UNIVERSIDADE FEDERAL DO RIO GRANDE DO SUL

FACULDADE DE MEDICINA

PROGRAMA DE PÓS-GRADUAÇÃO EM MEDICINA: CIÊNCIAS MÉDICAS

ESTUDO COMPARATIVO DA DISFUNÇÃO AUTONÔMICA NA DOENÇA DE PARKINSON COM MUTAÇÕES *LRRK2*, *PRKN* E *GBA*

BÁRBARA MALDOTTI DALLA CORTE

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Orientador: Prof. Dr. Carlos Roberto de Mello Rieder

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“Se não sais de ti, não chegas a saber quem és”

José Saramago em *O conto da ilha desconhecida*

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A existência dessa dissertação é uma surpresa interessante, até para mim. Olhando agora para o processo que levou até ela, parece que andei por uma estradinha tortuosa subindo uma montanha – você sobe devagar, às vezes fica um pouco nauseado, mas a vista lá do topo geralmente é deslumbrante. Talvez a vista do topo dessa dissertação não seja exatamente deslumbrante para todos que a leiam, mas, para mim, o deslumbramento está em algumas coisas que aprendi com ela e que vão muito além da disfunção autonômica na doença de Parkinson com mutações *LRRK2*, *PRKN* e *GBA*. Como, por exemplo, a importância de subir devagar para subir sempre (mas descansar eventualmente é fundamental, inclusive para não ficar nauseado) e que, não só o trajeto é mais agradável, como a vista é mais deslumbrante quando temos com quem compartilhar. E, aqui, agradeço aos que compartilharam comigo dessa estradinha de montanha.

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A todos os meus amigos e familiares, pelas múltiplas manifestações de carinho.

Aos pacientes, graças aos quais e para quem a ciência deve ser feita. À Michael J. Fox Foundation. Ao Hospital das Clínicas de Porto Alegre e à Universidade

Federal do Rio Grande do Sul, fontes de educação e saúde públicas, gratuitas e de qualidade.

Terminada a subjetividade, vamos aos fatos.

RESUMO

Base teórica: a doença de Parkinson (DP), apesar de ser amplamente conhecida pelas suas manifestações motoras, apresenta uma gama de sintomas não motores que têm, com frequência, maior impacto na qualidade de vida e até mesmo na mortalidade dos pacientes. Dentre esses sintomas não-motores, as disautonomias estão entre os mais significativos. **Objetivo:** este estudo buscou avaliar as diferenças de manifestação da disfunção autonômica em pacientes com DP esporádica e genética, esta última em três formas – com mutações no gene da *PRKN*, com mutações no gene do *LRRK2* e com mutações no gene da *GBA*. **Métodos:** foi realizado um estudo caso-controle em que o grupo controle eram os pacientes com DP esporádica. Um total de 742 pacientes foram incluídos (485 esporádicos, 9 *PRKN*, 165 *LRRK2* e 85 *GBA* – dois pacientes apresentam mutações nos genes *LRRK2* e *GBA* simultaneamente) e a avaliação dos sintomas disautonômicos se deu através do questionário SCOPA-AUT e de algumas questões da escala MDS-UPDRS. Quando possível, os achados foram controlados para potenciais confundidores. **Resultados:** considerando-se a pontuação total do questionário SCOPA-AUT, uma análise através de regressão linear demonstrou que o grupo de indivíduos com DP esporádica apresentou menor pontuação em comparação ao grupo com mutação no *GBA* (B= -4.668; p 0.050), mesmo quando controlado para fatores como tempo de doença, pontuação na escala Hoehn&Yahr e dose diária equivalente de levodopa (LEDD). Avaliando-se a disfunção autonômica por sistemas, o grupo *GBA* apresentou maior prevalência de sintomas cardiovasculares (p 0.007) e termorregulatórios (p 0.006). O grupo *LRRK2* não apresentou diferenças na pontuação do SCOPA-AUT total em comparação ao grupo com DP esporádica quando a avaliação é controlada para os fatores citados anteriormente (B= -3.105; p 0.189); entretanto, análise de subgrupo de sintomas evidencia maior prevalência de sintomas gastrointestinais (p 0.007), termorregulatórios (p <0.001) e cardiovasculares (p 0.011). O grupo *PRKN* não apresentou manifestações disautonômicos com diferenças estatisticamente significativas em relação ao grupo esporádico sob nenhum aspecto. **Conclusão:** as manifestações disautonômicos diferem em alguns grupos de pacientes com DP genética comparativamente a pacientes com doença esporádica. Isso traz à luz esse

grupo de sintomas, de tão grande impacto nos pacientes, reforçando uma busca ativa por tais manifestações e uma abordagem individualizada. Mais estudos são necessários para avaliar mutações específicas em cada gene e para melhor compreender se essas diferenças correspondem a mecanismos fisiopatológicos distintos dos já conhecidos.

