

**EVOLUCIÓN Y PRONÓSTICO DEL DETERIORO COGNITIVO
INCIPIENTE EN ENFERMEDAD DE PARKINSON**

Jon Rodríguez-Antigüedad Muñoz

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TESIS DOCTORAL

**EVOLUCIÓN Y PRONÓSTICO DEL DETERIORO COGNITIVO
INCIPIENTE EN ENFERMEDAD DE PARKINSON**

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A la ama, al aita, y a Imanol

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ABREVIATURAS

A β 42	Beta-amiloide ₁₋₄₂
α -syn	Alfa-sinucleina
AMS	Atrofia multisistémica
COPPADIS	COhort of Patients with PArkinson's Disease in Spain
CSF	Cerebrospinal fluid
D-EP	Demencia en EP
DC-EP	Deterioro cognitivo en EP
DCL-EP	Deterioro cognitivo leve en EP
DCS-EP	Deterioro cognitivo subjetivo en EP
EA	Enfermedad de Alzheimer
ECL	Enfermedad por cuerpos de Lewy
EP	Enfermedad de Parkinson
FAP	Fallo autonómico primario
GWAS	Genome wide association study
IACE	Inhibidor de la acetilcolinesterasa
ICOMT	Inhibidor de la catecol-O-metiltransferasa
IMAO-B	Inhibidor de la monoamino-oxidasa B
LCR	Líquido cefalorraquídeo
MDRS-2	Mattis Dementia Rating Scale Second Edition
MDS	Movement Disorders Society
MDS-NMS	MDS-Non Motor rating Scale
MDS-UPDRS	MDS-Unified Parkinson's Disease Rating Scale
MIBG	Metayodobenzilguanidina
MLEM	Modelo lineal de efectos mixtos
MoCA	Montreal Cognitive Assessment
NfL	Neurofilamento de cadena ligera
NIA-AA	National Institute on Aging-Alzheimer's Association
NMDA	N-metil-D-aspartato
NMSS	Non-Motor Symptom Scale

p-tau	Tau fosforilada
PD	Parkinson's disease
PD-CI	PD associated cognitive impairment
PD-CRS	Parkinson's Disease-Cognitive Rating Scale
PD-SCD	PD associated subjective cognitive decline
PET	Positron emission tomography
PPMI	Parkinson's Progression Markers Initiative
RCI	Reliable change index
SNM	Síntomas no motores
SPECT	Single photon emission computed tomography
TCI	Trastorno del control de impulsos
TCSR	Trastorno de conducta del sueño REM
t-tau	Tau total

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RESUMEN

La Enfermedad de Parkinson (EP) es la segunda enfermedad neurodegenerativa más frecuente y se manifiesta entre los 50-70 años en forma de bradicinesia, temblor, rigidez, inestabilidad postural, y una gran variedad de síntomas no motores acompañantes. A medida que la enfermedad avanza, los síntomas no motores acaban convirtiéndose en el principal motivo de pérdida de calidad de vida. Entre estos síntomas, el deterioro cognitivo (DC-EP) es uno de los más discapacitantes incluso desde etapas iniciales. No existe ningún tratamiento capaz de modificar el curso del DC-EP y el tratamiento sintomático está limitado a la rivastigmina. Por este motivo, en la última década los estudios se han centrado en explorar las fases prodrómicas del DC-EP, en la que existen quejas cognitivas referidas por el paciente sin una alteración objetiva en las pruebas neuropsicológicas. Esta fase, también llamada deterioro cognitivo subjetivo (DCS-EP), se ha asociado en términos globales a un mayor riesgo de DC-EP futuro. Sin embargo, algunos estudios concretos no han sido capaces de detectar este riesgo, lo que sugiere una evolución heterogénea entre pacientes.

Los principales objetivos de este trabajo eran identificar diferentes patrones de evolución cognitiva en pacientes con DCS-EP, así como identificar marcadores clínicos y biológicos asociados a un riesgo aumentado de DC-EP en este grupo de pacientes. Para ello se analizaron dos grandes cohortes de EP: la cohorte nacional española COhort of Patients with PARKinson's Disease in Spain (COPPADIS) y la cohorte internacional Parkinson's Progression Markers Initiative (PPMI).

En el primer artículo con la cohorte COPPADIS identificamos dos patrones de progresión cognitiva diferentes (progresores y no progresores con curso estable) con patrones de progresión motora similares. Los marcadores clínicos asociados al grupo de progresión fueron la edad, la severidad motora y el trastorno de conducta del sueño REM. El segundo artículo con la cohorte PPMI complementa al primero mediante la identificación de marcadores biológicos en líquido cefalorraquídeo (LCR) asociados a una peor progresión cognitiva. Pacientes con niveles bajos de beta-amiloide₁₋₄₂ (A β 42) y con perfil

de enfermedad de Alzheimer en LCR en la visita basal mostraron una peor progresión cognitiva con respecto a aquellos con niveles normales de A β 42.

Mediante este trabajo de dos artículos hemos identificado nuevos biomarcadores pronósticos en el DCS-EP. Estos estudios aportan una contribución relevante y novedosa dentro del área específica del DCS-EP, un campo hasta ahora muy poco explorado en la literatura. La identificación de subgrupos de pacientes con diferentes riesgos de progresión cognitiva, y la asociación de biomarcadores tipo EA con una peor evolución, representan hallazgos innovadores que refuerzan la importancia de la identificación temprana del DCS-EP. Poder clasificar a estos pacientes según su riesgo de deterioro cognitivo no solo permitirá optimizar el consejo clínico, sino que abre la puerta al diseño de ensayos clínicos específicos y dirigidos tanto a fases prodrómicas de la EP como a las fases más tempranas del DC-EP en la enfermedad clínicamente manifiesta.

ABSTRACT

Parkinson's disease (PD) is the second most common neurodegenerative disorder, typically manifesting between the ages of 50-70 with bradykinesia, tremor, rigidity, postural instability, and a variety of non-motor symptoms. As the disease progresses, non-motor symptoms often become the main determinant of reduced quality of life. Cognitive impairment (PD-CI) is one of the most disabling non-motor symptoms, even from the early stages. Currently, there are no disease modifying treatments for PD-CI, and symptomatic therapy is limited to rivastigmine. For this reason, in the past decade research has increasingly focused on the prodromal phase of PD-CI, in which patients report cognitive complaints without objective impairment on neuropsychological testing. This stage, also referred to as subjective cognitive decline (PD-SCD) has globally been associated with an increased risk of future PD-CI. However, some studies have failed to confirm this risk, suggesting a heterogeneous course across patients.

The main objectives of this work were to identify different patterns of cognitive trajectories in patients with PD-SCD, and to determine clinical and biological markers associated with an increased risk of PD-CI in this population. To this end, we analyzed two large PD cohorts: the Spanish nationwide COhort of Patients with PArkinson's Disease in Spain (COPPADIS) and the international Parkinson's Progression Markers Initiative (PPMI).

In the first paper, using the COPPADIS cohort, we identified two distinct patterns of cognitive progression (progressors and non-progressors) despite similar motor progression. Clinical markers associated with progression included age, motor severity, and REM sleep behavior disorder. The second paper, based on the PPMI cohort, complemented these findings by identifying cerebrospinal fluid (CSF) biomarkers linked to worse cognitive outcomes. Patients with low levels of beta-amyloid₁₋₄₂ (A β 42) and an Alzheimer's disease CSF profile showed more rapid cognitive decline compared to those with normal A β 42 levels.

Through this two-part work, we identified novel prognostic biomarkers in PD-SCD. These studies make a significant and novel contribution to the specific field of PD-SCD, which has been largely unexplored in the literature. The identification of patient subgroups with different risks of cognitive progression, along with the association of Alzheimer's disease biomarkers with worse outcomes, represents an innovative finding that underscores the importance of early detection of PD-SCD. Stratifying PD-SCD patients into higher- or lower-risk groups for cognitive progression will not only optimize clinical guidance but also pave the way for the design of targeted clinical trials, both for prodromal stages of PD and the earliest phases of PD-CI in clinically established disease.

1. INTRODUCCIÓN

1.1. ENFERMEDAD DE PARKINSON

La enfermedad de Parkinson (EP) es la segunda enfermedad neurodegenerativa más frecuente después de la enfermedad de Alzheimer (EA), con más de seis millones de afectados en todo el mundo y una incidencia al alza por razones no bien conocidas (1). Por ello, se espera que su impacto social y económico aumente considerablemente en los próximos años (2,3).

La EP ha evolucionado desde una visión clásica de enfermedad puramente motora, a una condición más compleja caracterizada por la presencia de síntomas motores y no motores (SNM) (4). Los síntomas motores abarcan la bradicinesia, rigidez, temblor de reposo, e inestabilidad postural, como síntomas cardinales, además de otros como la congelación de la marcha, fluctuaciones motoras, o discinesias, que aparecen en fases más avanzadas (5). Los SNM incluyen hiposmia, deterioro cognitivo, síntomas neuropsiquiátricos (psicosis, depresión, ansiedad, apatía, trastorno del control de impulsos (TCI)), disautonomía (estreñimiento, hipotensión ortostática, urgencia miccional), trastornos del sueño (trastorno de conducta del sueño REM (TCSR), insomnio, somnolencia excesiva diurna), sialorrea, dolor, o fatiga, entre otros (5).

Igualmente, mientras que clásicamente se la concebía como una enfermedad que afectaba de forma aislada a la vía nigroestriada dopaminérgica, hoy sabemos que hay otros sistemas de neurotransmisión y redes neuronales implicadas, que tienen como consecuencia esta gran variedad de síntomas. Sin embargo, más de 200 años tras la primera descripción clínica de la enfermedad, y a pesar de los avances en torno a su fisiopatología, no existe una teoría patogénica unificada que explique la EP.

1.2. FISIOPATOLOGÍA

Desde el descubrimiento de la alfa-sinucleína (α -syn) como hallazgo patológico característico en las neuronas de pacientes con EP, esta enfermedad ha sido considerada una sinucleinopatía primaria (6). Bajo esta etiqueta se engloban la EP, la enfermedad por cuerpos de Lewy (ECL), la atrofia multisistémica (AMS) y el fallo autonómico primario (FAP). Estas enfermedades se caracterizan por el acúmulo predominante de α -syn en neuronas (EP y ECL), oligodendrocitos (AMS), y sistema nervioso simpático (FAP) (7–9). En torno a esta idea con una base anatomopatológica, la mayor parte de la investigación se ha centrado en demostrar como principal mecanismo patogénico la acumulación tóxica de α -syn (10). Sin embargo, en la actualidad conocemos múltiples factores de riesgo, hallazgos patológicos, y diferentes mecanismos moleculares implicados en la EP, que sugieren una mayor complejidad fisiopatológica.

La edad avanzada, el sexo biológico masculino, factores ambientales, y determinadas variantes genéticas, especialmente en el gen *GBA*, se consideran los principales factores de riesgo de EP (11,12).

Los principales hallazgos anatomopatológicos son la neurodegeneración y la patología Lewy. La degeneración afecta no solo a neuronas dopaminérgicas de la sustancia negra, sino también al sistema serotoninérgico, noradrenérgico o colinérgico, y a estructuras/redes que se extienden más allá de la vía nigroestriada (13,14). Los cuerpos y neuritas de Lewy son inclusiones neuronales de α -syn fibrilar, junto con acúmulos de membranas, vesículas, orgánulos dismórficos, y proteínas, entre otros (6,14,15). Aunque ambos hallazgos patológicos son necesarios para el diagnóstico definitivo, ninguno es exclusivo de la EP (4). Las teorías clásicas proponen una propagación interneuronal de la patología Lewy que se inicia en la periferia o en el propio cerebro, mientras que propuestas recientes sugieren la posibilidad de un desarrollo de carácter multicéntrico (16–18).

Se han descrito una gran variedad de mecanismos moleculares que interconectan los factores de riesgo con los hallazgos anatomopatológicos típicos: agregación patológica de α -syn, disfunción mitocondrial, estrés oxidativo, disfunción lisosomal, neuroinflamación, dishomeostasis del calcio, disfunción de vesículas sinápticas, o toxicidad de la dopamina (**Figura 1**) (4). Qué mecanismo/s inicia/n o perpetúa/n la enfermedad es una incógnita.

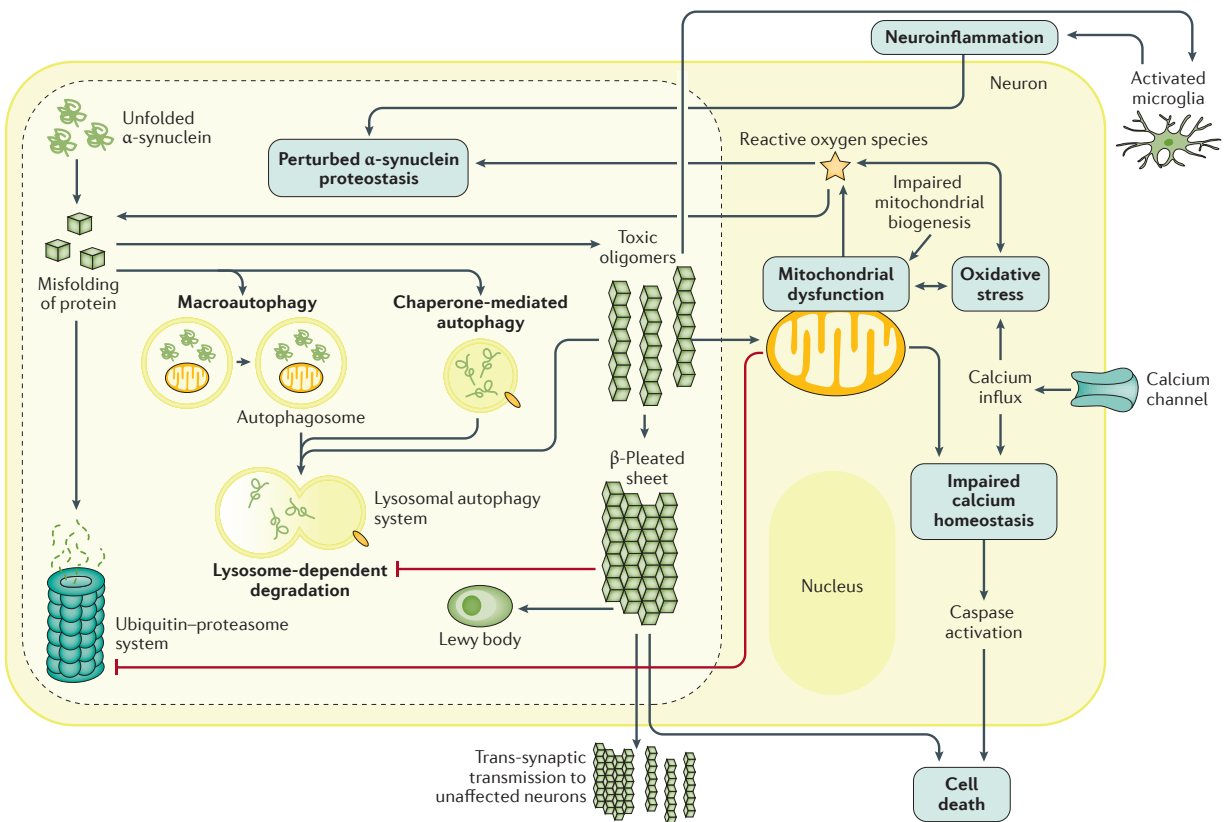


Figura 1. Mecanismos moleculares implicados en la EP (4).

Todo el desconocimiento descrito en torno a la fisiopatología de la EP es una de las principales razones por la que las herramientas diagnósticas y las opciones terapéuticas siguen siendo muy limitadas.

1.3. DIAGNÓSTICO

Los criterios diagnósticos vigentes de EP *in vivo* son esencialmente clínicos, apoyado en pruebas complementarias puntuales como el Single Photon Emission Computed Tomography (SPECT) del transportador de dopamina o la gammagrafía cardiaca con metayodobenzilguanidina (MIBG) (19). En concreto, estos criterios exigen un diagnóstico sindrómico de parkinsonismo, y establecen criterios de apoyo, banderas rojas y criterios de exclusión, mediante los cuales llegar con mayor o menor grado de confianza al diagnóstico de EP *clínicamente establecida* o EP *clínicamente probable*, respectivamente. Estos criterios no exigen la realización de otras pruebas complementarias, pero en la práctica clínica es frecuente apoyarse, entre otras, en la neuroimagen estructural para descartar causas alternativas de parkinsonismo, análisis genético en casos de inicio precoz o con historia familiar para detectar formas mendelianas o variantes de riesgo, u otras pruebas que nos ayuden a orientar con mayor precisión el diagnóstico (5).

Aunque dos estudios recientes han evidenciado una mejora del 80.6% al 97.2% en la precisión diagnóstica de EP con los nuevos criterios, esta percepción no parece trasladable a la práctica clínica (20,21). A esto se le suma el reto de diagnosticar la enfermedad en su fase prodrómica, durante la cual pueden aparecer SNM en ausencia de síntomas motores evidentes (22). Esta fase puede preceder en hasta 10-20 años a la fase motora y se caracteriza por síntomas como TCSR, hiposmia, disautonomía, depresión o ansiedad (22–24). La inespecificidad de estos síntomas así como su solapamiento con la fase prodrómica de otras sinucleinopatías dificulta aún más el diagnóstico precoz (25,26).

En los últimos años se ha avanzado considerablemente en la identificación de biomarcadores diagnósticos y pronósticos de EP. Entre ellos, destacan biomarcadores moleculares como α -syn, beta-amiloide₁₋₄₂ (A β 42), tau total (t-tau), tau fosforilada (p-tau), y neurofilamento de cadena ligera (NfL), que han sido estudiados principalmente en líquido cefalorraquídeo (LCR) por su proximidad al sistema nervioso central. En términos

generales, los pacientes con EP suelen mostrar un declive progresivo en los niveles de α -syn y A β 42 en LCR a lo largo del tiempo, y un incremento progresivo de t-tau, p-tau, y NfL (27). El avance en el estudio de biomarcadores tanto en LCR como en otros tejidos y biofluidos será de gran importancia para mejorar la precisión diagnóstica y pronóstica actual.

