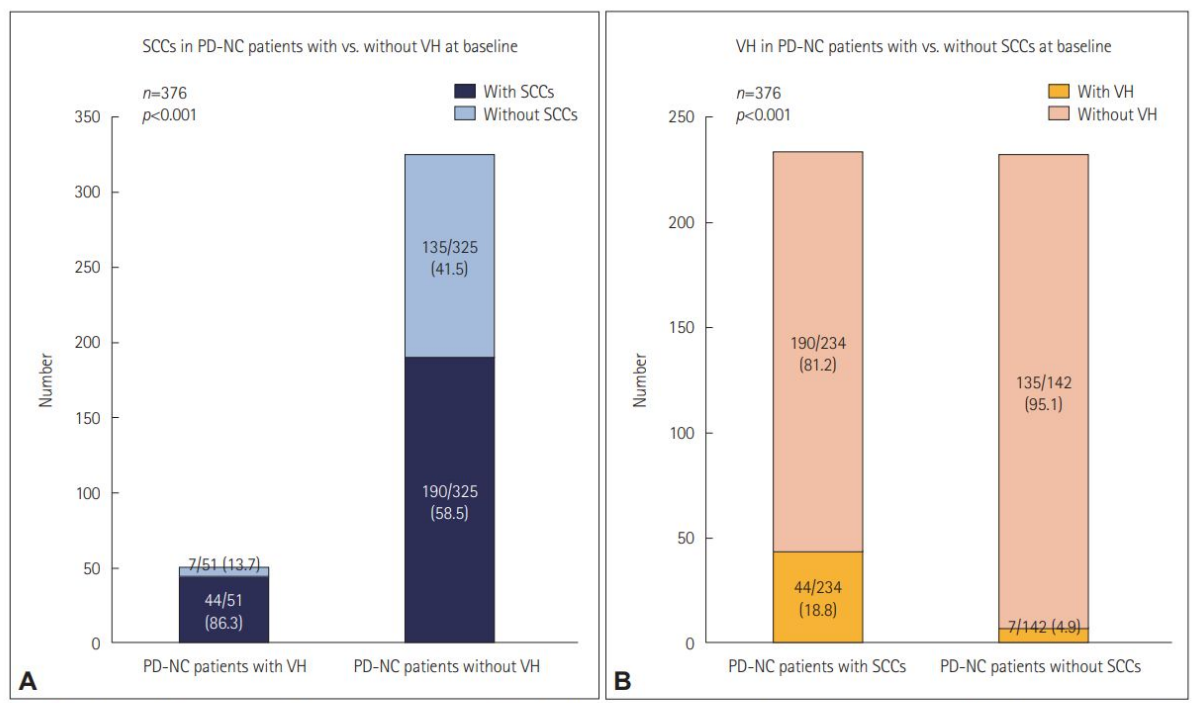
- Hubungan antara Keluhan kognitif subyektif, visual halusinasi, dan gangguan kognitif tidak diketahui, dan tidak jelas bagaimana VH dan keluhan kognitif subjektif berkontribusi terhadap perkembangan gangguan kognitif pada pasien parkinson.
- Hipotesis:
    - Prevalensi VH lebih tinggi pada pasien parkinson kognisi normal dengan keluhan kognitif subjektif dibandingkan dengan pasien yang tidak memiliki keluhan kognitif subjektif
    - VH dan SCC dapat meningkatkan risiko perkembangan gangguan kognitif pada pasien parkinson
- Tujuan : untuk menentukan hubungan antara fungsi kognitif dan faktor yang terkait dengan visual halusinasi dan risiko perkembangan gangguan koginitif pada 2 tahun tindak lanjut.

METHODS

- Pasien yang didiagnosis dengan PD dari Januari 2016 hingga November 2017, data diambil dari COPPADIS (COhort of Patients with PArkinson's DIsease in Spain) untuk dimasukkan dalam penelitian dan dievaluasi lagi pada tindak lanjut 2 tahun di 35 pusat di Spanyol.
- Evaluasi yang dilakukan pada V0 (baseline) dan V2 (2 tahun tindak lanjut)
- Status kognitif pada V0 dan V2 ini dinilai menggunakan PD-CRS (Parkinson Diseases Cognitive Rating Scale) dan total skor akhir akan klasifikasikan menjadi PD-NC: skor >80 dan PD dengan gangguan kognitif: skor <81
- Halusinasi visual dan keluhan kognitif subjektif dinilai menggunakan NMSS (Non-Motor Symptom Scale)

Data diolah menggunakan perangkat lunak SPSS (versi 20.0 for Windows, IBM Corp, Armonk, NY, USA). Perbandingan antara pasien dan kontrol dan antara pasien dengan dan tanpa VH dan/atau SCC dilakukan dengan menggunakan uji T, uji Mann-Whitney U, uji chi-square, atau uji Fisher yang sesuai

RESULTS



Total sampel yang digunakan dalam bentuk grafik tabel.