Palavras chave: doença de Parkinson, disautonomia, genética, *PRKN*, *LRRK2*, *GBA*, SCOPA-AUT

ABSTRACT

Background: Parkinson's disease (PD), despite being known for its motor symptoms, exhibits a variety of non-motor symptoms whose frequently have more impact on quality of life and even on mortality of patients. Among those non-motor symptoms, dysautonomias are among the most significant ones. **Objective:** this study aims assess differences of manifestation of autonomic disfunction in patients with sporadic and genetic PD, the last one in three groups – with *PRKN* gene mutations, with *LRRK2* gene mutations and with *GBA* gene mutations. **Methods:** a case-control study was performed where the control group were the sporadic PD subjects. The total sample size was 742 (485 sporadic, 9 *PRKN*, 165 *LRRK2* and 85 *GBA* – two patients have *LRRK2* and *GBA* simultaneously) and the dysautonomic evaluation were through SCOPA-AUT and some questions of the MDS-UPDRS scale. When possible, the results were controlled for potential confounders. **Results:** considering SCOPA-AUT total score, a linear regression showed that the sporadic group has lower scores compared to the *GBA* group (B= -4.668; p 0.050), even when controlled for disease duration, Hoehn&Yahr score and LEDD. Assessing autonomic disfunction by systems, the *GBA* group present more prevalence of cardiovascular (p 0.007) and thermoregulatory (p 0.006) symptoms. The *LRRK2* group did not show differences regarding the SCOPA-AUT total score compared to the sporadic group when controlling to the factors mentioned earlier (B= -3.105; p 0.189); however, subgroup analysis exhibited more gastrointestinal (p 0.007), thermoregulatory (p <0.001) and cardiovascular (p 0.011) symptoms. The *PRKN* group did not show any different dysautonomic features compared to the sporadic group. **Conclusion:** the dysautonomic symptoms differ between some groups of genetic PD compared to the sporadic disease. This highlights the group of symptoms, with big impact in patients, reinforcing an active search for those manifestations and a personal approach. More studies are needed to evaluate specific mutations on each gene and to better understand if those differences correspond to distinct pathophysiological mechanisms from those already known.

Key words: Parkinson's disease, dysautonomia, genetic, *PRKN*, *LRRK2*, *GBA*, SCOPA-AUT

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AMS	Atrofia de múltiplos sistemas
ATP13A2	*Adenosine Triphospatease Cation Transporting 13A2*
Ascl1	*Achaete-scute family BHLH transcription factor 1*
BDNF	*Brain-derived neurotrophic factor*
BMP	*Bone morphogenetic protein*
CXCL12	*C-X-C motif chemokine ligand 12*
CXCR4	*C-X-C chemokine receptor type 4*
DCSREM	Distúrbio comportamental do sono REM
DNAJC6	*DnaJ Heat Shock Protein Family Member C6*
DP	Doença de Parkinson
EdnrB	*Endothelin receptor type B*
FoxD3	*Forkead box D3*
GATA	*Globin transcription factor*
GBA	Glicocerebrosidase
GDNF	*Glial-derived neurotrophic factor*
Gfra1	*GDNF family receptor alpha 1*
GWAS	*Genome wide association studies*
Hand2	*Heart and neural crest derivative expressed 2*
Hif1-alpha	*Hypoxia inducible factor 1 subunit alpha*
INAD	Distrofia infantil neuroaxonal
LEDD	Dose diária equivalente de levodopa
LR	*Likelihood ratio*
LRRK2	*Leucine-rich repeat kinase 2*
Mash	*Mammalian achaete-scute homologue*
MBIG	Metaiodobenzilguanidina
MDS	*Movement Disorders Society*
MDS-PD	*Movement Disorders Society Clinical Diagnostic Criteria for Parkinson's Disease*
MDS-UPDRS	*Movement Disorders Society – Unified Parkinson's Disease Rating Scale*