1.4. TRATAMIENTO

Ningún fármaco ha demostrado claramente un cambio positivo en el curso natural de la EP. Los ensayos clínicos completados hasta el momento no han demostrado eficacia con inmunoterapia pasiva frente a α -syn (cinpanemab, prasinezumab, buntanetab), con inhibidores del malplegamiento de α -syn (minzasolmin), con inhibidores de la tirosin quinasa Abl (K0706), ni con quelantes de hierro (deferiprona) (28–30). Recientemente, un ensayo con lixisenatida (agonista glucagon-like peptide-1) ha sido el único en demostrar una mejor progresión motora con respecto a placebo, aunque la corta duración del ensayo no permite valorar adecuadamente el potencial efecto sobre la progresión natural de la enfermedad (31). Actualmente hay en marcha ensayos clínicos que utilizan fármacos con mecanismos de acción a diferentes niveles (*GBA*, *LRRK2*, α -syn): BIA 28-6156 (NCT05819359), con reclutamiento finalizado, o BIIB122 (NCT05348785) y ACI-7104.056 (NCT06015841), todavía en fase de reclutamiento. Sin embargo, el tratamiento a día de hoy continúa siendo puramente sintomático.

El tratamiento inicial de los síntomas motores se basa en el uso de terapias dopaminérgicas orales (**Figura 2**) (32). La levodopa es el principal fármaco, pero la aparición de fluctuaciones y discinesias a medida que la enfermedad avanza suele requerir un aumento de dosis o su combinación con agonistas dopaminérgicos, inhibidores de la monoamino-oxidasa B (IMAO-B), inhibidores de la catecol-O-metiltransferasa (COMT), o amantadina. Recientemente están surgiendo alternativas para un control a demanda de las fluctuaciones, como la levodopa inhalada o la apomorfina sublingual, que se añade a su versión homóloga subcutánea (33,34).

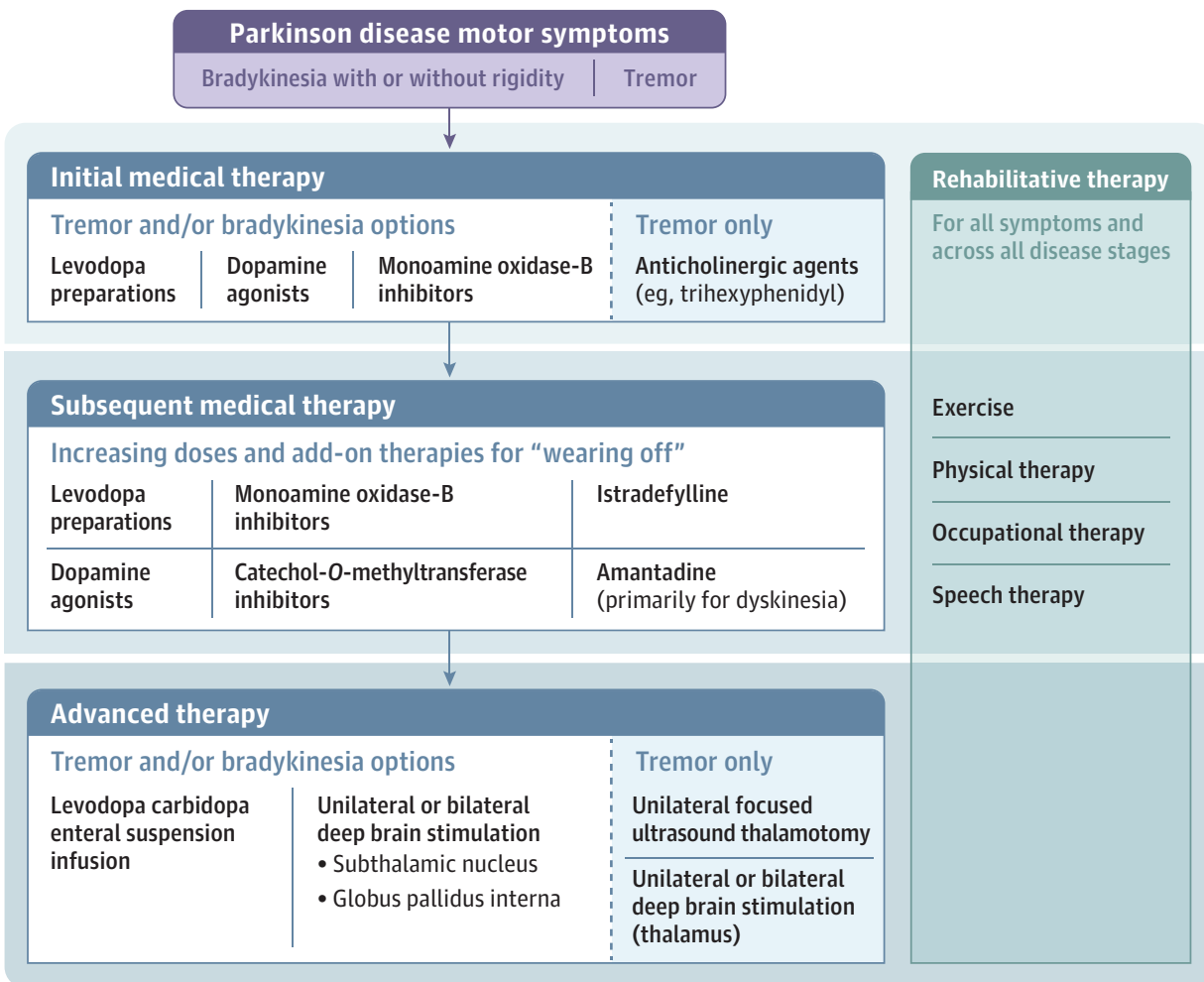


Figura 2. Algoritmo de tratamiento de síntomas motores de la EP (35).

En fases avanzadas con mal control de síntomas, se deben valorar terapias como la estimulación cerebral profunda o los ultrasonidos de alta frecuencia, en ambos casos con el núcleo subtalámico como objetivo principal (36,37). Estas terapias son eficaces sobre los síntomas motores apendiculares, mientras que no lo son tanto sobre los síntomas axiales y los SNM. En aquellos casos no candidatos a cirugía, se deben valorar otras terapias como la apomorfina subcutánea, la levodopa subcutánea, o la levodopa intrayeyunal (38).

Los SNM se han asociado a alteraciones en diferentes sistemas de neurotransmisión, incluidos no dopaminérgicos, por lo que su tratamiento sintomático es muy variado: estimulación cognitiva y/o inhibidores de la acetilcolinesterasa (IACEs) para del deterioro

cognitivo; reducción de la medicación dopaminérgica, IACEs, o neurolépticos para la psicosis; antidepresivos para la depresión y ansiedad; IACEs, dopaminérgicos o metilfenidato para la apatía; reducción de la medicación dopaminérgica o neurolépticos para el TCI; clonazepam o melatonina para TCSR; macrogol para el estreñimiento; toxina botulínica para la sialorrea; solifenacina y mirabregón para la disautonomía urinaria; o fludrocortisona y midrodrine para la hipotensión ortostática (39,40). Igualmente, abordar los SNM con medidas no farmacológicas como la estimulación cognitiva para el deterioro cognitivo, terapia cognitivo conductual para depresión, ansiedad, apatía o TCI, higiene del sueño para el TCSR, o dieta y medidas generales para el estreñimiento y la hipotensión ortostática, entre otros, es igual de importante o más que el abordaje farmacológico (39,40).

Por último, es imprescindible recomendar ejercicio y dieta sana a cualquier persona con EP ya que se han asociado a una mejor evolución de la enfermedad y a una menor mortalidad (41,42).

1.5. CURSO NATURAL DE LA EP

Los síntomas suelen comenzar años antes del inicio de los síntomas motores y del diagnóstico, en lo que conocemos como EP prodrómica (**Figura 3**). En esta fase, el proceso fisiopatológico ya ha comenzado y típicamente se manifiesta en forma de TCSR, hiposmia o estreñimiento (22). Existen criterios para el diagnóstico de EP prodrómica, aunque por el momento solo son aplicables al ámbito de la investigación (23).

Una vez comienzan los síntomas motores, ya podremos hacer un diagnóstico clínico de EP. Los síntomas motores comienzan en forma de bradicinesia, rigidez, temblor de reposo, o inestabilidad postural, típicamente asimétricos (5). Con el tiempo, la degeneración va progresando y los tratamientos orales son insuficientes para suplir la función neuronal perdida, dando lugar a la aparición de fluctuaciones motoras y discinesias. En las fases más avanzadas, la inestabilidad y los problemas de la marcha acaban por convertirse en los síntomas motores más discapacitantes (5).

Los SNM comienzan en muchas ocasiones antes que los síntomas motores, aunque suelen pasar desapercibidos, y van progresando junto con la degeneración. En las fases tardías de la enfermedad, estos SNM, especialmente los cognitivos y neuropsiquiátricos, acaban convirtiéndose en la principal causa de disminución de la calidad de vida tanto para pacientes como cuidadores (43).

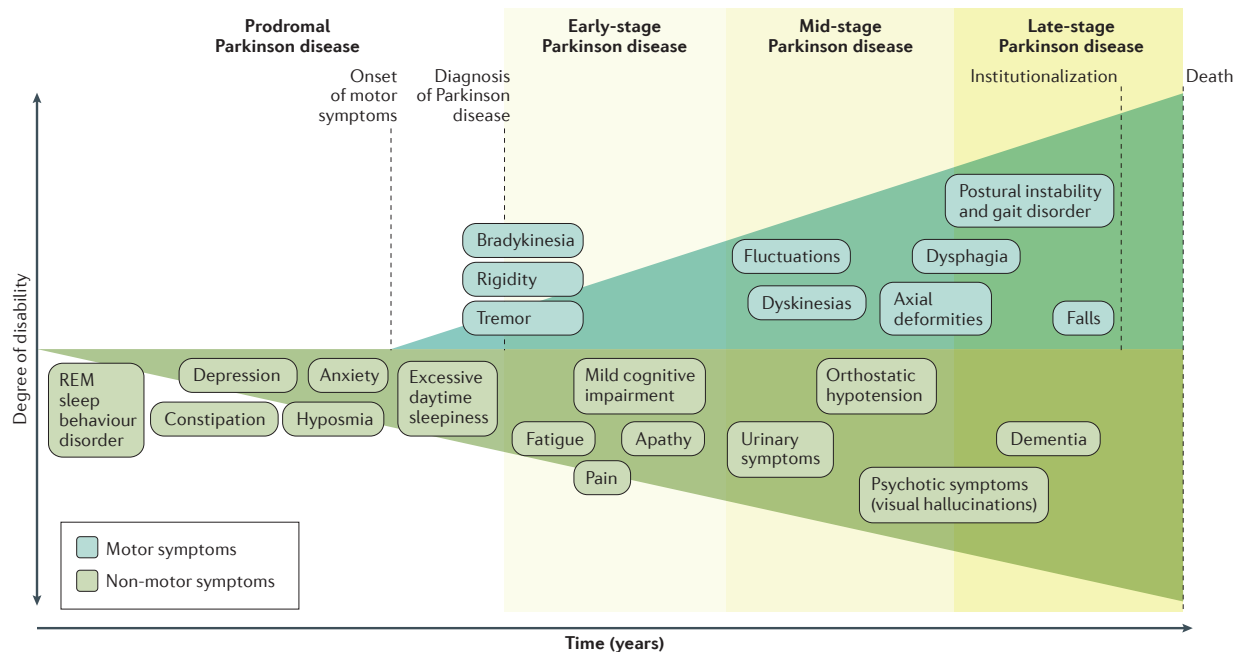


Figura 3. Evolución natural de la EP (4).

La velocidad de progresión de la EP es muy variable entre pacientes. Se estima una esperanza de vida de entre 6.9 y 14.3 años desde el diagnóstico, aunque los estudios son muy heterogéneos (44). La presencia de síntomas motores más severos, deterioro cognitivo, TCSR, disautonomía o mutaciones en el gen *GBA*, entre otros, parecen asociarse a formas más agresivas (45).

1.6. DETERIORO COGNITIVO ASOCIADO A EP

1.6.1. Espectro clínico y epidemiología del DC-EP

El deterioro cognitivo en la EP (DC-EP) es uno de los SNM más discapacitantes, afectando a la calidad de vida incluso desde estadíos iniciales, cuando los pacientes tienen el *insight* preservado, y son capaces de reconocer el síntoma y sentirse frustrados por el mismo (46).

El espectro clínico del DC-EP es un *continuum* que típicamente se divide en tres categorías (47):

- Deterioro cognitivo subjetivo (DCS-EP): Esta fase es la más precoz, en la que el paciente presenta quejas cognitivas que no se traducen en una disminución del rendimiento en la evaluación neuropsicológica (48). Se estima una prevalencia del 39% (48).
- Deterioro cognitivo leve (DCL-EP): En esta fase, los pacientes presentan un deterioro cognitivo objetivable en la evaluación neuropsicológica que no afecta a la independencia funcional (49). Se estima una prevalencia del 40% (50).
- Demencia (D-EP): La fase más avanzada, en la que el paciente presenta un deterioro cognitivo en grado moderado o severo que impide una completa independencia funcional (51). Se estima una prevalencia del 24-31% (52).

La presencia de DCS-EP y DCL-EP es frecuente en fases iniciales e incluso prodrómicas de enfermedad, mientras que la D-EP solo se ve en fases avanzadas, dado que una aparición precoz obligaría a pensar en la ECL (47). Aunque lo esperable es un deterioro progresivo de las capacidades cognitivas en todos los pacientes, la evolución natural puede ser muy heterogénea (**Figura 4**) (47). Tanto DCS-EP como DCL-EP son un factor de riesgo de DCL-EP y de D-EP, respectivamente, pero hay pacientes con una progresión muy rápida, así como pacientes estables que no se deterioran o que lo hacen lentamente (53,54). A los 10 años del diagnóstico se estima que al menos el 50% de los pacientes desarrollará D-EP (55).

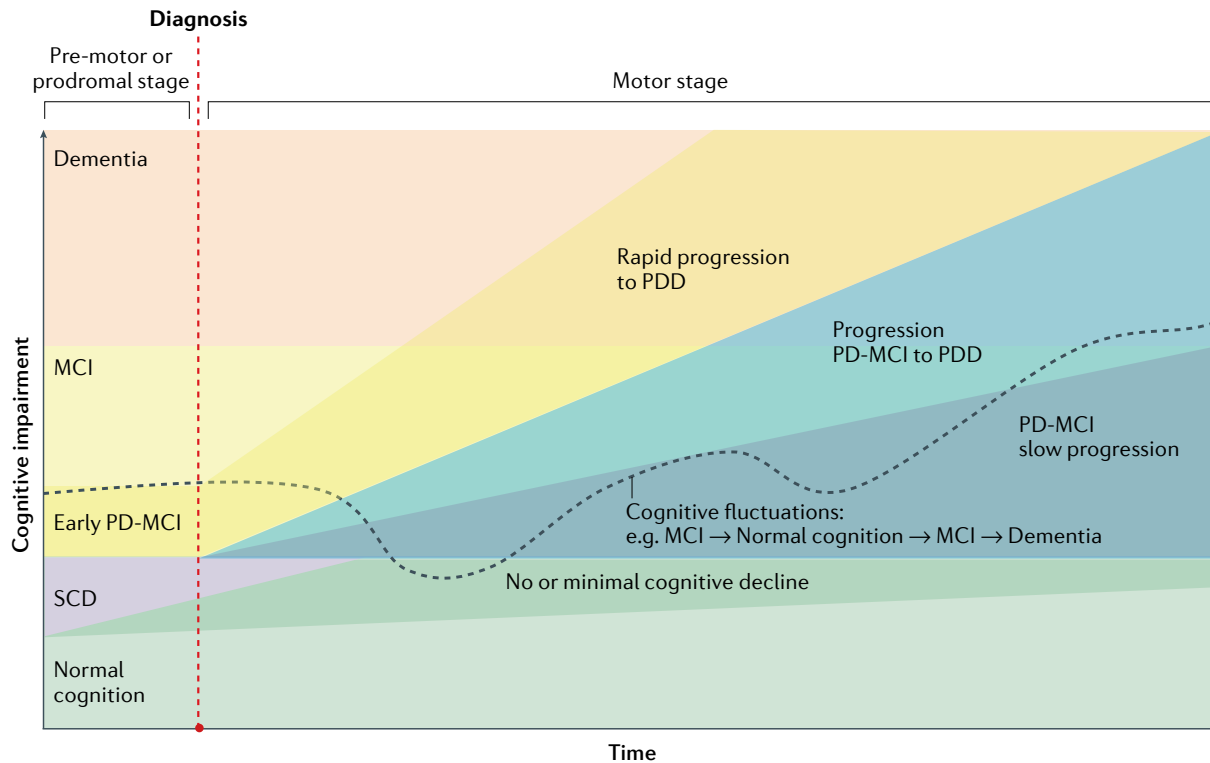


Figura 4. Evolución natural del DC-EP (47).

Es importante recalcar que estas etiquetas se basan en puntos de corte en las pruebas neuropsicológicas y tienen una función pragmática, pero no representan la realidad del DC-EP. En consecuencia, cada vez más estudios se apoyan en modelos que evalúan las trayectorias individuales, independientemente de la base de la que parta cada paciente.

1.6.2. Clínica y diagnóstico del DC-EP

El patrón neuropsicológico habitual del DCL-EP es predominantemente disejecutivo-frontal con alteración de velocidad de procesamiento, atención, memoria de trabajo, y/o planificación (56). Este perfil se atribuye al estado hipodopaminérgico del circuito asociativo que conecta el núcleo caudado dorsal con la corteza prefrontal dorso-lateral (57). Sin embargo, hasta el 40% de los pacientes con DCL-EP muestran alteraciones en otros dominios cognitivos (58). Alteraciones en dominios corticales como la memoria, el

lenguaje o el visuoespacial se han asociado a un mayor riesgo de progresión a demencia y conforman el perfil cognitivo habitual de la D-EP (51,59).