- Dikelompokkan menjadi 2: pasien PD-NC dengan VH dan PD-NC dengan SCC
- Pasien PD-NC dengan visual halusinasi tanpa keluhan kognitif subjektif sebanyak 86,3% (44/51)
- Pasien PD-NC dengan keluhan kognitif subjektif tanpa visual halusinasi sebanyak 81,2% (190/234)

	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

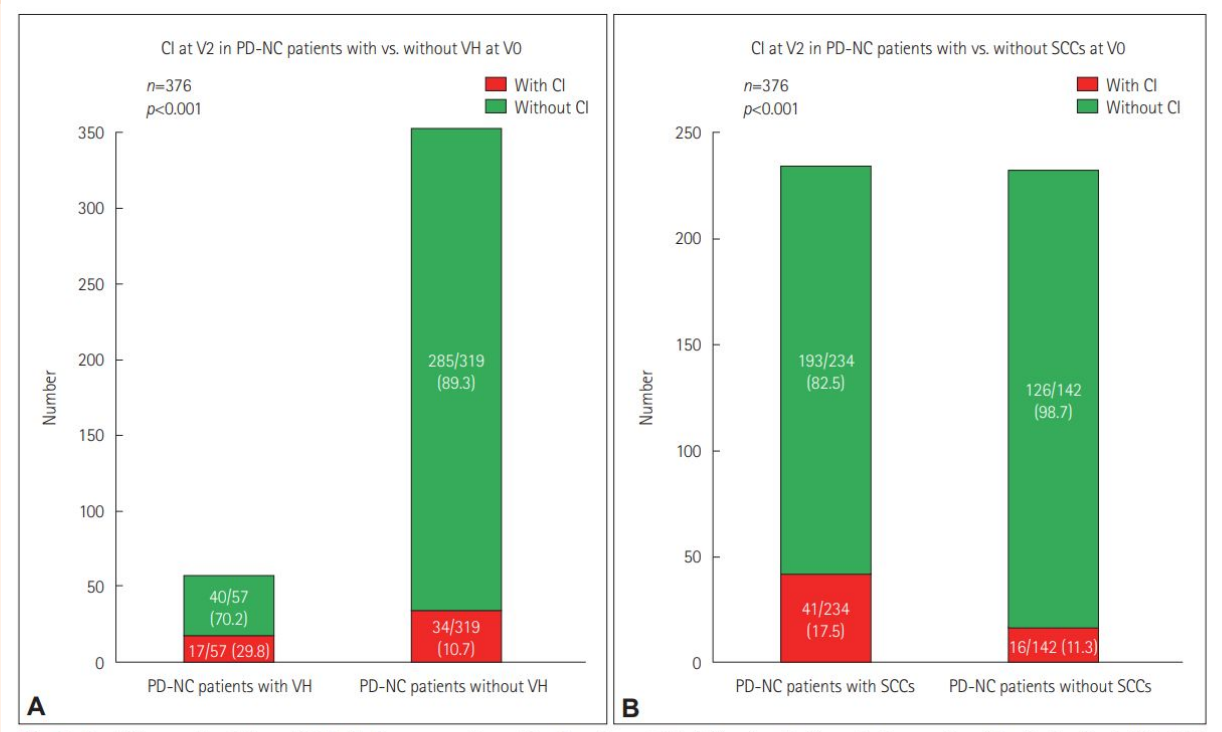
Tabel 1. Karakteristik terkait penyakit, gejala motorik dan non motorik, kemandirian dalam melakukan aktivitas kehidupan sehari-hari, dan kualitas hidup pada pasien dengan PD-NC (didefinisikan sebagai skor total pada PD-CRS >80) dengan dan tanpa VH pada awal (n=376)

	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

Tabel 2. Karakteristik terkait penyakit, gejala motorik dan non motorik, kemandirian dalam melakukan aktivitas hidup sehari-hari, dan kualitas hidup pada pasien dengan PD dengan dan tanpa SCC pada awal.

	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	$p^{\dagger}$	$p^{\dagger}$	$p^{\S}$
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.