NBIA	Neurodegeneração com acúmulo cerebral de ferro
NGF	*Nerve growth factor*
NT	*Neurotrophin*
PD	Parkinson's disease
PET	Tomografia por emissão de pósitrons
Phox2b	*Paired like homeobox 2b*
PINK1	*PTEN (Phosphatase and tensin homolog) induced kinase1*
PLA2G6	*Phospholipase A2 group VI gen*
PPMI	*Parkinson's Progression Markers Initiative*
PRKN	Parkina
Ret	*Rearranged during transfection*
SCOPA-AUT	*Scales for Outcomes in Parkinson's Disease – Autonomic Dysfunction*
SDF1	*Stromal cell-derived factor 1*
Sox10	*SRY-box transcription factor 10*
SPECT	Tomografia computadorizada por emissão de fóton único
STROBE	*Strengthening the reporting of observational studies in epidemiology*
TGF-beta	*Transforming growth factor beta*
TrkB	*Tyrosine receptor kinase B*
VPS13C	*Vacuolar protein sorting 13 homolog C*

SUMÁRIO

1. INTRODUÇÃO

A doença de Parkinson é uma doença neurodegenerativa descrita há mais de 200 anos e a segunda doença neurodegenerativa mais prevalente no mundo, acometendo 0,3% da população geral e com uma estimativa de crescimento exponencial para as próximas duas décadas.[6] Apesar de ser conhecida de longa data e de ter uma prevalência bastante significativa, muitas descobertas sobre sua fisiopatologia e sobre suas bases genéticas ainda estão sendo feitas nos últimos anos.

O diagnóstico da DP só pode ser feito a partir do momento em que sintomas motores se apresentam[8,9], mas isso só ocorre após a perda de pelo menos 50% dos neurônios dopaminérgicos da *substantia nigra pars compacta*[10]. Muito antes disso, até duas décadas antes, há evidências de que o processo patológico de depósito de proteína alfa-sinucleína anormal já se inicia e isso é corroborado em estudos retrospectivos e coortes prospectivas que evidenciam a presença de sintomas não motores até mesmo anos antes do início dos sintomas motores. [11,12,13,14]

O espectro de sintomas não motores tem sido alvo de estudos devido à sua precocidade de manifestação no processo da doença, à sua proeminência e ao impacto que apresenta, inclusive em termos de qualidade de vida e mortalidade.[21] Sob essa ótica, os sintomas disautonômicos são um grupo de especial interesse – estão entre os achados não motores mais comuns, com prevalência de 30-65% e têm correlação com prejuízo nas atividades diárias, depressão, maior taxa de progressão da doença e menor sobrevida.[18,22,23]