La Movement Disorders Society (MDS) ha establecido unos criterios clínicos que permiten homogeneizar el diagnóstico de DCL-EP y de D-EP (51,60). Los criterios clínicos para el diagnóstico de DCL-EP requieren un declive cognitivo observado por el paciente o el médico, la objetivación del deterioro cognitivo mediante una evaluación neuropsicológica, que este deterioro cognitivo no afecte a la independencia funcional del paciente, y la ausencia de otras condiciones que puedan explicar mejor los síntomas (**Tabla 1**) (60). Para la exploración neuropsicológica, estos criterios permiten utilizar una evaluación abreviada (Level I) con escalas globales como la Montreal Cognitive Assessment (MoCA), la Mattis Dementia Rating Scale Second Edition (MDRS-2) o la Parkinson's Disease-Cognitive Rating Scale (PD-CRS), o una evaluación más completa (Level II), que ofrece un diagnóstico más preciso mediante la realización de dos pruebas para cada uno de los cinco dominios cognitivos. Dentro de las escalas globales cabe destacar la PD-CRS, ya que es la única diseñada específicamente para la EP y su amplio rango permite evitar el efecto techo que puede aparecer con otras como el MoCA, que dificulta la valoración real de la progresión cognitiva (61,62). Debido a la amplia gama de pruebas neuropsicológicas para la evaluación de cada uno de los cinco dominios típicamente afectados en la EP, desde la MDS se han realizado dos revisiones recientes para establecer unas recomendaciones oficiales (**Tabla 2**) (63,64).

I. Inclusion criteria

- Diagnosis of Parkinson's disease as based on the UK PD Brain Bank Criteria
- Gradual decline, in the context of established PD, in cognitive ability reported by either the patient or informant, or observed by the clinician
- Cognitive deficits on either formal neuropsychological testing or a scale of global cognitive abilities (detailed in section III)
- Cognitive deficits are not sufficient to interfere significantly with functional independence, although subtle difficulties on complex functional tasks may be present

II. Exclusion criteria

- Diagnosis of PD dementia based on MDS Task Force proposed criteria¹⁸
 - Other primary explanations for cognitive impairment (e.g., delirium, stroke, major depression, metabolic abnormalities, adverse effects of medication, or head trauma)
-

- Other PD-associated comorbid conditions (e.g., motor impairment or severe anxiety, depression, excessive daytime sleepiness, or psychosis) that, in the opinion of the clinician, significantly influence cognitive testing

III. Specific guidelines for PD-MCI level I and level II categories

A. Level I (abbreviated assessment)

- Impairment on a scale of global cognitive abilities validated for use in PD or
- Impairment on at least two tests, when a limited battery of neuropsychological tests is performed (i.e., the battery includes less than two tests within each of the five cognitive domains, or less than five cognitive domains are assessed)

B. Level II (comprehensive assessment)

- Neuropsychological testing that includes two tests within each of the five cognitive domains (i.e., attention and working memory, executive, language, memory, and visuospatial)
- Impairment on at least two neuropsychological tests, represented by either two impaired tests in one cognitive domain or one impaired test in two different cognitive domains
- Impairment on neuropsychological tests may be demonstrated by:
 - o Performance approximately 1 to 2 SDs below appropriate norms or
 - o Significant decline demonstrated on serial cognitive testing or
 - o Significant decline from estimated premorbid levels

IV. Subtype classification for PD-MCI (optional, requires two tests for each of the five cognitive domains assessed and is strongly suggested for research purposes)

- PD-MCI single-domain—abnormalities on two tests within a single cognitive domain (specify the domain), with other domains unimpaired or
- PD-MCI multiple-domain—abnormalities on at least one test in two or more cognitive domains (specify the domains)

Tabla 1. Criterios clínicos para el diagnóstico de DCL-EP (60).

Abreviaciones: PD: Parkinson's disease; MDS: Movement Disorders Society; PD-MCI: PD-Mild Cognitive Impairment; SD: standard deviation

Atención/memoria de trabajo	Ejecutivo	Memoria	Lenguaje	Visuoespacial
	WAIS-IV Similarities	RAVLT		
WAIS-IV Digit Span/Coding/Symbol Search	Wisconsin Card Sorting Test	CVLT/CVLT-II/CVLT3 and PVL	BNT-60; BNT-30; BNT-15	WAIS-III/IV: Matrix Reasoning
TMT	Verbal Fluency Tests	HVLT/HVLT-R		
	Stroop Color-Word Test	RBMT/ RBMT II/RBMT III		

Tabla 2. Pruebas neuropsicológicas recomendadas para la evaluación de pacientes con EP. Adaptado de (63,64).

Abreviaciones: WAIS: Wechsler Adult Intelligence Scale; TMT: Trail-Making Test; RAVLT: Rey's Auditory Verbal Learning Test; CVLT and PVL: California and Philadelphia Verbal Learning Test; HVLT: Hopkins Verbal Learning Test; RBMT: Rivermead Behavioral Memory Test; BNT: Boston Naming Test

Por otro lado, también existen unos criterios diagnósticos para la D-EP (51). Estos criterios, aunque más antiguos, son similares a los del DCL-EP: requieren un diagnóstico de EP y de demencia asociada, con la consecuente afectación de la independencia funcional, y la ausencia de otras condiciones que expliquen mejor la demencia (**Tabla 3**).

I. Core features

1. Diagnosis of Parkinson's disease according to Queen Square Brain Bank criteria
2. A dementia syndrome with insidious onset and slow progression, developing within the context of established Parkinson's disease and diagnosed by history, clinical, and mental examination, defined as:
 - Impairment in more than one cognitive domain
 - Representing a decline from premorbid level
 - Deficits severe enough to impair daily life (social, occupational, or personal care), independent of the impairment ascribable to motor or autonomic symptoms

II. Associated clinical features

1. Cognitive features:
 - Attention: Impaired. Impairment in spontaneous and focused attention, poor performance in attentional tasks; performance may fluctuate during the day and from day to day
 - Executive functions: Impaired. Impairment in tasks requiring initiation, planning, concept formation, rule finding, set shifting or set maintenance; impaired mental speed (bradyphrenia)
 - Visuo-spatial functions: Impaired. Impairment in tasks requiring visual-spatial orientation, perception, or construction
 - Memory: Impaired. Impairment in free recall of recent events or in tasks requiring learning new material, memory usually improves with cueing, recognition is usually better than free recall
 - Language: Core functions largely preserved. Word finding difficulties and impaired comprehension of complex sentences may be present
2. Behavioral features:
 - Apathy: decreased spontaneity; loss of motivation, interest, and effortful behavior
 - Changes in personality and mood including depressive features and anxiety
 - Hallucinations: mostly visual, usually complex, formed visions of people, animals or objects
 - Delusions: usually paranoid, such as infidelity, or phantom boarder (unwelcome guests living in the home) delusions
 - Excessive daytime sleepiness

III. Features which do not exclude PD-D but make the diagnosis uncertain

- Co-existence of any other abnormality which may by itself cause cognitive impairment, but judged not to be the cause of dementia, e.g. presence of relevant vascular disease in imaging
 - Time interval between the development of motor and cognitive symptoms not known
 - IV. Features suggesting other conditions or diseases as cause of mental impairment, which, when present make it impossible to reliably diagnose PD-D
 - Cognitive and behavioral symptoms appearing solely in the context of other conditions such as:
 - Acute confusion due to:
 - a. Systemic diseases or abnormalities
 - b. Drug intoxication
 - Major Depression according to DSM IV
 - Features compatible with "Probable Vascular dementia" criteria according to NINDS-AIREN (dementia in the context of cerebrovascular disease as indicated by focal signs in neurological exam such as hemiparesis, sensory deficits, and evidence of
-

relevant cerebrovascular disease by brain imaging AND a relationship between the two as indicated by the presence of one or more of the following: onset of dementia within 3 months after a recognized stroke, abrupt deterioration in cognitive functions, and fluctuating, stepwise progression of cognitive deficits)

Probable PD-D

A. Core features: Both must be present

B. Associated clinical features:

- Typical profile of cognitive deficits including impairment in at least two of the four core cognitive domains (impaired attention which may fluctuate, impaired executive functions, impairment in visuo-spatial functions, and impaired free recall memory which usually improves with cueing)
- The presence of at least one behavioral symptom (apathy, depressed or anxious mood, hallucinations, delusions, excessive daytime sleepiness) supports the diagnosis of Probable PD-D, lack of behavioral symptoms, however, does not exclude the diagnosis

C. None of the group III features present

D. None of the group IV features present

Possible PD-D

A. Core features: Both must be present

B. Associated clinical features:

- Atypical profile of cognitive impairment in one or more domains, such as prominent or receptive-type (fluent) aphasia, or pure storage-failure type amnesia (memory does not improve with cueing or in recognition tasks) with preserved attention
- Behavioral symptoms may or may not be present

OR

C. One or more of the group III features present

D. None of the group IV features present

Tabla 3. Criterios clínicos para el diagnóstico de D-EP (51).

Abreviaciones: PD-D: Parkinson's disease associated dementia; MDS: Movement Disorders Society; PD-MCI: PD-Mild Cognitive Impairment; SD: standard deviation

Además de las características neuropsicológicas descritas, en el DC-EP es muy frecuente encontrar síntomas neuropsiquiátricos concurrentes como la psicosis (ilusiones, alucinaciones, delirios) o la apatía. Esto se cree que se debe al solapamiento entre los circuitos neuronales y los sistemas de neurotransmisión implicados en ellos. Por un lado, tanto la psicosis como la apatía se han asociado a alteraciones en circuitos y estructuras imprescindibles en la arquitectura cognitiva como núcleo estriado ventral, núcleo accumbens, corteza orbitofrontal, corteza prefrontal ventromedial y dorsolateral, estructuras temporal mediales, o corteza parietal posterior (65,66). Por el otro, la disfunción del sistema colinérgico, que tiene un papel muy relevante en el DC-EP, está implicado tanto en la psicosis como en el componente cognitivo de la apatía, hasta el punto de que los IACEs son uno de los principales tratamientos farmacológicos en ambos (39,65,66).

También es importante considerar otros síntomas como la severidad de la afectación motora, fenotipos rigidoacinéuticos, déficits corticales posteriores, o SNM como la hiposmia o el TCSR, ya que son factores pronósticos de una peor evolución cognitiva (67). Igualmente, factores independientes de la EP como la edad avanzada, un nivel educacional bajo, o la comorbilidad cardiovascular se han asociado a una progresión más rápida o a un riesgo aumentado de DC-EP (67).

1.6.3. Fisiopatología del DC-EP

El DC-EP es una consecuencia de la neurodegeneración propia de la EP (47). Sin embargo, la fisiopatología y los mecanismos que difieren de aquellos pacientes con EP que no lo desarrollan no son del todo conocidos. Existen una gran variedad de factores genéticos y medioambientales que parecen contribuir a la alteración de los mecanismos moleculares y las redes neuronales implicadas en el DC-EP.

Neurotransmisores y redes neuronales

En el DC-EP hay tres sistemas de neurotransmisores principalmente afectados: dopaminérgico frontoestriatal, colinérgico cortical y noradrenérgico (**Figura 5**) (68). La degeneración dopaminérgica de los circuitos asociativos entre los ganglios basales y la corteza prefrontal dorsolateral es una alteración precoz que da lugar al fenotipo frontoestriatal típico de estadios iniciales (67). Las alteraciones visuoperceptivas y mnésicas más típicas de estadios avanzados se han asociado a la degeneración de las proyecciones colinérgicas desde el prosencéfalo basal a neocorteza, hipocampo, o amígdala (69). La disfunción del sistema colinérgico parece ser uno de los principales mecanismos implicados en la progresión a D-EP, y es hasta ahora la única diana efectiva en el tratamiento sintomático (70). La degeneración de proyecciones noradrenérgicas desde el *locus coeruleus* a la corteza frontal o al hipocampo se ha asociado a déficits atencionales, así como a un mayor deterioro cognitivo debido a la denervación cardíaca y la consecuente hipotensión ortostática (47,68).

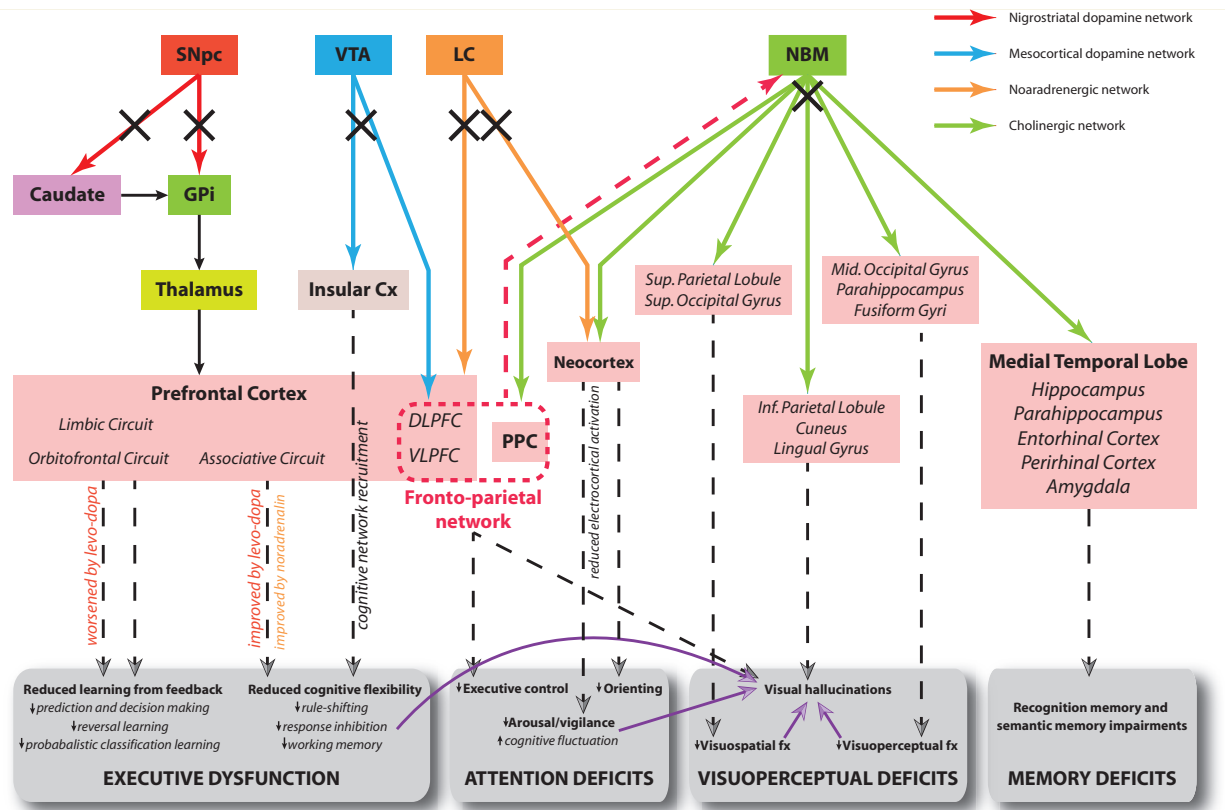


Figura 5. Modelo de sistemas afectados en el DC-EP (68).

Mecanismos moleculares y neuropatología

Los mecanismos moleculares que llevan al desarrollo del DC-EP son similares a los de la EP, con especial importancia de la agregación proteica, la genética o la neuroinflamación (47).

Al igual que en la EP en general, la agregación proteica y la neurodegeneración son hallazgos distintivos y con características ligeramente diferenciales con respecto a los pacientes con EP sin deterioro cognitivo. La presencia de patología Lewy límbica y cortical es el principal hallazgo asociado a un mayor riesgo de DC-EP (47). La presencia de patología de EA cortical como el acúmulo de beta-amiloide extracelular o tau intracelular también se ha asociado a DC-EP, tanto por su potencial efecto nocivo aislado como por su interacción con la patología Lewy (47). Múltiples estudios han investigado la presencia de estas proteínas en LCR (71–77). En términos generales, Aβ42 es un

buen predictor de DC-EP, mientras que α -syn, t-tau, o p-tau han generado resultados más inconsistentes (77).

Estudios recientes de Genome Wide Association Study (GWAS) han demostrado la implicación en la susceptibilidad y la progresión del DC-EP de *loci* propios de la EP (ej. *RIMS2*, *TMEM108*), *loci* compartidos con la ECL (ej. *APOE*, *GBA*), y *loci* compartidos con la EA (ej. *APOE*, *MAPT*, *WWOX*) (78). Por otro lado, existen formas monogénicas de EP asociadas a un mayor riesgo de D-EP como la triplicación o la mutación E46K de *SNCA*, y formas con un menor riesgo como la duplicación *SNCA* o mutaciones en *LRRK2*, mientras que el DC-EP en las formas recesivas es más variable (79).

Por último, cabe destacar que cada vez más estudios asocian parámetros inflamatorios tanto centrales como periféricos (neuroinflamación asociada beta-amiloide, activación de células T CD4⁺ en sangre, ratio sangre:LCR de células B de memoria, o captación en la sustancia negra del marcador ¹¹C-PK11195 en Positron Emission Tomography (PET)) al desarrollo de DC-EP y a la progresión de la enfermedad en general (80).

1.6.4. Tratamiento del DC-EP

Al igual que en el tratamiento general de la EP, el desconocimiento de la fisiopatología es uno de los principales responsables de que no existan fármacos capaces de modificar su curso natural, y de que los únicos fármacos aprobados para el tratamiento sintomático tengan efectos muy modestos.