Tabel 3. Perubahan kognisi pada pasien PD-NC dengan vs tanpa VH pada V0 (baseline) dari V0 ke V2 (follow-up 2 tahun, plus atau minus 1 bulan)



Gambar 2. Perubahan kognitif pada V2 mengenai VH dan SCC. A: Frekuensi gangguan kognitif (CI, didefinisikan sebagai Skala Peringkat Kognitif Penyakit Parkinson [PD-CRS] skor total <81) pada pasien dengan penyakit Parkinson dengan kognisi normal (PD-NC) dengan vs tanpa halusinasi visual (VH) di tindak lanjut 2 tahun (V2). B: Frekuensi CI pada pasien dengan PD-NC dengan vs tanpa keluhan kognitif subjektif (SCC) di 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	$p^{\dagger}$	$p^{\ddagger}$	$p^{\S}$
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.

Tabel 4. Perubahan kognisi pada pasien PD-NC dengan vs tanpa SCC dari V0 menjadi V2

	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.

Tabel 5. Analisis risiko perbaikan kognitif (didefinisikan sebagai skor total PD-CRS <81) pada tindak lanjut 2 tahun terkait dengan VH dan/atau SCC pada pasien dengan PD-NC (n=376)

DISCUSSION

- Studi ini menemukan bahwa VH dan SCC sering terjadi pada pasien dengan PD tanpa CI, masing-masing mempengaruhi sekitar satu dari tujuh dan lebih dari separuh pasien
- Studi ini juga didapatkan bahwa tidak ada faktor lain seperti usia, jenis kelamin, durasi penyakit yang berhubungan dengan VH dan SCC
- Sebuah studi baru-baru ini menemukan bahwa 34 dari 154 (22%) pasien yang baru didiagnosis dengan PD melaporkan VH, dengan VH minor yang paling umum. Prevalensi VH dalam jurnal ini adalah 13,6% pada awal dan 17,6% pada follow-up 2 tahun.
- Hubungan antara VH dan SCC, dan menemukan bahwa VH empat kali lebih sering terjadi pada pasien dengan PD-NC dan SCC dibandingkan dengan pasien tanpa SCC. Sejalan dengan temuan kami, Bejr-Kasem et al. mengamati 131 pasien de novo dengan PD dari Parkinson's Progression Marker Initiative, dan menemukan bahwa 35,1% pasien mengalami halusinasi minor selama 5 tahun pertama masa tindak lanjut

LIMITATIONS

Penelitian ini memiliki beberapa keterbatasan. Pertama, seperti yang ditunjukkan di atas, analisis post-hoc dilakukan di mana VH dan SCC dipertimbangkan berdasarkan jawaban atas pertanyaan dari NMSS (ya/tidak) mengacu pada 4 minggu sebelum penilaian, dan penilaian lengkap tentang gejala dan alat khusus tidak dilakukan. Kedua, bias seleksi mungkin ada karena penelitian ini melibatkan populasi pasien yang cenderung memiliki PD dini hingga sedang.

CONCLUSIONS

Kesimpulannya, VH dan SCC sering terjadi pada pasien dengan PD dengan kognisi objektif normal, kedua gejala tersebut saling terkait, dan bersama-sama secara signifikan meningkatkan jangka pendek risiko CI. Menanyakan tentang VH dan SCC dapat bermanfaat dalam praktik klinis.

Dalam praktik klinis, akan sangat berguna dan sangat mudah untuk pertama-tama bertanya kepada pasien dengan PD-NC tentang VH dan kemudian SCC. Jika kedua gejala tersebut ada, perlu dipertimbangkan bahwa itu tinggi jangka pendek risiko perkembangan CI dapat muncul secara independen dari usia, durasi penyakit, atau bahkan fungsi kognitif objektif.

ANALISIS PICO

- Population: pasien dengan penyakit parkinson dengan kognitif normal (PD-CRS → skor >80) pada Januri 2016 - November 2017 dengan follow up 2 tahun setelahnya.
- Intervention: gejala halusinasi visual dan keluhan kognitif subjektif pada pasien parkinson dengan kognitif normal, lalu di evaluasi kembali pada 2 tahun setelahnya
- Comparison: subjek dilakukan identifikasi pada awal penelitian, lalu setelah 2 tahun dilakukan tindak lanjut kembali.
- Outcome: VH dan SCC sering terjadi pada pasien dengan PD dengan kognisi objektif normal, kedua gejala tersebut saling terkait, dan bersama-sama secara signifikan meningkatkan jangka pendek risiko gangguan kognitif

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Terima Kasih!