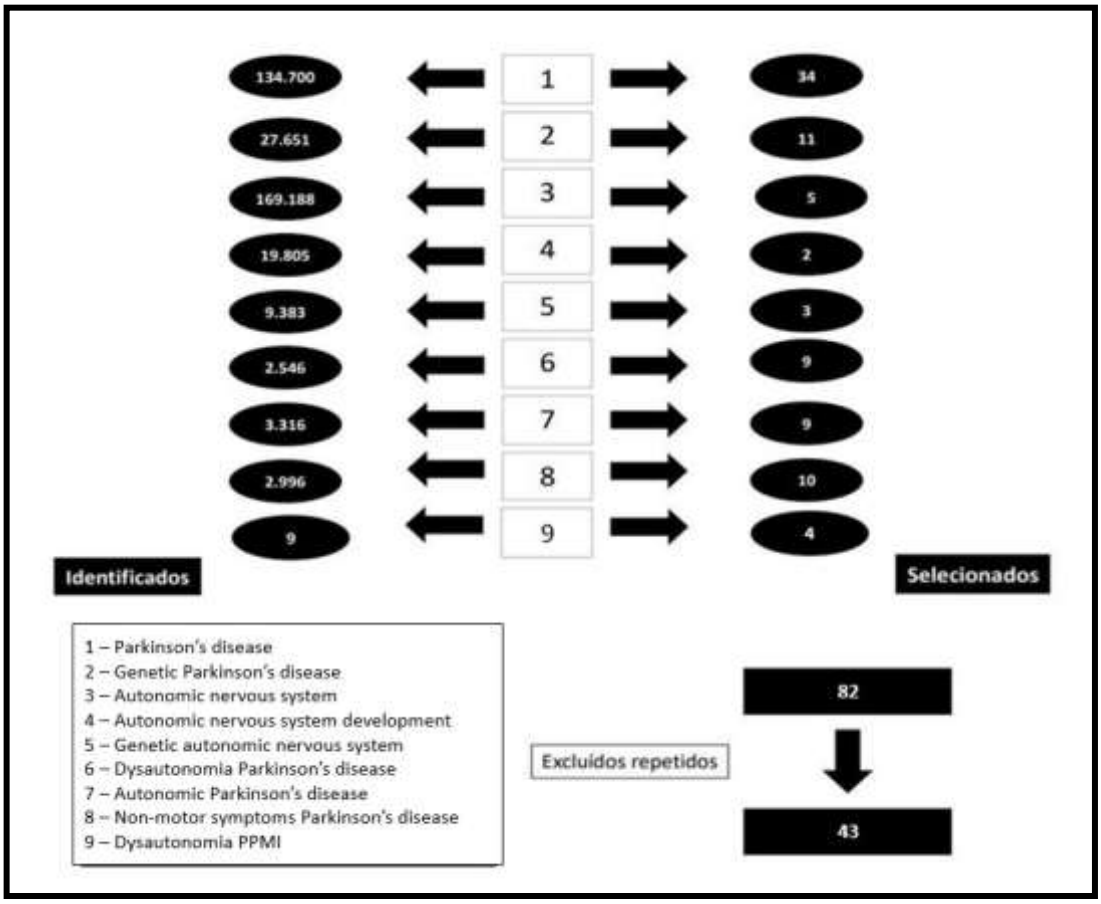
Do ponto de vista genético, tanto formas monogênicas quanto diversos *loci* de risco para a doença foram descritas desde a década de 1990[30] e isso propiciou novas visões sobre a fisiopatologia e ampliou as possibilidades de terapias neuroprotetoras e modificadoras da doença, muitas em estudo atualmente. Entretanto, pouco se sabe a respeito das influências genéticas sobre os sinais e sintomas disautonômicos dos pacientes com DP.

2. REVISÃO DA LITERATURA

2.1 ESTRATÉGIAS PARA LOCALIZAR E SELECIONAR AS INFORMAÇÕES

Esta revisão da literatura teve por objetivo revisar aspectos relacionados ao desenvolvimento embrionário do sistema nervoso autonômico e suas bases genéticas, bem como conceitos fisiopatológicos, anatômicos e genéticos já conhecidos sobre a DP, com enfoque nas suas manifestações disautonômicas. Foram realizadas buscas na base de dados PubMed. Os termos de busca utilizados foram “Parkinson’s disease”, “genetic Parkinson’s disease”, “autonomic nervous system”, “autonomic nervous system development”, “genetic autonomic nervous system”, “dysautonomia Parkinson’s disease”, “autonomic Parkinson’s disease” “non motor symptoms Parkinson’s disease”, “dysautonomia PPMI” e suas combinações. Artigos incluídos na revisão de literatura além dos obtidos com a busca na base de dados foram selecionados a partir de citações e referências de outros artigos provenientes da busca inicial.

FIGURA 1 – ESTRATÉGIAS PARA LOCALIZAR E SELECIONAR AS INFORMAÇÕES



Fluxograma da seleção de artigos. Fonte: elaborado pela autora.