La rivastigmina es el único fármaco aprobado para el DC-EP en su fase de demencia (D-EP), aunque otros IACEs como el donepezilo o la galantamina también son considerados potencialmente efectivos por la MDS (39,70). Hasta el momento, ninguno de los múltiples ensayos clínicos realizados con rivastigmina, rasagilina, atomoxetina, o donepezilo han demostrado eficacia en el DCL-EP (40). Dada la discapacidad que puede suponer el DC-EP incluso en sus fases más precoces, múltiples ensayos clínicos están investigando diferentes fármacos tanto para el tratamiento sintomático como para modificar su curso

natural con mecanismos de acción muy diversos: ANAVEX2-73 (blarcamesina), agonista del receptor Sigma-1 (NCT03774459, NCT04575259); DAAOI-P, inhibidor de la D-aminoácido oxidasa y facilitador de la subunidad 1 del receptor N-metil-D-aspartato (NMDA) (NCT04470037); ATH-1017 (fosgonimetón), modulador positivo del sistema neurotrófico del factor de crecimiento de hepatocitos (NCT04831281); SAGE-718, modulador alostérico positivo del receptor NMDA (NCT04476017); donepezilo, IACE (NCT05709301); levetiracetam, modulador de la liberación de neurotransmisores mediante la unión a la proteína vesicular sináptica SV2A (NCT04643327); o istradafinilo, antagonista del receptor de adenosina (NCT05333549) (40).

En este contexto, las intervenciones no farmacológicas adquieren especial relevancia. Por un lado, es importante evitar, en la medida de lo posible, medicaciones que puedan exacerbar el deterioro cognitivo como los anticolinérgicos o los sedantes, así como controlar los factores de riesgo cardiovascular, la hipotensión ortostática o los trastornos del sueño (40). Por otro lado, la estimulación cognitiva, física y social son imprescindibles en estos pacientes (40).

Finalmente, hay estudios novedosos que han explorado el papel de la estimulación magnética transcraneal repetitiva o de la sustitución de neuronas colinérgicas con neuronas derivadas de células madre (81,82). Es probable que la incorporación de nuevos biomarcadores y la inclusión de pacientes con DC-EP en fases iniciales (DCL-EP o DCS-EP) permitan identificar nuevas terapias efectivas en ensayos clínicos venideros.

2. HIPÓTESIS

2.1. JUSTIFICACIÓN

El DCS-EP se ha asociado a un riesgo global aumentado de deterioro cognitivo futuro, por lo que se asume que conforma la fase más precoz del DC-EP (48). Sin embargo, algunos estudios muestran que no todos los pacientes con DCS-EP desarrollarán un deterioro cognitivo clínicamente relevante (83). Con la puesta en marcha de cada vez más ensayos clínicos que tienen por objetivo modificar el curso de la EP en general, y del DC-EP en particular, es esencial identificar qué pacientes progresarán y cuáles no, desde las fases más precoces posibles. Los marcadores clínicos y biológicos serán de gran utilidad tanto en el consejo clínico como en el diseño de ensayos clínicos para el DC-EP.

2.2. HIPÓTESIS

Las preguntas científicas que se plantean en el presente trabajo son:

- 1.- ¿Existen diferentes patrones de evolución cognitiva en pacientes con DCS-EP?;
- 2.- ¿Existen marcadores clínicos y/o biológicos que permitan subtipificar a estos pacientes en función del riesgo de progresión cognitiva?

3. OBJETIVOS

Objetivo principal

1.- Identificar patrones de evolución cognitiva en DCS-EP.

Objetivos secundarios

2.- Identificar marcadores clínicos de mal pronóstico cognitivo en DCS-EP.

3.- Identificar marcadores biológicos de mal pronóstico cognitivo en DCS-EP.

4. COMPENDIO DE PUBLICACIONES

4.1. ARTÍCULO 1

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Heterogeneity of cognitive progression and clinical predictors in Parkinson's disease—subjective cognitive decline

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Abstract

Background Parkinson's Disease (PD)-associated subjective cognitive decline (PDSCD) is defined as cognitive complaints without objective cognitive impairment. Based on most studies, it is associated with a greater risk of cognitive decline and may represent a prodromal stage of cognitive impairment.

Methods The main objectives are to identify cognitive progression patterns and clinical predictors of worse cognitive decline within a large PD-SCD cohort with a 4-year followup. All patients belong to the prospective observational multicenter study COPPADIS.

Results A total of 198 PD-SCD subjects were analyzed. Mean age was 60.9, mean disease duration 5.2, and mean PD-Cognitive Rating Scale (PD-CRS) 97.6. Subjects were classified as Progressors if their Reliable Change Index was ≤ -1.64 at year 4, and as non-Progressors if it was > -1.64 (-1.64 corresponded to -16 on the PD-CRS). Progressors had significantly higher age, Movement Disorders Society-Unified PD Rating Scale (MDS-UPDRS) III, levodopa equivalent daily-dose, Non-Motor Symptom Scale total score, memory-related cognitive complaints, and prevalence of REM-sleep behavior disorder (RBD) at baseline. A linear mixed-effects model showed divergent cognitive trajectories between Progressors and non-Progressors (estimate = -26.8 ; $p < 0.001$), with no differences in motor trajectories. In the binary regression model, age (OR = 1.09; $p = 0.001$), MDS-UPDRS III (OR = 1.05, $p = 0.008$), and RBD (OR = 2.55, $p = 0.010$) at baseline were independent predictors of cognitive progression.

Conclusions Subjects with PD-SCD do not consistently show cognitive decline, but rather exhibit a heterogeneous progression. Age, MDS-UPDRS III and RBD significantly increase the risk of a more aggressive cognitive phenotype. Future research on biomarkers will help explore additional cognitive predictors in PD-SCD.

Keywords Parkinson's Disease · Cognitive complaints · Cognitive decline · PD-Subjective Cognitive Decline · REM-sleep behavior disorder

Introduction

Cognitive impairment is a frequent and disabling non-motor symptom (NMS) that can occur at any point along Parkinson's disease (PD) [1]. The spectrum of cognitive impairment in PD ranges from mild cognitive impairment

COPPADIS Study Group present in acknowledgements para.

Extended author information available on the last page of the article

(PD–MCI) to dementia (PDD), and its pattern of progression exhibits a significant heterogeneity between individuals [2, 3]. From a neuropsychological perspective, the most prominent characteristics of cognitive impairment in PD involve fronto-striatal-dependent features mostly in the form of attentional, working memory, planning and set-shifting deficits, whereas memory, language, and visuospatial compromise is more commonly observed in the transition to or in already established PDD [3, 4].

In recent decades, there has been growing interest in the concept of subjective cognitive decline in PD (PD–SCD), which is believed to represent an intermediate state between normal cognition (PD–NC) and PD–MCI [5–7]. The term PD–SCD has been borrowed from the field of Alzheimer’s disease and is defined as a self-reported decline in cognitive capacities with normal performance in cognitive tests in patients already diagnosed with PD [8]. Due to the lack of consensus on the assessment tools and diagnostic criteria for cognitive complaints and PD–SCD, data on its prevalence in persons with PD (PwP) are inconsistent, with studies reporting prevalences ranging from 15 to 83% [5, 9, 10]. A recent meta-analysis estimated a prevalence of 36% for cognitive complaints, and growing evidence suggests that PD–SCD is a precursor to future cognitive impairment, increasing its risk by 2.7 times [6, 9, 10].

While the majority of studies corroborate the heightened risk of developing cognitive impairment in PD–SCD, some of them have not evidenced this association [11, 12]. Similarly to other symptoms in PD, cognitive complaints may not invariably predict cognitive decline. Identifying diverse progression patterns and their predictors has significant implications for both clinical and research settings, as this population in the prodromal stage of cognitive impairment represents an ideal target for clinical trials focused on disease-modifying interventions.

The objectives of the present study are to describe *data-driven* patterns of cognitive progression using a PD-validated scale in a large longitudinal cohort, and to identify baseline clinical predictors of a more pronounced cognitive decline. For this purpose, we longitudinally analyzed a cognitively unimpaired PD cohort with PD–SCD, over a 4-year period.

Methods

Participants and study design

Participants were recruited between January 2016 and November 2017 from 35 centers across Spain for the COhort of Patients with PArkinson’s Disease in Spain, 2015 (COPPADIS). This is a prospective 5-year follow-up study designed to investigate the natural progression of PD.

Selection criteria included individuals aged 35–75 years, diagnosed with PD according to the UK PD Brain Bank criteria, without dementia, and without advanced therapies for PD such as infusion therapies or deep brain stimulation. This project received approval from the ethics committee in Galicia, Spain (2014/534; 02/DEC/2014). All participants voluntarily provided a written informed consent to participate. Additional study details can be found in the original publication [13]. For the present study, we selected PwP with normal cognitive performance as assessed with the Parkinson’s Disease–Cognitive Rating Scale total score (PD–CRS total score > 81) and with cognitive complaints as assessed with the NMS Scale (NMSS) domain 5 [4, 14]. All the included subjects had completed motor and cognitive assessments of the 4-year follow-up visit.

To assess the presence of cognitive complaints we used the NMSS domain 5, which includes three rater-administered questions: item 16 “Does the patient have problems sustaining concentration during activities?”, item 17 “Does the patient forget things that he/she has been told a short time ago or events that happened in the last few days?” and item 18 “Does the patient forget to do things?”. Participants were categorized as PD–SCD if the score in NMSS domain 5 was ≥ 1 .

Assessments

Demographic data, motor assessments [Movement Disorders Society–Unified PD Rating Scale (MDS–UPDRS) III, and Hoehn and Yahr scale (H&Y)], cognitive assessment (PD–CRS), neuropsychiatric and other NMS scales [Beck Depression Inventory II (BDI-II), and NMSS] were collected from all participants at baseline, 2 years, and 4 years. NMSS was used to assess the presence of different NMS: domain 1 for cardiovascular autonomic symptoms; domain 3 for depression, anxiety, and apathy; domain 5 for memory and concentration problems; domain 6 for gastrointestinal autonomic symptoms; and domain 7 for urinary autonomic symptoms [15]. The presence of visual hallucinations was determined using the item 13 of the NMSS (“Does the patient indicate that he/she sees things that are not there?”). A score > 0 was considered indicative of this symptom. The presence of hyposmia was considered when a score > 0 was obtained for the item 28 of the NMSS (“Does the patient report a change in ability to taste or smell?”). REM–sleep behavior disorder (RBD) was determined through a clinical interview conducted by a movement disorders neurologist.

Subjects were categorized into progression groups using the Reliable Change Index (RCI) for the PD–CRS total score. This index evaluates whether the change over time can be attributed to measurement error or not [16]. To calculate the RCI we applied the following formula: $RCI = (X_2 - X_1) / S_{diff}$, where X_1 is the patient’s PD–CRS score at baseline,

X_2 is the patient's PD-CRS score at 4 years, and S_{diff} is the standard error of the difference between the test scores. Similar to previous literature, we employed a 90% confidence level [17]. Subjects were labeled as PD-SCD Progressors if their RCI was ≤ -1.64 , and as non-progressors if their RCI > -1.64 .

Statistical analysis

Descriptive statistics for demographic and clinical features of each PD-SCD subgroup (progressors and non-progressors), as well as differences between them were explored using an independent two-tailed t test for continuous variables and the χ^2 test for categorical variables. Continuous variables are presented as means and standard deviations (SD), while categorical variables are presented as numbers and percentages. Linear mixed-effects model (LME) with the lme4 package was conducted to model the longitudinal trajectories of cognition and motor symptoms over time within each PD-SCD subgroup. Binary logistic regression was used to explore the independent association between the variables of interest and the PD-SCD subgroup (backward stepwise method). All the variables used for the LME and logistic regression model adjustments are specified in the *Results* section. The analyses were conducted using IBM-SPSS software (v26) and R (v4.3.3). A two-tailed p value of <0.05 was considered significant for all tests.

Data availability

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

Results

A total of 198 subjects with PD-SCD from a cohort of 326 cognitively unimpaired individuals were included for analysis. The mean age was 60.9 ± 8.6 years, and 41.1% were women. The sample consisted of subjects in the early stage of PD (mean disease duration of 5.2 ± 4 years, mean H&Y stage of 1.9 ± 0.6 and mean MDS-UPDRS III of 21.2 ± 11.1) with a PD-CRS total score significantly above the cutoff of ≤ 81 for PD-MCI (mean PD-CRS total score of 97.6 ± 10.5). The mean BDI-II score (8.7 ± 7.1) indicated minimal depressive symptoms [18]. The mean difference between PD-CRS total scores at the 4-year follow-up and baseline was -5.5 ± 14.8 . All demographics and baseline characteristics are reported in Table 1.

We calculated the RCI to categorize subjects into two distinct groups based on their progression in the PD-CRS. For this purpose, we determined internal

Table 1 Demographics and baseline characteristics of the PD-SCD cohort

PD-SCD cohort	<i>n</i> = 198
Demographics	
Age, years	60.9 (8.6)
Biological sex, women (%)	81–41.1%
Education level, years	11.9 (4.1)
Motor symptoms	
Disease duration, years	5.2 (4)
H&Y	1.9 (0.6)
MDS-UPDRS III	21.2 (11.1)
LEDD, mg	560 (379)
Cognitive/ neuropsychiatric	
PD-CRS frontal subcortical score	69.7 (10.2)
PD-CRS posterior cortical score	28 (3.3)
PD-CRS total score	97.6 (10.5)
Visual hallucinations (%)	60–30.3%
BDI-II total score	8.7 (7.1)
NMSS domain 3—mood	9.5 (11.9)
Other NMS	
RBD (%)	82–41.4%
Hyposmia (%)	141–71.2%
NMSS domain 1—cardiovascular	1.5 (2.4)
NMSS domain 6—gastrointestinal	3.9 (4.7)
NMSS domain 7—urinary	8.3 (7.9)
NMSS total score	52.1 (38.5)

Continuous variables are presented as mean (standard deviation), and categorical variables are presented as number–percentage. *PD-SCD* PD–subjective cognitive decline; *H&Y* Hoehn and Yahr scale; *MDS-UPDRS* Movement Disorders Society–Unified PD Rating Scale; *LEDD* Levodopa equivalent daily dose; *NMSS* non-motor symptom scale; *PD-CRS* PD–Cognitive Rating Scale; *BDI-II* beck depression inventory II; *RBD* REM–sleep behavior disorder

reliability using Cronbach's alpha (0.782 for the 9 items of the PD-CRS). Subjects were labeled as Progressors if their RCI was ≤ -1.64 , whereas those with an RCI > -1.64 were labeled as non-Progressors. The threshold of -1.64 corresponded to a loss of 16 points in the PD-CRS total score at the 4-year follow-up. At baseline, Progressors showed a significantly higher age [$t(196) = 3.3$; $p = 0.001$], MDS-UPDRS III [$t(193) = 2.4$; $p = 0.018$], LEDD [$t(196) = 3$; $p = 0.003$], and NMSS total score [$t(195) = 2.2$; $p = 0.030$], and higher prevalence of RBD ($p = 0.002$). Memory complaints were more severe in the Progressors group as measured by NMSS domain 5 items 17 [$t(195) = 2.1$; $p = 0.036$] and 18 [$t(195) = 2.3$; $p = 0.024$], while no significant differences were found in concentration/attention complaints, as measured by NMSS domain 5 item 16. The proportion of subjects diagnosed with PD-MCI level I at year 4 was markedly higher in the progressors group (87% vs 9.2%, $p < 0.001$), despite no

differences in PD–CRS total score at baseline. Baseline characteristics of both subgroups are summarized in Table 2.

To explore the size of the PD–CRS trajectory differences between the two subgroups, an LME model was employed. The fixed effects included age, disease duration, MDS–UPDRS III, LEDD, and NMSS total score. Random effects were incorporated to account for potential variations between individuals. The model predicted a marked worsening in PD–CRS total score at 4 years in progressors [estimate (β) -26.9 , standard error (SE) 1.6 , $p < 0.001$] compared to non-progressors (Fig. 1, left; Table 3). A subsequent LME model to examine the trajectories of MDS–UPDRS III after adjusting for age, disease duration, LEDD and NMSS total score as fixed effects, did not show statistically significant differences between Progressors (β 2.5 , SE 1.9 , $p = 0.179$) and non-progressors (Fig. 1, right; Table 3).

Finally, we incorporated into a binary regression model (progressors vs non-progressors) those baseline variables that had shown significant association in the univariate analysis and had no multicollinearity between them, as well as other variables of interest (age, MDS–UPDRS III, LEDD, PD–CRS total score, prevalence of RBD, and NMSS total score). The analyses revealed that age [Odds Ratio (OR) 1.1 , $p = 0.001$], MDS–UPDRS III (OR 1.1 , $p = 0.008$), and RBD (OR 2.6 , $p = 0.011$) were independent predictors of a more pronounced cognitive progression (Table 4).

Discussion

In this study we conducted a longitudinal analysis of 198 patients with PD–SCD which is, to our knowledge, the largest longitudinal cohort of PD–SCD subjects in whom

Table 2 Demographics and baseline characteristics of PD–SCD progressors and non-progressors

	Progressors (n = 46)	non-progressors (n = 152)	p value
Demographics			
Age, years	64.5 (7.1)	59.8 (8.8)	0.001
Biological sex, women (%)	20–43.5%	62–40.8%	0.746
Education level, years	11.1 (3.8)	12.2 (4.2)	0.122
Motor symptoms			
Disease duration, years	5.6 (4.9)	5.1 (3.7)	0.508
H&Y	2 (0.6)	1.9 (0.5)	0.060
MDS–UPDRS III	24.6 (11.5)	20.1 (10.9)	0.018
LEDD, mg	703 (438)	517 (350)	0.003
Cognitive/ neuropsychiatric			
NMSS domain 5 Item 16	2.4 (2.8)	2.2 (2.6)	0.611
NMSS domain 5 Item 17	2.4 (2.9)	1.6 (2.1)	0.036
NMSS domain 5 Item 18	1.8 (2.7)	1 (1.9)	0.024
PD–CRS frontal subcortical score	67.4 (8.2)	70.4 (10.6)	0.079
PD–CRS posterior cortical score	27.6 (3.9)	28.1 (3.1)	0.391
PD–CRS total score	95 (9.1)	98.4 (10.8)	0.054
Visual hallucinations (%)	18–39.1%	42–27.6%	0.137
BDI–II total score	8.8 (6.2)	8.7 (7.4)	0.914
NMSS domain 3—mood	11.7 (11.6)	8.8 (12)	0.157
Other NMS			
RBD (%)	28–60.9%	54–35.5%	0.002
Hyposmia (%)	36–78.3%	105–69.1%	0.228
NMSS domain 1—cardiovascular	2.2 (3)	1.3 (2.2)	0.050
NMSS domain 6—gastrointestinal	5 (5.4)	3.5 (4.4)	0.064
NMSS domain 7—urinary	10 (8.3)	7.8 (7.7)	0.095
NMSS total score	62.9 (42.4)	48.8 (36.7)	0.030

p values < 0.05 are highlighted in bold

Continuous variables are presented as mean (standard deviation), and categorical variables are presented as number–percentage. H&Y Hoehn and Yahr scale; MDS–UPDRS Movement Disorders Society–Unified PD Rating Scale; LEDD Levodopa equivalent daily dose; NMSS Non-Motor Symptom Scale; PD–CRS PD–Cognitive Rating Scale; BDI–II Beck Depression Inventory II; RBD: REM–sleep behavior disorder

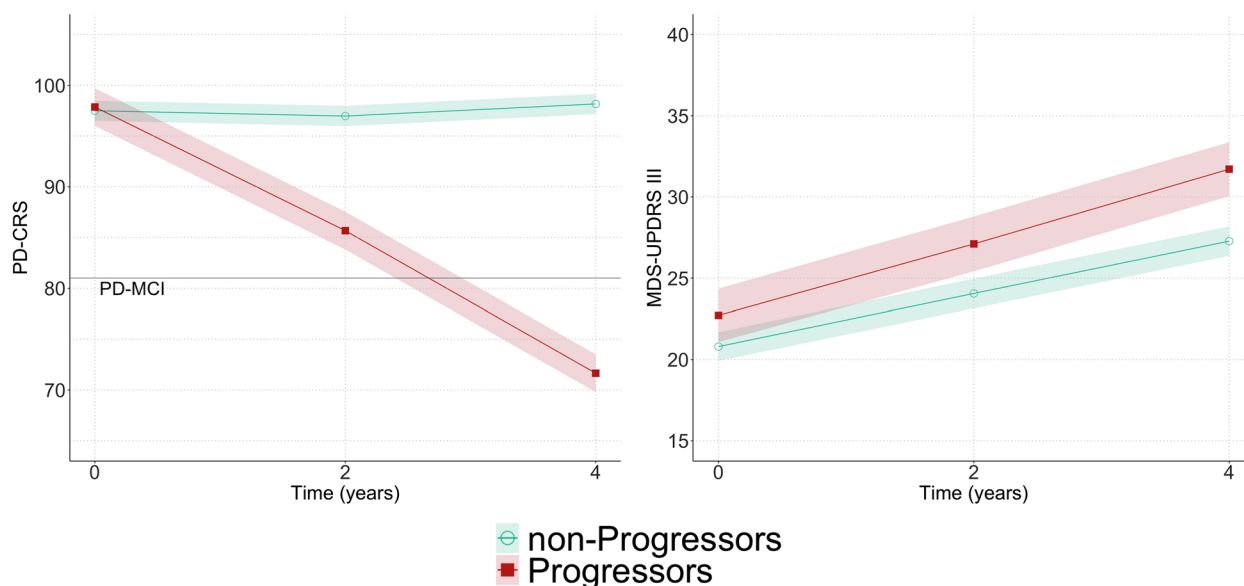


Fig. 1 Predictions of the LME model for the longitudinal trajectory of PD-CRS (left) and MDS-UPDRS III (right) in PD-SCD progressors and non-progressors

Table 3 Results of the LME model for PD-CRS and MDS-UPDRS (reference group: non-progressors)

	PD-CRS			MDS-UPDRS		
	Estimate	Standard error	<i>p</i> value	Estimate	Standard error	<i>p</i> value
Age	−0.58	0.09	< 0.001	−0.03	0.08	0.675
Disease duration	0.31	0.26	0.230	0.15	0.21	0.476
LEDD	−0.004	0.003	0.176	0.01	0.002	< 0.001
NMSS total score	−0.01	0.02	0.493	0.07	0.02	< 0.001
MDS-UPDRS III	−0.01	0.02	0.141	—	—	—
Progressors x Timepoint 1 (year 2)	−11.66	1.60	< 0.001	1.13	1.89	0.551
Progressors x Timepoint 2 (year 4)	−26.87	1.57	< 0.001	2.51	1.87	0.179

p values < 0.05 are highlighted in bold

PD-CRS PD-cognitive rating scale; MDS-UPDRS Movement Disorders Society–Unified PD Rating Scale; LEDD Levodopa equivalent daily dose

Table 4 Binary logistic regression (progressors vs non-progressors)

	OR (95% CI)	<i>p</i> value
Age	1.09 (1.04–1.14)	0.001
MDS-UPDRS III	1.05 (1.01–1.08)	0.008
RBD	2.55 (1.24–5.25)	0.010

OR Odds ratio; CI confidence interval; MDS-UPDRS Movement Disorders Society–Unified PD Rating Scale; RBD REM-sleep behavior disorder

cognitive evolution and the clinical variables involved in cognitive prognosis have been studied. The main results of the analysis showed that: (a) cognitive decline in PD-SCD is variable across individuals with either stability

or progression in the long term, and loss of 16 points was considered significant; and (b) age, MDS-UPDRS III and RBD at baseline are independent predictors of a worse cognitive progression.

The prevalence of cognitive complaints in our cohort was 60.7% (198 out of 326), significantly higher than the previously estimated 36% in a recent meta-analysis [6]. However, our data falls within the range observed in previous studies (6.3–82.9%) [9]. These differences could be due to the scales used to assess both cognitive complaints (NMSS domain 5) or cognitive status (PD-CRS). Notably, the same meta-analysis found significantly lower rates of complaints in subjects with cognitive impairment compared to those without, suggesting that reduced insight and/or increased focus on motor or other NMS may

contribute to this discrepancy in cognitively impaired PwP with more advanced PD. Our cohort includes relatively early and cognitively preserved PwP, thereby giving greater reliability to the complaints reported by the participants.

Most studies have indicated that cognitive complaints predict the development of cognitive impairment [6]. Nonetheless, cognitive decline is not uniform among PwP and thus, it is likely that not every PD–SCD patient follow the same pattern of progression [1]. To explore the differences between those experiencing more and less severe decline, we performed a *data-driven* approach to divide our PD–SCD cohort according to cognitive progression using the RCI for the PD–CRS, an instrument specifically validated for the assessment of cognitive status in PD [4, 19]. At baseline, PD–SCD Progressors were slightly older, presented more severe motor disease and more NMS, including higher rates of RBD. The LME model showed that the cognitive trajectory of these subgroups are significantly different with an estimated loss of 26.9 points in the PD–CRS total score at year 4, which is a clinically significant change [14]. Similarly, the proportion of PD–MCI in the long term was significantly higher in Progressors. However, there were no differences in terms of motor trajectories, despite significant MDS–UPDRS III differences at baseline, suggesting that the more aggressive cognitive phenotype is not necessarily associated with a similarly aggressive motor phenotype.

Data on the relationship between specific cognitive complaints and future cognitive impairment is scarce and has yielded varied results. Our data indicate that memory but not concentration/attention-related complaints, are associated with worse cognitive decline. Conversely, other studies have reported that complaints in executive abilities rather than those related to memory, attention or decision-making, are associated with cognitive decline [20]. A recent study by Weintraub et al. demonstrated that complaints in executive abilities, followed by those related to memory and cognitive slowing are the most frequently associated with future cognitive impairment [21]. Overall, these findings suggest that a broad range of complaints can serve as predictors of cognitive decline. Therefore, in both clinical and research settings, a comprehensive assessment of cognitive complaints across all cognitive domains is essential. This can be appropriately achieved by utilizing broader scales, such as the MDS–Non Motor Scale (MDS–NMS), which it specifically assesses the subjective perception of difficulties in attention, executive functions, memory, language, and visuospatial domains [22].

Neuropsychiatric manifestations such as depression, apathy or visual hallucinations have also been associated with an increased risk of cognitive impairment in PD [23, 24]. In the present study, the severity of depressive symptoms was not sufficient to classify participants as having depression. Similarly, the data suggest that mood-related

symptoms, which have been previously associated with PD–SCD, are not reliable indicators of a more aggressive cognitive progression in PD–SCD individuals. Visual hallucinations were reported in 30.3% of the cohort, which falls within the previously reported prevalence in early stage PD [25]. However, similar to mood-related symptoms, they were not associated with a more aggressive phenotype in PD–SCD. Given the consistent association between hallucinations and cognitive decline, further longitudinal studies are needed to determine whether these results are due to sample size, assessment methods, or if baseline visual hallucinations simply do not provide additional information about cognitive decline in PD–SCD [24].

The association between age and more severe motor disease with cognitive decline is well documented [26]. In our analysis, the presence of RBD also emerged as an independent risk factor for more pronounced cognitive decline in PD–SCD. Besides the specific pathologic changes subserving RBD and cognitive decline in PD, one can hypothesize a common neurotransmitter link, mainly cholinergic, gathering these symptoms [27, 28]. RBD is believed to stem from the dysfunction of pedunculopontine nucleus–laterodorsal tegmental complex cholinergic neurons [29]. Most cholinergic projections in the central nervous system originate from the basal forebrain and mesopontine tegmental area connecting with the brainstem, striatum, thalamus, hypothalamus, and cortex [27]. Cholinergic dysfunction in PD has been associated not only with RBD and cognitive impairment, but also with hallucinations, gait impairment, hyposmia, and other neuropsychiatric and autonomic symptoms [29]. Our results align with the suggested existence of a *cholinergic phenotype* in PD, characterized by a more malignant and diffuse disease [29, 30]. Although RBD has been previously linked to cognitive impairment in PD, it is relevant identifying these progression risk factors in selected patients with PD–SCD, as this population represents an ideal target for future clinical trials [31].

This study is not devoid of some limitations. On the one hand, the definition used for PD–SCD was based on NMSS domain 5 [15]. We acknowledge that this is a rater-administered instrument and, unlike other comprehensive instruments such as the MDS–NMS, it does not cover the entire spectrum of cognitive problems that may occur in PD [3]. However, it might be a reliable tool in the absence of validated methods for assessing the presence of cognitive complaints in PD, and has been previously used in other studies [10]. On the other hand, RBD was not assessed using polysomnography or a validated tool. Nonetheless, the clinical interview conducted by a movement disorders specialist familiarized with RBD could suffice for the clinical approach of the study. The study also has strengths to consider, such as the sample size and the clinical follow-up over a 4-year period. In addition, we used PD–CRS for

cognitive assessment, a PD-validated tool with a broad scoring range that allows for the identification of subtle progressions over time. While these aspects could have been explored in greater depth, they constitute one of the most extensive longitudinal studies carried out on PD–SCD to date, and its results can be informative for the design of future studies.

In summary, our results indicate that PD–SCD is frequent, but its presence can have different prognostic implications. Subjects with PD–SCD do not consistently show cognitive decline, but rather a variable cognitive progression. Age, MDS–UPDRS III and RBD at baseline significantly increase the risk of developing a more aggressive cognitive phenotype over a 4-year period. These findings are clinically relevant, and they should be considered for the characterization and prognosis of PwP. At the same time, they provide new insights into PD–SCD and how to study preclinical forms of cognitive impairment in PD. Future research incorporating ancillary tests such as fluid, genetic, neuroimaging, or neurophysiological measures will help explore additional interactions and prognostic markers in PD–SCD.

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Declarations

Conflicts of interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

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4.2. ARTÍCULO 2

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RESEARCH ARTICLE OPEN ACCESS

CSF Biomarker-Based Cognitive Trajectories in Parkinson's Disease-Subjective Cognitive Decline

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Keywords: Alzheimer's Disease | amyloid | Parkinson's Disease | PD-SCD | Subjective Cognitive Decline

ABSTRACT

Objective: Cognitive complaints without objective cognitive impairment in Parkinson's Disease, termed Parkinson's Disease-Subjective Cognitive Decline (PD-SCD), have been associated with cognitive decline. However, its progression is heterogeneous, highlighting the need for improved identification of patients at greater risk for deterioration. This cohort study aims to investigate associations between CSF biomarkers and cognitive decline in PD-SCD.

Methods: We included patients from the PPMI cohort with PD-SCD, available baseline CSF beta-amyloid₁₋₄₂ ($A\beta_{42}$) and phosphorylated-tau₁₈₁ (p-tau₁₈₁), and longitudinal Montreal Cognitive Assessment (MoCA).

Results: A total of 80 patients were included, with a mean age of 62.1 years and a median disease duration of 5.6 months at baseline. Five patients were identified with biological AD, who showed a more pronounced decline in MoCA (year 7: $\beta = -4.15$, $p = 0.009$). After excluding AD patients, linear mixed-effects models (LMEM) demonstrated an association between baseline log-transformed $A\beta_{42}$ and MoCA progression ($\beta = 2$, $p = 0.004$). Based on these data, we created three CSF-based subgroups: *Normal* $A\beta_{42}$ ($n = 50$), *Low* $A\beta_{42}$ ($n = 25$), and *Biological AD* ($n = 5$). LMEM predicted greater cognitive decline for *Low* $A\beta_{42}$ versus *Normal* $A\beta_{42}$ ($\beta = -0.161$ points-per-year, $p = 0.007$), and for *Biological AD* versus *Normal* $A\beta_{42}$ ($\beta = -0.390$ points-per-year, $p < 0.001$). The risk of dementia was increased for *Low* $A\beta_{42}$ ($HR = 5.2$, $p = 0.029$) and *Biological AD* subgroups ($HR = 7.7$, $p = 0.013$).

Interpretation: In PD-SCD, baseline CSF $A\beta_{42}$ is associated with cognitive progression. Furthermore, we identified three CSF biomarker-based cognitive trajectories (*Normal* $A\beta_{42}$, *Low* $A\beta_{42}$, and *Biological AD*), each characterized by progressively worse cognitive outcomes. These findings could be useful for implementing enrichment strategies in future clinical trials targeting PD-associated cognitive decline.

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1 | Introduction

Cognitive impairment is a common and disabling non-motor symptom in Parkinson's Disease (PD) that can occur at any stage of the disease [1]. Attention, working memory, and executive functions are the most prominently affected domains in the early stages, whereas language, visuospatial, and memory impairment generally appear in the later stages [2]. The progression of cognitive decline in PD is heterogeneous, with a typically gradual evolution from mild cognitive impairment (PD-MCI) to dementia (PDD) [2, 3]. However, patients often report cognitive complaints before a formal PD-MCI can be established. This prodromal phase of PD-MCI is known as PD-Subjective Cognitive Decline (PD-SCD) [1, 4].

A recent meta-analysis demonstrated that PD-SCD is associated with an increased risk of long-term cognitive decline, suggesting that it may represent the earliest detectable phase of cognitive impairment [5]. However, progression among patients labeled with PD-SCD is not uniform, and not all patients will experience a clinically relevant cognitive decline [6, 7]. With clinical trials investigating disease-modifying therapies in the pipeline, it becomes crucial to identify biomarkers that can predict forms of PD-SCD associated with more pronounced deterioration. From a clinical perspective, it is important to understand the significance of PD-SCD and its associated risk for future cognitive decline.

The precise neurobiological basis of cognitive impairment in PD remains elusive, although it is widely accepted that both Lewy and Alzheimer's Disease (AD)-associated pathologies play significant roles [8]. Numerous studies have explored how CSF levels of these proteins can predict cognitive decline both in cognitively unimpaired early PD and in PD-associated cognitive impairment [9–15]. Baseline levels of CSF beta-amyloid_{1–42} (A β ₄₂), especially when combined with other biomarkers like neurofilament light chain (NfL), have demonstrated to predict worse cognitive outcomes [15, 16]. This evidence aligns with the heightened risk of cognitive decline observed among *ApoE4* carriers [17]. Recently, one study suggested that the AT(N) biomarker system, which uses amyloid (A), tau (T), and neurodegeneration (N) markers to biologically classify AD, could be useful for identifying biological subtypes that help predict cognitive decline in early PD⁹. The axonal injury biomarker NfL has also shown associations with cognitive decline in early PD, both in CSF and plasma measurements [18, 19]. Conversely, biomarkers such as CSF alpha-synuclein (a-syn), total-tau (t-tau), or phosphorylated-tau (p-tau) have yielded inconsistent results across studies, and their association with cognitive decline in PD requires further research [15].

A recent study showed that cognitive complaints and AD-related biomarkers are associated with earlier cognitive decline in PD-MCI, suggesting not only an independent role of these proteins in PD-associated cognitive impairment, but also the potential implication of concomitant AD [20]. Yet, studies exploring the predictive value of CSF biomarkers in the earliest clinical stage of cognitive impairment in PD, PD-SCD, are still lacking.

The objective of the present study is to explore the association between CSF biomarkers and cognitive decline in PD-SCD, with a particular focus on whether these biomarkers can help

distinguish PD-SCD individuals who experience cognitive progression from those who do not. For this purpose, we conducted a longitudinal analysis of a PD-SCD cohort over a span of 7 years.

2 | Methods

2.1 | Sample

Data used in the preparation of this article were obtained on July 27, 2024, from the Parkinson's Progression Markers Initiative (PPMI) database (www.ppmi-info.org/access-dataspecimens/download-data), RRID: SCR 006431. PPMI is an ongoing longitudinal, observational, multi-center study assessing clinical, imaging, and biological features of PD across all stages of the disease. The PPMI protocol received approval from the institutional review boards of all participating sites, and written informed consent was obtained from all participants. For additional and up-to-date information on the study, visit www.ppmi-info.org.