2.2 SISTEMA NERVOSO AUTONÔMICO

2.2.1 Anatomia e fisiologia do sistema nervoso autonômico

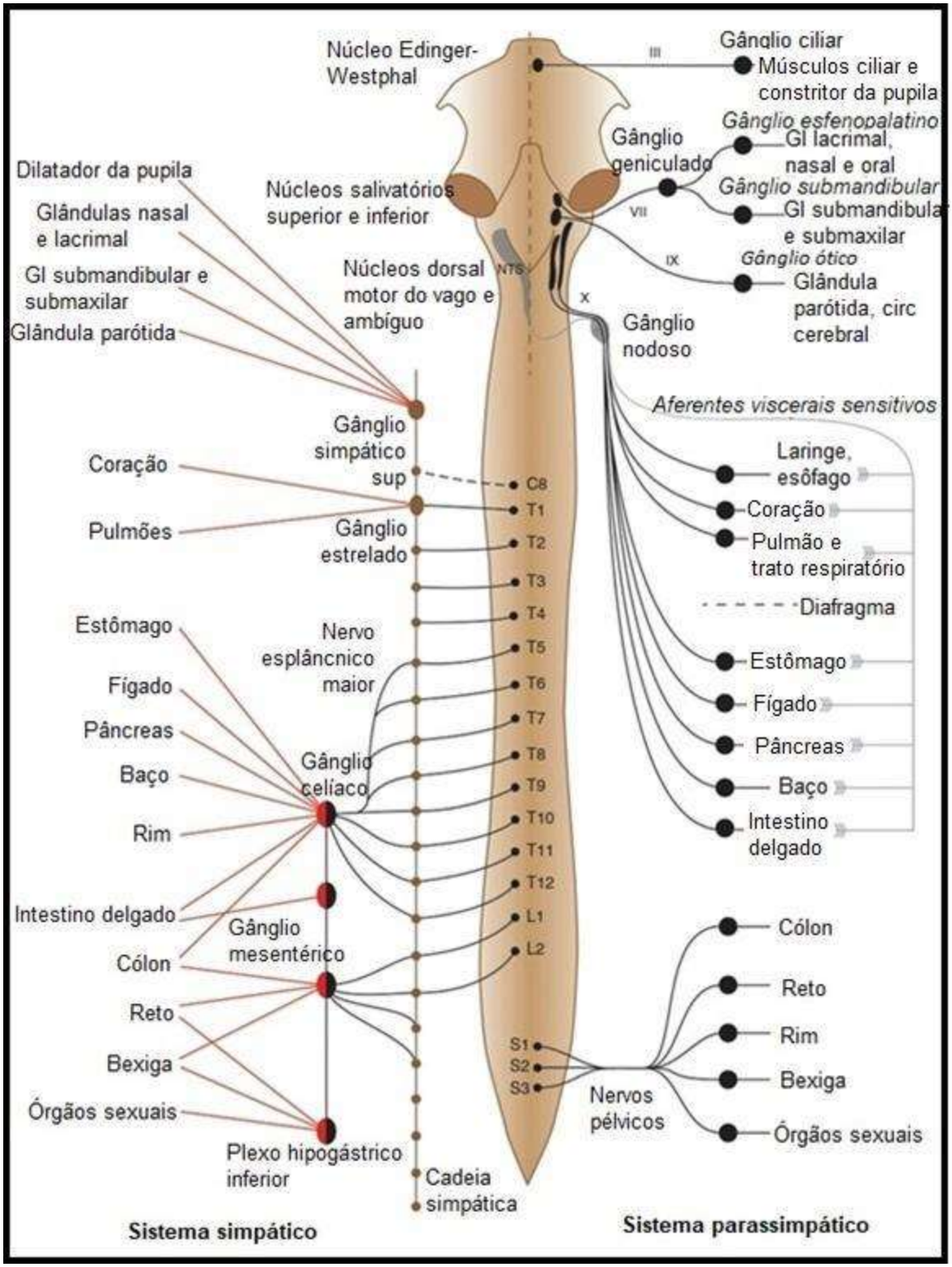
O sistema nervoso autonômico deriva de células da crista neural e se desenvolve fenotipicamente com base em sinalizações de neurotransmissores. Ele se distribui de forma complexa anatomicamente, tanto ao longo do sistema nervoso central quanto do periférico e seu controle é modulado via central em resposta a estímulos aferentes provenientes de todo o corpo (Figura 2)[1]. A conexão entre os centros autonômicos do tronco cerebral e do prosencéfalo (hipotálamo, ínsula, córtex anterior do cíngulo e amígdala) integram as eferências autonômicas às funções