PD-SCD was defined as: Montreal Cognitive Assessment (MoCA) ≥ 26 and Movement Disorders Society-Unified PD Rating scale part I item 1 (MDS-UPDRS 1.1) ≥ 1 . Patients from the PD cohort were included if they met the following criteria: PD-SCD criteria at screening, at least one longitudinal MoCA available, and CSF A β ₄₂ and p-tau₁₈₁ available at screening. Patients with monogenic forms of PD (*SNCA*, *LRRK2*, *PINK1*, or *PRKN*) were excluded. No patients from the Prodromal cohort, the SWEDD cohort, or the Healthy Control cohort were included.

2.2 | Clinical Assessments

Motor symptoms were assessed with the MDS-UPDRS III, Hoehn & Yahr (H&Y) scale, and clinical phenotype. Cognitive performance was evaluated with the MoCA total score and the domain-specific tests Hopkins Verbal Learning Test (HVLT) for memory, Letter Number Sequencing (LNS) for executive functions, Symbol Digit Modalities Test (SDMT) for attention and processing speed, animal fluency for language, and Judgment of Line Orientation (JLO) for visuospatial abilities. Neuropsychiatric symptoms were assessed with MDS-UPDRS 1.2 for hallucinations, the Geriatric Depression Scale (GDS) for depression, State-Trait Anxiety Inventory (STAI) total score for anxiety, and MDS-UPDRS 1.5 for apathy. Olfactory function was assessed with the University of Pennsylvania Smell Identification Test (UPSIT) and REM-sleep behavior disorder (RBD) with the RBD questionnaire (RBDQ).

In the follow-up, patients were considered as having PD-MCI if MoCA was < 26 , and as PDD if MoCA was < 20 [21]. Hallucinations were identified by a score of ≥ 1 on the MDS-UPDRS 1.2. The presence of RBD was determined by a score of > 5 points on the RBDQ [22].

2.3 | CSF Biomarkers

CSF collection, shipment, storage, and analysis was performed at each study site according to the protocols detailed

in the PPMI biologics manual (<http://www.ppmi-info.org/>). In brief, $A\beta_{42}$, t -tau, and p -tau₁₈₁ were measured using the electrochemiluminescence immunoassays on a cobas e601 analyzer (Elecsys, Roche diagnostic); a-syn was analyzed using sandwich type ELISA kits (Covance, Dedham, MA); and NfL was quantified using Roche NTK on a cobas e411 analyzer (Translational Biomarker Solutions, Indiana, USA) [14, 23, 24].

Following recommendations of previous studies analyzing the PPMI database, and based on the Elecsys assay, we used a cut-off of ≤ 683 pg/mL to identify patients with low levels of $A\beta_{42}$ (A+), and a cut-off of ≥ 24 pg/mL to identify patients with high levels of p -tau₁₈₁ (T+) [23, 25]. According to the biological definition of AD by the National Institute on Aging-Alzheimer's Association (NIA-AA) and the AT(N) system, patients were categorized as *Biological AD* if they exhibited both A+ and T+, while patients with A+ and T- were classified as *Low $A\beta_{42}$* [25–27]. All CSF biomarkers were log-transformed to approximate a normal distribution prior to their inclusion into the linear models.

2.4 | Statistical Analysis

Descriptive statistics were calculated for demographic and clinical variables. Group differences were analyzed using the t -test and one-way ANOVA for normally distributed continuous variables, the Mann–Whitney U test and Kruskal–Wallis test for non-normally distributed continuous variables, and the χ^2 -test for categorical variables, using exact tests when appropriate. Bivariate correlations were used to evaluate baseline associations between CSF biomarkers and continuous variables. Continuous variables are presented as means and standard deviations (SD) or medians and interquartile ranges (IQR), while categorical variables are presented as numbers and percentages.

Linear mixed-effects models (LMEM) were conducted using the *lme4* package to model the longitudinal trajectories of cognition and motor symptoms over time and to test their associations with CSF biomarkers and PD-SCD subgroups. The variables used as fixed effects for the adjustment of each model are specified in the Results section (Section 3). All models included a random intercept for each patient. Slopes of the trajectories over time were derived using the *emmeans* package, and Tukey-adjusted pairwise comparisons were performed to assess differences between subgroups. We used MoCA scores to assess the slopes of cognitive progression.

Multivariate Cox proportional hazards regression models were used to estimate the risk of developing PD-MCI and PDD for each subgroup. Crude and adjusted hazard ratios (HR) and 95% confidence intervals (CI) were calculated. The variables used for model adjustment are specified in the Results section (Section 3), with the analysis adhering to a ratio of one covariate per ten events [28]. The Schoenfeld test was employed to evaluate the proportional hazards assumption, confirming the appropriateness of the models.

A two-tailed $p < 0.05$ was considered significant for all tests. False Discovery Rate (FDR) correction was applied to adjust for multiple comparisons. Analyses were conducted using R software (v4.4.2).

3 | Results

3.1 | Baseline Characteristics of the Entire PD-SCD Cohort

The sample consisted of 80 early PD patients with a median disease duration of 5.6 months (IQR 3–10.7), a median MDS-UPDRS III of 20 (IQR 16–26), and a median H&Y of 2 (IQR 1–2). The mean age was 62.1 ± 9.2 years, and 36.3% were women. The median GDS (2, IQR 1–4.8), STAI (69, IQR 56.5–80) and MDS-UPDRS 1.5–apathy (0, IQR 0–1) scores indicated that the cohort did not exhibit significant neuropsychiatric symptoms [29, 30]. The median follow-up with MoCA assessment was 7 years (IQR 5–7). Data availability for baseline CSF biomarkers was as follows: $A\beta_{42}$ $n = 80$, t -tau $n = 78$, p -tau₁₈₁ $n = 80$, a-syn $n = 74$, and NfL $n = 42$. All demographics and baseline characteristics are reported in Table 1.

3.2 | Differences Between Patients With and Without Biological AD

To evaluate the potential confounding effect of AD on cognitive progression, we first explored baseline and longitudinal characteristics of patients according to the presence/absence of biological AD. Patients with biological AD (6.3%) had lower $A\beta_{42}$ ($Z = -3.2$, $p = 0.009$), higher p -tau₁₈₁ ($Z = 3.7$, $p = 0.009$), and t -tau ($Z = 3.6$, $p = 0.009$) (Table S1). Although not statistically significant, it is noteworthy that patients with biological AD were older, did not experience hallucinations, and had a higher prevalence of *ApoE4* carriers. The longitudinal analysis of MoCA trajectories using LMEM showed a significantly more pronounced decline in patients with biological AD, with no differences in MDS-UPDRS III trajectories (Figure 1 and Table S2). Both models were adjusted for CSF biomarker status, time, the interaction between CSF biomarker status and time, age, and disease duration as fixed effects, with the MoCA model additionally adjusted for MDS-UPDRS III.

3.3 | Associations Between Baseline CSF Biomarkers and Cognitive Progression ('Biological AD' Excluded)

To better understand the independent association of CSF biomarkers with cognition in PD-SCD, we excluded patients with biological AD from these analyses. At baseline, we found associations between: $A\beta_{42}$ and LEDD ($r = -0.258$, $p = 0.021$) and hallucinations ($Z = -2.8$, $p = 0.006$); t -tau and age ($r = 0.292$, $p = 0.012$); p -tau₁₈₁ and age ($r = 0.237$, $p = 0.041$); a-syn and hallucinations ($Z = -2.1$, $p = 0.032$); and NfL and age ($r = 0.326$, $p = 0.049$). No significant associations were found between baseline biomarkers and any other clinical feature at baseline.

TABLE 1 | Baseline characteristics of the entire PD-SCD cohort.

PD-SCD cohort	
<i>n</i>	80
Demographics	
Biological sex, women (%)	29 (36.3%)
Age at baseline, years	62.1 (9.2)
Education level, years	16 (13.3–16)
Parkinson's Disease	
Disease duration, months	5.6 (3–10.7)
MDS-UPDRS III	20 (16–26)
LEDD	0 (0–0)
H&Y	2 (1–2)
PIGD phenotype (%)	26 (32.5%)
Cognition	
MoCA	27.5 (27–28.8)
HVLT immediate recall	24 (4.7)
HVLT retention	0.9 (0.8–1)
HVLT delayed recall	9 (7–10)
LNS	10 (9–12)
SDMT	39.4 (11.4)
Animal fluency	21.1 (5.2)
JLO	13 (11–14)
Neuropsychiatric	
Hallucinations (%)	8 (10%)
GDS	2 (1–4.8)
STAI	69 (56.5–80)
Apathy, MDS-UPDRS 1.5	0 (0–1)
Other NMS	
UPSIT	18.6 (8.1)
RBD (%)	33 (41.3%)
CSF biomarkers	
A β_{42}	803 (561–1132)
<i>t</i> -tau	172 (136–213)
p-tau ₁₈₁	14.9 (11.3–18.3)
a-syn	1540 (1035–1804)
NfL	96.8 (69.9–132.2)
Biological AD (%)	5 (6.3%)
Genetics	
ApoE4 carrier (%)	27 (33.8%)
GBA carrier (%)	13 (16.3%)

Note: Continuous variables are presented as mean (standard deviation) or median (interquartile range), and categorical variables are presented as number (percentage).

Abbreviations: AD: Alzheimer's Disease; a-syn: alpha-synuclein; A β_{42} : beta-amyloid_{1–42}; GDS: Geriatric Depression Scale; H&Y: Hoehn and Yahr; HVLT: Hopkins Verbal Learning Test; JLO: Judgment of Line Orientation; LEDD: levodopa equivalent daily dose; LNS: Letter Number Sequencing; MDS-UPDRS: Movement Disorders Society-Unified PD Rating scale; MoCA: Montreal Cognitive Assessment; NfL: neurofilament light chain; NMS: non-motor symptoms; PD-SCD: PD-Subjective Cognitive Decline; PIGD: postural instability and gait difficulties; p-tau₁₈₁: phosphorylated tau 181; RBD: REM-sleep behavior disorder; SDMT: Symbol Digit Modalities Test; STAI: State-Trait Anxiety Inventory; *t*-tau: total tau; UPSIT: University of Pennsylvania Smell Identification Test.

Adjusted LMEM revealed associations between baseline A β_{42} and progression in MoCA ($p=0.025$), HVLT immediate recall ($p=0.025$), HVLT retention ($p=0.025$), HVLT delayed recall ($p=0.025$), and SDMT ($p=0.048$) (Table 2). No other associations between biomarkers and cognitive progression were found after correction for multiple comparisons. All models were adjusted for each CSF biomarker, time, age, disease duration, MDS-UPDRS III, and LEDD as fixed effects.

3.4 | Cognitive Trajectories of PD-SCD According to CSF A β_{42} and “Biological AD” Status

Given the associations between A β_{42} and biological AD diagnosis with cognitive decline both in our data and in previous literature, we divided the entire PD-SCD sample into three subgroups: *Normal A β_{42}* ($n=50$), *Low A β_{42}* ($n=25$), and *Biological AD* ($n=5$) (Table 3).

Adjusted LMEM predicted a worse cognitive slope for *Low A β_{42}* versus *Normal A β_{42}* ($\beta=-0.161$ points-per-year, SE=0.05, $p=0.007$), and for *Biological AD* versus *Normal A β_{42}* ($\beta=-0.390$ points-per-year, SE=0.09, $p<0.001$) (Figure 2 and Table S3). For *Biological AD* versus *Low A β_{42}* , β was -0.230 points-per-year (SE=0.10) but not statistically significant ($p=0.061$). MDS-UPDRS III trajectories did not differ between subgroups (*Low A β_{42}* vs. *Normal A β_{42}* : $p=0.231$; *Biological AD* vs. *Normal A β_{42}* : $p=0.571$; *Biological AD* vs. *Low A β_{42}* : $p=0.166$). Both models were adjusted for CSF biomarker status, time, interaction between CSF biomarker status and time, age, disease duration, LEDD, and GBA carrier status, with the MoCA model additionally adjusted for MDS-UPDRS III. Differences in GBA carrier status were significant and disappeared after correction for multiple comparisons, but given the potential effects of this variable on cognitive progression, we incorporated it into the model. Data availability of cognitive scores for each subgroup and timepoint is summarized in Table S4.

On the adjusted Cox proportional hazards analysis, both *Low A β_{42}* (HR 5.2, 95% CI 1.2–22.8, $p=0.029$) and *Biological AD* (HR 7.7, 95% CI 1.6–38.4, $p=0.013$) subgroups were associated with a higher risk of developing PDD, but not with developing PD-MCI (Table 4).

Further LMEM conducted for each cognitive test revealed significant differences in the slope of decline between *Normal A β_{42}* and *Biological AD* for all tests, and between *Normal A β_{42}* and *Low A β_{42}* for all tests except for animal fluency and JLO (Tables S5, S6, Figure S1). Differences between *Low A β_{42}* and *Biological AD* were only found for HVLT delayed recall ($\beta=-0.290$ points-per-year, SE=0.09, $p=0.004$). All models were adjusted for CSF biomarker status, time, interaction between CSF biomarker status and time, age, disease duration, MDS-UPDRS III, LEDD, and GBA carrier status.

4 | Discussion

In the present study, we analyzed a sample of 80 patients with PD-SCD in the early stages of the disease over a span of 7 years.

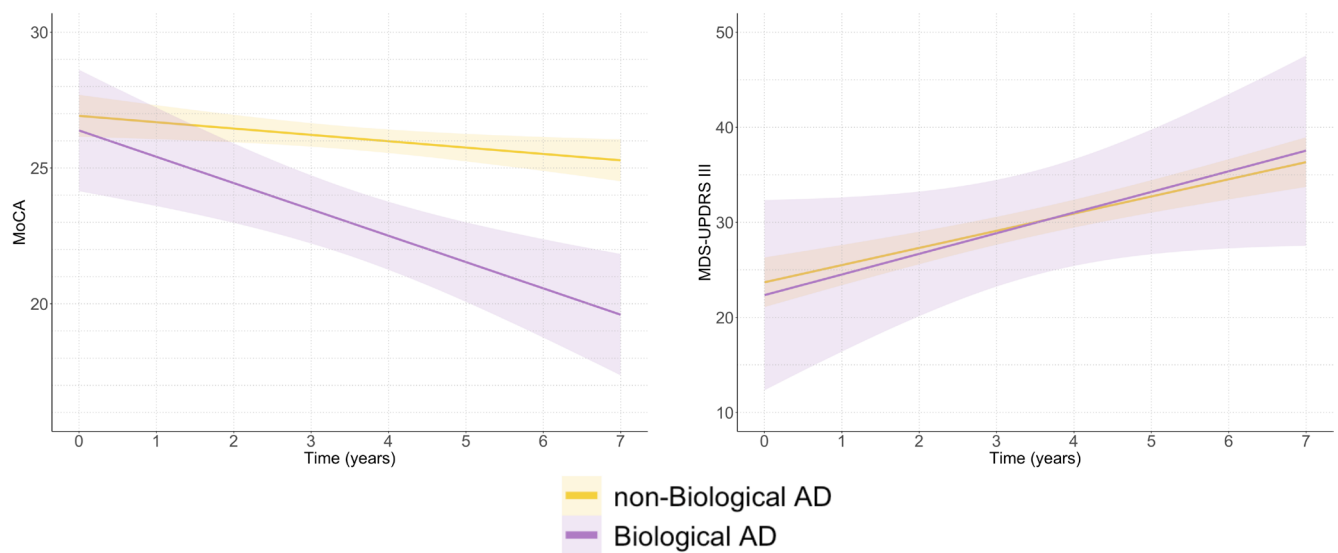


FIGURE 1 | Predictions of the LMEM for the MoCA (left) and MDS-UPDRS III (right) trajectories in patients with and without Biological AD. AD, Alzheimer's Disease; MDS-UPDRS III, Movement Disorders Society-Unified PD Rating Scale Part III; MoCA, Montreal Cognitive Assessment.

TABLE 2 | Prediction of the effect of each baseline CSF biomarker (log-transformed) on the longitudinal progression of cognitive test scores.

	$A\beta_{42}$		t -tau		p -tau ₁₈₁		a-syn		NfL	
	β (SE)	<i>p</i>	β (SE)	<i>p</i>	β (SE)	<i>p</i>	β (SE)	<i>p</i>	β (SE)	<i>p</i>
MoCA	1.6 (0.6)	0.025	-0.3 (0.9)	0.817	0.7 (0.8)	0.649	1.1 (0.6)	0.318	-1.2 (0.9)	0.275
HVLT imm rec	3.2 (1.3)	0.025	1.9 (2)	0.550	2 (1.7)	0.520	1.6 (1.3)	0.346	-2.7 (1.7)	0.275
HVLT retention	0.1 (0.1)	0.025	0.1 (0.1)	0.133	0.1 (0.1)	0.179	0.1 (0.1)	0.308	-0.04 (0.1)	0.636
HVLT del rec	1.9 (0.6)	0.025	1.9 (0.9)	0.133	1.7 (0.8)	0.179	0.9 (0.6)	0.308	-1.2 (0.9)	0.275
LNS	0.7 (0.6)	0.335	-1.2 (0.9)	0.416	-0.5 (0.8)	0.649	-0.4 (0.6)	0.518	-2 (0.7)	0.072
SDMT	6.1 (2.8)	0.048	1 (4.3)	0.817	2.2 (3.8)	0.649	4 (2.8)	0.308	1.5 (3.2)	0.636
Animal fluency	0.1 (1.2)	0.965	0.6 (1.9)	0.817	0.03 (1.6)	0.984	-1.3 (1.2)	0.346	-3.2 (1.7)	0.244
JLO	0.2 (0.6)	0.965	-2 (0.8)	0.133	-1.4 (0.7)	0.179	-0.6 (0.5)	0.346	-0.7 (0.5)	0.275

Note: Each row and column represent an individual LMEM. Bold values indicate statistical significance.

Abbreviations: a-syn, alpha-synuclein; $A\beta_{42}$, beta-amyloid₁₋₄₂; HVLT del rec, Hopkins Verbal Learning Test delayed recall; HVLT imm rec, Hopkins Verbal Learning Test immediate recall; JLO, Judgment of Line Orientation; LNS, Letter Number Sequencing; MoCA, Montreal Cognitive Assessment; NfL, neurofilament light chain; p -tau₁₈₁, phosphorylated tau 181; SDMT, Symbol Digit Modalities Test; SE, standard error; t -tau, total tau; β , estimate.

The main findings indicate that baseline CSF $A\beta_{42}$ can predict cognitive progression in PD-SCD. Furthermore, we identified three distinct cognitive trajectories based on CSF biomarkers: a severe decline in patients with biological AD, a moderate decline in patients with low $A\beta_{42}$, and a slow decline in patients with normal $A\beta_{42}$. While similar findings have been reported in the general PD population and in PD-associated cognitive impairment, here we provide new evidence on the specific association between PD-SCD and CSF biomarkers.

AD co-pathology is frequent among patients with PD and dementia with Lewy bodies, and is characterized by a gradient of accumulation; notably, higher levels are present in those with

PDD and PD-MCI compared to cognitively unimpaired individuals [31]. Although the mechanisms behind AD co-pathology in PD are only partially understood, it is widely accepted that factors such as age, sex, or Lewy pathology contribute to its development, and it is known to exacerbate both disease progression and cognitive decline [31]. The estimated prevalence of a biological AD CSF profile in PD ranges from 2% to 10%, which parallels the 6.3% prevalence identified in our cohort of cognitively unimpaired PD, and it has shown to increase the risk of cognitive deterioration [9, 31, 32].

Previous studies have shown a progressive reduction over time in CSF $A\beta_{42}$ and a-syn, along with increasing levels of t -tau,

TABLE 3 | Baseline characteristics of PD-SCD subgroups (*Normal A β_{42} , Low A β_{42} , Biological AD*).

	<i>Normal Aβ_{42}</i>	<i>Low Aβ_{42}</i>	<i>Biological AD</i>	<i>p</i>
<i>n</i>	50 (62.4%)	25 (31.3%)	5 (6.3%)	
Demographics				
Biological sex, women (%)	21 (42%)	6 (24%)	2 (40%)	0.322
Age at baseline, years	61 (10.2)	63 (7.1)	68.8 (4.5)	0.167
Education level, years	16 (14–16)	16 (12–17.5)	16 (15.5–19)	0.335
Parkinson's Disease				
Disease duration, months	5.5 (2.6–9.6)	9 (3.5–23.3)	3 (1.3–8.8)	0.116
MDS-UPDRS III	20 (16–26)	20 (16–30)	17 (13.5–20.5)	0.458
LEDD	0 (0–0)	0 (0–75)	0 (0–0)	0.005*
H&Y	2 (1–2)	2 (1–2)	2 (1–2)	0.918
PIGD phenotype (%)	17 (34%)	8 (34.8%)	1 (20%)	1.000
Cognition				
MoCA	28 (27–29)	27 (27–28)	27 (26–28.5)	0.585
HVLT immediate recall	24.5 (4.3)	22.8 (5.2)	25.8 (4.4)	0.238
HVLT retention	0.9 (0.8–1)	1 (0.7–1)	0.9 (0.9–1.2)	0.305
HVLT delayed recall	9 (7–10)	8 (6–10.5)	10 (9.5–11)	0.111
LNS	10.5 (8–12)	10 (9–12)	12 (8–13)	0.763
SDMT	40.5 (9.8)	37.1 (14.9)	40.2 (4)	0.471
Animal fluency	20.9 (5)	21.6 (5.5)	20.6 (7.4)	0.830
JLO	13 (11–14)	13 (11.5–14.5)	13 (10–14)	0.774
Neuropsychiatric				
Hallucinations (%)	2 (4%)	6 (24%)	0 (0%)	0.026*
GDS	2 (1–4)	3 (1.5–6.5)	3 (2–3)	0.540
STAI	69 (57.5–78.3)	70 (57.5–89.5)	48 (42.5–63)	0.061
Apathy, MDS-UPDRS 1.5	0 (0–1)	0 (0–1)	0 (0–0.5)	0.784
Other NMS				
UPSIT	18.9 (9.2)	18.5 (5.9)	16.2 (5.8)	0.786
RBD (%)	17 (34%)	12 (50%)	4 (80%)	0.080
CSF biomarkers				
A β_{42}	1024 (826–1241)	535 (429–595)	402 (378–489)	< 0.001***
<i>t</i> -tau	178 (154–213)	125 (105–180)	303 (254–321)	< 0.001****
p-tau ₁₈₁	15.5 (12.1–18.4)	10.4 (8.2–16)	27.4 (25.7–30.7)	< 0.001****
a-syn	1643 (1195–1886)	1007 (805–1246)	2349 (1508–3101)	< 0.001****
NfL	99 (66–131)	85 (66–107)	152 (95–184)	0.131
Genetics				
<i>ApoE4</i> carrier (%)	14 (28%)	10 (40%)	3 (60%)	0.233
<i>GBA</i> carrier (%)	5 (10%)	8 (32%)	0 (0%)	0.043*

Note: Continuous variables are presented as mean (standard deviation) or median (interquartile range), and categorical variables are presented as number (percentage). Bold values indicate statistical significance.

Abbreviations: AD, Alzheimer's Disease; a-syn: alpha-synuclein; A β_{42} : beta-amyloid_{1–42}; GDS: Geriatric Depression Scale; H&Y: Hoehn and Yahr; HVLT: Hopkins Verbal Learning Test; JLO: Judgment of Line Orientation; LEDD: levodopa equivalent daily dose; LNS: Letter Number Sequencing; MDS-UPDRS: Movement Disorders Society-Unified PD Rating scale; MoCA: Montreal Cognitive Assessment; NfL: neurofilament light chain; NMS: non-motor symptoms; PIGD: postural instability and gait difficulties; p-tau: phosphorylated tau 181; RBD: REM-sleep behavior disorder; SDMT: Symbol Digit Modalities Test; STAI: State-Trait Anxiety Inventory; *t*-tau: total tau; UPSIT: University of Pennsylvania Smell Identification Test.

**p* < 0.05: *Normal A β_{42}* versus *Low A β_{42}* .

***p* < 0.05: *Normal A β_{42}* versus *Biological AD*.

****p* < 0.05: *Low A β_{42}* versus *Biological AD*.

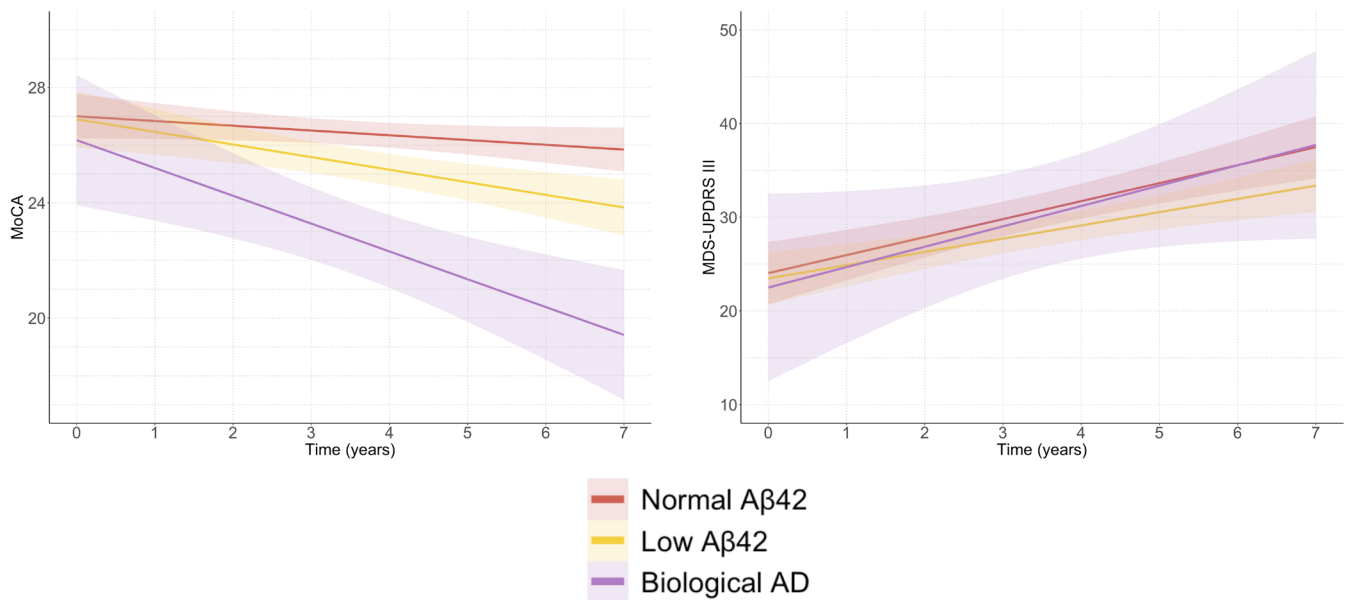


FIGURE 2 | Predictions of the LMEM for the MoCA (left) and MDS-UPDRS III (right) trajectories in *Normal A β_{42}* , *Low A β_{42}* , and *Biological AD*. AD, Alzheimer's Disease; A β_{42} , beta-amyloid₁₋₄₂; MDS-UPDRS III: Movement Disorders Society-Unified PD Rating scale part III; MoCA: Montreal Cognitive Assessment.

TABLE 4 | Multivariate Cox proportional hazards regression estimating the risk of PD-MCI and PDD for each PD-SCD subgroup (reference subgroup: *Normal A β_{42}*).

	MoCA < 26 (PD-MCI)				MoCA < 20 (PDD)			
	Crude HR (95% CI)	p	Adjusted HR (95% CI)	p	Crude HR (95% CI)	p	Adjusted HR (95% CI)	p
Low A β_{42}	1.61 (0.90–2.87)	0.109	1.56 (0.81–2.99)	0.184	4.60 (1.09–19.40)	0.038	5.19 (1.18–22.77)	0.029
Biological AD	2.31 (0.89–6.00)	0.087	2.07 (0.77–5.57)	0.151	5.51 (2.28–56.06)	0.003	7.71 (1.55–38.35)	0.013
Age	1.07 (1.03–1.10)	<0.001	1.07 (1.03–1.11)	<0.001	1.09 (1.01–1.18)	0.025	1.10 (1.00–1.21)	0.050
Disease duration	1.01 (0.99–1.02)	0.587	1.00 (0.96–1.05)	0.863	1.02 (0.99–1.06)	0.198	NA	NA
LEDD	1.00 (0.99–1.00)	0.769	1.00 (0.99–1.00)	0.319	1.00 (1.00–1.01)	0.038	NA	NA
MDS-UPDRS III	1.04 (1.00–1.07)	0.035	1.03 (1.00–1.07)	0.053	1.00 (0.91–1.09)	0.957	NA	NA
GBA carrier	0.94 (0.45–2.00)	0.877	1.68 (0.50–5.69)	0.404	4.09 (1.18–14.19)	0.026	NA	NA

Note: Bold values indicate statistical significance.

Abbreviations: AD, Alzheimer's Disease; A β_{42} , beta-amyloid₁₋₄₂; CI: confidence interval; HR: hazards ratio; LEDD: levodopa equivalent daily dose; MDS-UPDRS: Movement Disorders Society-Unified PD Rating scale; MoCA: Montreal Cognitive Assessment; PDD: PD-dementia; PD-MCI: PD-mild cognitive impairment.

p-tau, and NfL in the general PD population [25]. This progression is more pronounced for A β_{42} and NfL in patients with cognitive impairment, whereas differences between cognitively unimpaired and impaired patients in t-tau, p-tau, and a-syn progression show more variable results [15, 19, 25]. Similarly, baseline A β_{42} and NfL have proven to be good predictors of long-term cognitive deterioration, while the results for t-tau, p-tau,

and a-syn remain inconsistent [19, 23, 33]. In our cohort without biological AD, significant associations were found between baseline A β_{42} and progression in global cognition, as well as in memory, attention, and processing speed. These associations demonstrate that CSF AD biomarkers not only exacerbate global cognitive impairment in PD, but also lead to domain-specific dysfunctions, particularly in memory and language [34].

Based on the aforementioned data, we were also able to identify three distinct CSF biomarker-based cognitive trajectories in our PD-SCD cohort:

1. PD-SCD with CSF biomarkers confirming a biological diagnosis of AD, characterized by a severe decline in MoCA. In 2018, the NIA-AA proposed a biological definition of AD for research purposes [26]. This definition accepts various biomarker profiles, such as reduced $A\beta_{42}$ and increased p-tau₁₈₁ in CSF. While the causality of these proteins is still debated, their presence is characteristic of AD among all dementia-related diseases, making them critical for its diagnosis. In our sample, we only identified five patients with PD-SCD and a concurrent biological diagnosis of AD. At baseline, these patients showed non-statistically significant older age and lower incidence of hallucinations, and significantly higher t -tau and α -syn. The elevated levels of biomarkers may reflect not only more severe neurodegeneration, but also the frequent co-occurrence and interaction between α -syn and AD-pathology, which are believed to be the primary drivers of cognitive decline in PD and to promote their mutual aggregation [35, 36]. However, it remains to be elucidated whether the accumulation of both proteins is a consequence of their interaction or the result of an upstream dysfunctional pathway that promotes the aggregation of various proteins. Patients with a biological diagnosis of AD might develop less pure forms of PD-associated cognitive impairment, where AD-related cognitive impairment plays a more prominent or a synergistic role [1]. The number of clinical trials investigating disease-modifying therapies for AD is on the rise, especially those targeting patients in early/prodromal stages with a confirmed biological diagnosis [37, 38]. Although many clinical trials exclude patients with neurological diseases that could contribute to cognitive impairment, identifying these patients could help them benefit from emerging therapies in the future, and prevent their condition from being overshadowed by another neurodegenerative disease like PD.
2. PD-SCD with low CSF $A\beta_{42}$, characterized by a moderate decline in MoCA compared to patients with normal $A\beta_{42}$. $A\beta_{42}$ is a core biomarker for AD diagnosis and is the first biomarker to start decreasing in CSF, years before the onset of symptoms [39]. However, reduced levels are also observed in other conditions such as PD, dementia with Lewy bodies, vascular dementia, or frontotemporal lobar degeneration [40]. In PD, low CSF $A\beta_{42}$ and $A\beta$ deposition in pathology studies have been consistently associated with earlier and more severe cognitive decline, suggesting an independent role of $A\beta$ beyond a potential sign of prodromal AD [41, 42]. Post-mortem studies have revealed that most patients with PDD exhibit predominant synucleinopathy with $A\beta$ plaques and minimal/absent cortical tauopathy [43]. Concurrent cortical tauopathy is rare, suggesting that, similar to our findings, AD is not a common cause of cognitive impairment in PD [43]. Although it remains unclear whether $A\beta$ alone is sufficient to cause cognitive deterioration, it may interact with other proteins, leading to downstream pathologic changes [26]. Patients with low $A\beta_{42}$ show a clear but slower cognitive decline related to PD

and might be good candidates for clinical trials targeting PD-associated cognitive impairment. Notably, the rates of hallucinations and *GBA* carriers, which have been linked to more severe PD phenotypes, were higher compared to patients with normal $A\beta_{42}$ [44, 45]. Given the lack of clear association between *GBA* and $A\beta$, the deleterious effect of *GBA* is likely an independent contributor to cognitive worsening in this subgroup [46].

3. PD-SCD with normal CSF $A\beta_{42}$, characterized by a slower cognitive decline. Normal CSF $A\beta_{42}$ appears to be associated with milder phenotypes, suggesting that more conservative strategies may be more appropriate for these cases. No differences in motor phenotype or motor progression were observed between the milder cognitive phenotype and the more severe ones. Unlike α -syn, which has been implicated in motor symptoms, $A\beta$ deposits have not been definitively linked to motor symptomatology in PD, highlighting their specific role in cognition [41].

Furthermore, we identified differences between *Low $A\beta_{42}$* and *Biological AD* subgroups regarding delayed recall memory, underscoring the significant role of the complete CSF AD profile in memory. CSF AD profiles have been associated with more atypical PD phenotypes with fewer parkinsonian signs, fewer visual hallucinations, faster cognitive decline, and more pronounced memory and language impairments, which might not merely represent a combination of AD and PD symptoms, but rather a distinct condition yet to be fully described [31]. Beyond cognitive trajectories, we also found differences in the risk of developing PDD both in the *Low $A\beta_{42}$* and in the *Biological AD* subgroups, but not a greater risk of PD-MCI. While this elevated risk of PDD suggests more severe deterioration, tracking cognitive trajectories, as we did in the main analysis, may provide deeper insights than relying on single timepoint cut-offs in longitudinal cognitive studies [47]. In our sample, the estimates of annual change in MoCA relative to the reference subgroup were modest, and many patients had a baseline MoCA score of 30, likely due to a ceiling effect. Therefore, in research settings, using scales with a broader range, such as the PD-Cognitive Rating Scale, may provide clearer assessment of the progression [48].

We acknowledge that these findings are not new in the field of PD-associated cognitive impairment, and the link between AD pathology and cognitive decline is well established [9, 10, 16, 20, 35, 41]. The novelty of our study lies in replicating these associations within a specific PD population that is easily detectable in daily practice, and which has until now been categorized under the clinical label PD-SCD, insufficiently reflecting its variable progression. While we aim to enhance understanding of the risk posed by PD-SCD in conjunction with other biomarkers, we do not intend to challenge the potential role of alternative mechanisms in the development of different cognitive phenotypes.

There are several limitations to this study that should be noted. Firstly, cognitively unimpaired patients were selected based on the MoCA, which is a validated PD-MCI level I test, but lacks the precision of level II criteria and presents challenges in evaluating specific cognitive domains [21]. Secondly, PD-SCD was determined using MDS-UPDRS 1.1, which is less reliable than

newer tools like the MDS-Non Motor Scale, that specifically evaluates subjective perceptions in each cognitive domain [49]. Since a broad range of complaints can predict cognitive decline, a comprehensive assessment of cognitive complaints across all domains is essential in both clinical and research settings [50]. Lastly, the sample size, particularly in the *Biological AD* subgroup, is small and disproportionate compared to the other subgroups; however, this aligns with the low prevalence of the condition and reflects the expected representation in similar cohorts. Consequently, these results should be interpreted with caution, and further studies with larger sample sizes are necessary to validate their reliability.

In conclusion, both CSF A β_{42} and AD profile predict a worse cognitive progression in PD-SCD compared to patients with normal A β_{42} . In line with previous studies on PD-associated cognitive impairment that highlight the relevance of AD biomarkers, our findings not only support this idea but also emphasize that these associations are evident in the prodromal stage cognitive impairment. This study also shows how a broad clinical marker in cognitively unimpaired PD, such as cognitive complaints, can be refined and stratified into different risks of progression through the integration of biological markers. The combination of these clinical and biological markers could be useful for the implementation of enrichment strategies in emerging clinical trials targeting PD-associated cognitive impairment, as well as for improving personalized management in clinical practice. Future research with larger samples and new biomarkers will allow categorization of these patients into more precise biological subtypes for a better personalized medicine.

Author Contributions

J.R.-A.: design; execution; analysis; writing; editing of final version. A.P.-D., I.R.-B.: analysis; execution; review and critique. A.H.-B., J.P., A.V.-O.: review and critique. S.M.-H.: design; execution; analysis; writing. J.K.: design, execution; review and critique.

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

All data used in this study is openly available from PPMI (www.ppmi-info.org/access-dataspecimens/download-data).

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.

5. RESUMEN GLOBAL DE LOS RESULTADOS

Las primeras preguntas que este trabajo trata de responder son “¿Existen diferentes patrones de evolución cognitiva en pacientes con DCS-EP?” y “¿Existen marcadores clínicos que permitan subtipificar a estos pacientes en función del riesgo de progresión cognitiva?”, mediante el análisis longitudinal de 4 años de la cohorte nacional COhort of Patients with PArkinson’s Disease in Spain (COPPADIS). Para ello se seleccionaron todos los pacientes con DCS-EP en la cohorte en base a los siguientes criterios: PD-CRS >81 (rendimiento cognitivo normal) y dominio 5 de la escala Non-Motor Symptom (NMSS) Scale ≥ 1 (presencia de alguna queja cognitiva). Se incluyeron 198 pacientes con edad media de 60.9 años, duración de la enfermedad de 5.2 años, MDS-Unified Parkinson’s Disease Rating Scale (MDS-UPDRS III) de 21.2 y PD-CRS 97.6 en la visita basal.

Dado que el principal objetivo del estudio era valorar si existía un grupo progresor y otro no progresor, así como detectar las diferencias clínicas entre ambos, primeramente se crearon estos grupos mediante el Reliable Change Index (RCI). Este índice valora si el cambio a lo largo del tiempo puede ser atribuido o no a un error de medición y se calcula mediante la fórmula $((PD-CRS_{4años} - PD-CRS_{basal}) / \text{Error estándar de la diferencia})$. Usando un intervalo de confianza del 90%, los pacientes fueron categorizados en progresores si el RCI era ≤ -1.64 , y en no progresores si el RCI era > -1.64 . El umbral de -1.64 correspondía a una pérdida de 16 puntos en la PD-CRS a los 4 años. En un segundo paso, se realizaron modelos lineales de efectos mixtos (MLEM) para evaluar las diferencias en la progresión cognitiva y motora entre ambos grupos. Pudimos observar una clara diferencia de progresión cognitiva entre grupos (diferencia de 11.66 en la PD-CRS a los 2 años y de 26.87 a los 4 años), frente a una relativa estabilidad motora (diferencia de 1.13 en la MDS-UPDRS III a los 2 años y de 2.51 a los 4 años). Finalmente realizamos una regresión logística binaria (progresores vs no progresores) para explorar diferencias clínicas basales que pudieran predecir la pertenencia a cada grupo. Pudimos ver que la edad, la severidad motora (medida por MDS-UPDRS III) y la presencia de TCSR se asociaban de forma independiente al grupo progresor.

Seguidamente, tratamos de responder a la pregunta “¿Existen marcadores biológicos que permitan subtipificar a estos pacientes en función del riesgo de progresión cognitiva?” mediante el análisis longitudinal de 7 años de la cohorte internacional Parkinson's Progression Markers Initiative (PPMI). Se seleccionaron todos los pacientes con DCS-EP en base a los siguientes criterios: MoCA ≥ 26 (rendimiento cognitivo normal) y MDS-UPDRS 1.1 ≥ 1 (presencia de quejas cognitivas). Además, todos debían tener disponible los niveles basales de A β 42 y p-tau₁₈₁ en LCR, y al menos una visita de seguimiento clínico longitudinal. Se incluyeron 80 pacientes con una media de edad de 62.1 años, duración de la enfermedad de 0.47 años, y MDS-UPDRS III de 20.

Inicialmente dividimos la muestra en pacientes con y sin diagnóstico biológico de EA en base a los niveles basales de A β 42 y p-tau en LCR. Mediante MLEM pudimos ver que los pacientes con diagnóstico biológico de EA (n=5) tenían una evolución cognitiva claramente peor que aquellos sin biomarcadores de EA (n=75). Posteriormente, realizamos nuevos MLEM en la cohorte (excluyendo a los pacientes con EA biológico para evitar este factor de confusión), y pudimos observar que niveles basales más elevados de A β 42 predecían un mejor rendimiento cognitivo a lo largo del tiempo tanto en MoCA como en subtests de memoria, y de atención y velocidad de procesamiento. Estos resultados nos llevaron a categorizar la cohorte completa en tres grupos: A β 42 normal, A β 42 bajo, y diagnóstico biológico de EA. Un último análisis mostró que los pacientes con A β 42 normal tenían una mejor progresión cognitiva (medida con MoCA) que aquellos con A β 42 bajo, y los de A β 42 bajo mejor que aquellos con diagnóstico biológico de EA, a pesar de trayectorias motoras similares. Cuando analizamos las trayectorias de estos tres grupos en los subtests cognitivos, vimos diferencias entre A β 42 normal y los otros dos grupos en todos los dominios, mientras que entre A β 42 bajo y diagnóstico biológico de EA solo vimos diferencias en los subtests de memoria.

6. RESUMEN GLOBAL DE LA DISCUSIÓN

El DCS-EP es la fase clínica más precoz del DC-EP, muchas veces una fase intermedia entre un estado de cognición normal y el DCL-EP, y como tal, el interés en torno a este concepto ha crecido considerablemente en los últimos años (47). Debido a la falta de consenso sobre las herramientas para diagnosticarlo, la frecuencia es muy variable entre estudios. Un metaanálisis reciente estimó una prevalencia del 39% aproximadamente (48). En el primer artículo obtuvimos una prevalencia del 60.7%, ligeramente superior a estudios previos. Es probable que el uso de la NMSS y la PD-CRS, escalas que evalúan las quejas y el rendimiento cognitivo de forma más detallada que otras muy usadas como el MoCA o la MDS-UPDRS 1.1, respectivamente, sea uno de los factores responsables.

El metaanálisis previamente mencionado también calculó un riesgo 2.7 veces mayor de DC-EP en este grupo de pacientes con respecto a aquellos sin quejas cognitivas. Sin embargo, es llamativo que algunos estudios no hayan detectado este riesgo aumentado, lo que sugiere no solo una variabilidad en las medidas utilizadas, sino también una heterogeneidad en la evolución de estos pacientes. Esta evolución heterogénea es bien conocida para los síntomas motores de la EP, para los que algunos pacientes mantienen una estabilidad durante muchos años, mientras que otros desarrollan complicaciones motoras en pocos años. En el primer estudio hicimos una aproximación impulsada por datos para categorizar de forma artificial una muestra amplia de pacientes en un grupo de progresión y otro de no progresión. Los MLEM confirmaron trayectorias cognitivas muy divergentes a pesar de trayectorias motoras similares en dos grupos que, *a priori*, estaban englobados bajo una misma etiqueta clínica (DCS-EP).

No está claro qué tipo de quejas son las que más riesgo de progresión a DC-EP confieren. Mientras que en nuestro estudio detectamos más quejas de memoria pero no de concentración/atención en el grupo de progresores, la literatura previa ofrece resultados variados. Algunos estudios han asociado quejas disejecutivas a una peor evolución, mientras que otros hacen referencia a quejas de memoria o de enlentecimiento mental (84,85). De esto se infiere que prácticamente cualquier queja

puede ser relevante y para detectarlas es necesaria una evaluación completa mediante escalas como la MDS-Non Motor rating Scale (MDS-NMS), que es la única que evalúa las quejas en cada uno de los cinco dominios típicamente afectados en la EP (atención, funciones ejecutivas, memoria, lenguaje y visuoespacial).

Los principales marcadores clínicos de riesgo conocidos de DC-EP incluyen sexo masculino, edad, nivel educacional, severidad motora, síntomas axiales, alucinaciones, depresión, apatía, hiposmia, o TCSR (86). En nuestra muestra de pacientes con síntomas cognitivos prodrómicos (DCS-EP) la edad, la severidad motora y el TCSR mostraban una asociación independiente. Es interesante la asociación con el TCSR, un síntoma que se cree que es consecuencia de la degeneración de neuronas colinérgicas pedunculopontinas (87). Como ya hemos mencionado en la introducción, el sistema colinérgico está muy implicado en el DC-EP, por lo que pacientes con TCSR con DCS-EP podrían representar subtipos de EP caracterizados por una disfunción colinérgica, que a su vez se han asociado a fenotipos más agresivos (45). Aunque no pudimos objetivar diferencias significativas entre grupos en cuanto a alucinaciones visuales o trastornos del estado de ánimo, su asociación con DC-EP está bien documentada y serán necesarios más estudios en este grupo de pacientes para poder confirmar o refutar nuestros hallazgos.

El papel de los marcadores biológicos en fluidos y tejidos no ha sido previamente estudiado en el DCS-EP. En un primer análisis del segundo artículo pudimos observar que el perfil en LCR de EA estaba asociado a una peor evolución cognitiva. Ya hemos mencionado en la introducción que la patología Lewy cortical y, en menor medida, la co-patología EA cortical, son los principales marcadores patológicos asociados a DC-EP (79,88). Igualmente hay estudios que han asociado el perfil en LCR de EA a mayor riesgo cognitivo (89). Se piensa que factores como la edad, el sexo o la patología Lewy contribuyen tanto al DC-EP como a la presencia de una mayor cantidad de co-patología EA (88). A pesar de ello, los mecanismos fisiopatológicos de la co-patología EA implicados en la peor evolución cognitiva no son bien conocidos.

Independientemente de la presencia de un perfil de EA, ya se había visto que marcadores en LCR como A β 42 o NfL están asociados a una peor evolución cognitiva, mientras que otros como t-tau, p-tau, o α -syn han mostrado resultados menos contundentes (77,90,91). La exclusión de los pacientes con perfil de EA en nuestra cohorte de DCS-EP nos permitió ver que la asociación de A β 42 con la peor evolución cognitiva era independiente, con una afectación más específica de memoria, atención y velocidad de procesamiento.

En base a estos resultados, elaboramos tres grupos artificiales que nos permitieron definir trayectorias cognitivas diferentes en pacientes con DCS-EP:

- El grupo con perfil en LCR de EA presentaba el deterioro cognitivo más marcado. Este grupo se definió en base a los criterios de la National Institute on Aging-Alzheimer's Association (NIA-AA), por niveles bajos de A β 42 y niveles elevados de p-tau en LCR (92). Es posible que la peor evolución pueda ser una consecuencia tanto del efecto independiente de estas proteínas como de su interacción con α -syn (93). En cualquier caso, no queda claro si la co-ocurrencia es dependiente de α -syn o es debida a alguna alteración en algún punto superior de la cascada metabólica. En cuanto al perfil clínico, era llamativa la ausencia de alucinaciones, las cuales son muy típicas en el DC-EP, y la mayor asociación con la evolución amnésica. Esto podría indicar la presencia de fenotipos específicos en función del subtipo biológico de DC-EP.
- El grupo con niveles bajos de A β 42 presentaba un deterioro cognitivo intermedio. Dado que A β 42 es el primer biomarcador que desciende en LCR en EA, años antes del diagnóstico, cabría la posibilidad de que se trataran de casos de EA incipiente (94). Sin embargo, A β 42 también desciende en otras enfermedades como EP, ECL, demencia vascular, o demencia frontotemporal, y los estudios en EP han demostrado de forma consistente su asociación con un peor pronóstico independientemente de los acúmulos de tau (95–97). Por ello, se piensa que estos pacientes representan un fenotipo específico de DC-EP y no de EA incipiente.
- El grupo con niveles normales de A β 42 presentaba la evolución cognitiva más estable, a pesar de una progresión motora similar a los otros dos grupos. Esto

demuestra el probable papel que juega A β 42 en la cognición pero no en la sintomatología motora (97).

Con el número de ensayos clínicos al alza, la posibilidad de identificar pacientes con diferentes subtipos biológicos, entre ellos con algunos con perfil EA, resulta interesante ya que en un futuro podrían servir para reclutar candidatos a ensayos clínicos de específicos tanto de EA o de DC-EP.

Este trabajo tiene varias limitaciones. Primeramente, la presencia de quejas cognitivas fue evaluada con la NMSS en el primer artículo, y con la MDS-UPDRS 1.1 en el segundo. Aunque ambas escalas han sido previamente usadas para detectar este síntoma, la realidad es que no cubren adecuadamente todos los dominios que pueden verse afectados en la EP. Segundo, la valoración cognitiva global del segundo estudio fue realizada con la escala MoCA. A pesar de estar aceptada para el diagnóstico de DCL-EP, se trata de una escala con un rango estrecho y con efecto techo que dificulta la valoración de cambios en el tiempo. Siempre que no sea posible una evaluación específica de cada dominio, escalas como la PD-CRS, utilizada en el primer artículo, son más adecuadas por su amplio rango y el improbable efecto techo. Por último, el grupo con perfil en LCR de EA en el segundo artículo era muy pequeño. Aunque el PPMI es una cohorte grande, dado que eran necesarios pacientes con marcadores en LCR y con seguimiento longitudinal, fue difícil encontrar más pacientes asumiendo una prevalencia de DCS-EP del 39% y una prevalencia de EA del 2-10%.

Hay varios puntos fuertes a destacar. Por un lado, son cohortes longitudinales relativamente grandes y con muchos años de seguimiento (4 y 7 en el primer y segundo artículo, respectivamente) para un síntoma no muy frecuente. Por el otro, es un estudio que valora de una forma óptima la progresión de síntomas mediante trayectorias individuales, en vez de mediante los puntos de corte artificiales habitualmente utilizados para estas escalas (ej. MoCA <26 para DCL-EP).

Este trabajo es relevante y novedoso dentro del área específica del DCS-EP, un campo hasta ahora poco explorado en la literatura. La identificación de subgrupos de pacientes

con diferentes riesgos de progresión cognitiva, y la asociación de biomarcadores tipo EA con peor evolución, representan hallazgos innovadores que refuerzan la importancia de la identificación temprana del DCS-EP. Poder clasificar a estos pacientes según su riesgo de deterioro cognitivo no solo permitirá optimizar el consejo clínico, sino que abre la puerta al diseño de ensayos clínicos dirigidos tanto a fases prodrómicas de EP como a las fases más tempranas del DC-EP en la enfermedad clínicamente manifiesta.

7. CONCLUSIONES

1.- El DCS-EP, pese a su frecuencia, no siempre implica una evolución cognitiva maligna. Si bien hay pacientes con un deterioro cognitivo franco, muchos pacientes se mantienen estables a lo largo del tiempo. Los pacientes con DCS-EP son candidatos idóneos para ensayos clínicos que buscan modificar el curso clínico del deterioro cognitivo, por lo que incorporar este concepto ayudará a enriquecer los diseños, y a seleccionar en fases precoces a pacientes con alto riesgo de deterioro.

2.- Existen marcadores clínicos y biológicos en DCS-EP que predicen un mayor riesgo de progresión cognitiva. Entre los marcadores clínicos destacan la edad, la severidad motora y la presencia de TCSR. Entre los marcadores biológicos destacan los niveles bajos de A β 42 y los marcadores de diagnóstico biológico de EA en LCR. La importancia de replicar en la fase clínica más precoz algo que ya era conocido en el DC-EP, radica en la aplicabilidad tanto al diseño de ensayos como al potencial papel pronóstico en la asistencia clínica.

3.- El DCS-EP, un marcador clínico muy amplio y asociado globalmente a mayor deterioro cognitivo, puede ser refinado y estratificado en diferentes riesgos de progresión mediante la incorporación biomarcadores multimodales. Esto es esencial para la subtipificación biológica de la EP y para una mejor medicina personalizada en el futuro.

8. LÍNEAS DE FUTURO

El DCS-EP es un concepto relativamente nuevo, por lo que su investigación está en fases preliminares. El primer objetivo será seleccionar escala/s específica/s y establecer unos criterios diagnósticos que permitan homogeneizar la selección de pacientes entre estudios, tanto para los observacionales como para ensayos clínicos. Esto permitirá aumentar el número de estudios de diseño longitudinal y comparables que ayuden a extender la evidencia existente. Los biomarcadores serán un pilar fundamental para entender las implicaciones del DCS-EP en los pacientes y para establecer diferentes subtipos biológicos que permitan pronosticar la evolución. Aunque los biomarcadores en LCR son los más estudiados hasta el momento, serán imprescindibles estudios de neuroimagen funcional y estructural, o el análisis de biomarcadores en otros fluidos y tejidos como la sangre o la piel, entre otros. Debido a su accesibilidad, la sangre es previsible que en el futuro sea la principal fuente para identificar biomarcadores en DCS-EP y en EP en general. Finalmente, todo esto permitirá enriquecer los ensayos clínicos con pacientes muy bien seleccionados, de tal forma que podamos ver el efecto de intervenciones en grupos de pacientes muy similares. Al ser una fase prodrómica, los pacientes con DCS-EP son una oportunidad para estudiar e intervenir sobre el DC-EP en una etapa muy incipiente, que probablemente representa el estadio más temprano de degeneración al que poder acceder clínicamente.

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