cerebrais superiores. A ínsula integra informações nociceptivas ao processamento emocional e cognitivo além de fornecer eferências simpáticas e parassimpáticas para o controle visceromotor. A amígdala é responsável pela resposta autonômica emocional e controla eferências neuroendócrinas e autonômicas ao estresse e ao medo. O hipotálamo faz o controle homeostático em resposta a mudanças em fatores como temperatura, osmolaridade, glicemia, ritmo circadiano, sono, vigília e modificações ambientais das mais diversas. No tronco encefálico, diversos centros celulares têm funções no controle autonômico – a substância cinzenta periaquedutal integra respostas somáticas e autonômicas à dor e ao estresse, facilitando a resposta cardiovascular, controlando a micção e controlando a respiração; o tegmento dorsal da ponte coordena o reflexo da micção e faz parte do controle das funções gastrointestinal e sexual; o núcleo do trato solitário é um centro intermediário para o paladar, sensibilidade visceral, função cardíaca e barorreflexa, quimiorreflexo carotídeo e motilidade gastrointestinal; o bulbo ventrolateral rostral é fundamental no controle da pressão arterial através de conexões com neurônios simpáticos pré-ganglionares que controlam a ejeção cardíaca, a resistência vascular periférica e media barorreflexos, quimiorreflexos e reflexos cardiopulmonares; o bulbo ventrolateral caudal tem função inibitória sobre seu homônimo rostral; o bulbo ventromedial e o núcleo caudal da rafe mediam termorregulação, respiração e dor; o núcleo dorsal da rafe também faz controle da vasoconstrição em resposta ao frio; o núcleo dorsal motor do bulbo e a porção ventrolateral do núcleo ambíguo contêm neurônios parassimpáticos pré-ganglionares que fazem eferência vagal e se conectam com gânglios no coração, trato respiratório, sistema nervoso entérico, fígado e pâncreas. De diversos segmentos da medula, partem eferências autonômicas – entre T1 e L2 há neurônios pré-ganglionares simpáticos que controlam pressão arterial, termorregulação e redistribuição do fluxo sanguíneo durante atividade física e estresse; entre S2 e S4 há o controle da micção, defecação e função sexual.[2]

No sistema nervoso periférico, as fibras simpáticas pré-ganglionares são curtas e se originam de corpos celulares na medula toracolombar entre T1 e L2[3] e fazem sinapse com gânglios ao longo de toda a extensão paravertebral através da acetilcolina em receptores pós-ganglionares nicotínicos; as fibras pós-ganglionares são longas e fazem sinapse através de norepinefrina com receptores adrenérgicos

nos órgãos-alvo[2] (com poucas exceções, como pro exemplo as glândulas sudoríparas que são colinérgicas).[3] Suas eferências são fundamentais para manutenção da homeostase em resposta ao estresse ortostático, exposição ao frio ou calor, hipoglicemia, hemorragias e emoções. As respostas simpáticas periféricas, conforme descrito anteriormente, são mediadas por impulsos provenientes do bulbo e do hipotálamo.[3] Já as fibras parassimpáticas pré-ganglionares são longas. Elas se originam nos III, VII, IX e X pares cranianos e nos 2º, 3º e 4º nervos sacrais e fazem sinapse com gânglios justapostos aos órgãos-alvo através da acetilcolina; os receptores pré-ganglionares são nicotínicos e os pós-ganglionares, muscarínicos. As fibras do III par craniano têm origem no núcleo de Edinger-Westphal e fazem sinapse no gânglio ciliar, de onde inerva a musculatura constritora da íris e o músculo ciliar. As fibras para o VII e IX pares cranianos se originam no núcleo salivatório superior e, através de diferentes gânglios, inervam glândulas lacrimais, sublinguais, submandibulares e a mucosa de seios, palato e nasofaringe. A glândula parótida recebe inervação partindo do núcleo salivatório superior através do gânglio óptico. O nervo vago, por fim, é componente fundamental do sistema parassimpático. Suas fibras se originam do núcleo ambíguo e do núcleo dorsal do vago e inervam pulmão, coração, fígado, pâncreas e trato gastrointestinal até a flexura esplênica sendo que as fibras originadas do primeiro são responsáveis pelo controle da musculatura lisa e do nó sinusal e as do segundo, pela função secretomotora. As fibras autonômicas que inervam o trato gastrointestinal são consideradas uma entidade à parte, o chamado sistema nervoso autonômico entérico. Ele recebe aferências simpáticas (originadas na região toracolombar) e parassimpáticas (originadas na região sacral) e, com elas, forma plexos ganglionares que modulam a atividade autonômica valendo-se de diversos neurotransmissores – plexo mucoso, plexo submucoso de Meissner, plexo mioentérico de Auerbach e plexo muscular profundo de Cajal.[2]

FIGURA 2 – DISTRIBUIÇÃO ANATÔMICA DO SISTEMA NERVOSO AUTONÔMICO



Distribuição anatômica dos sistemas nervosos autonômicos simpático (esquerda) e parassimpático (direita), com fibras colinérgicas (pretas), adrenérgicas (vermelhas) e aferentes parassimpáticos viscerais (cinza) representadas. Neurônios simpáticos pré-ganglionares se localizam do início do segmento torácico até o início do segmento lombar e se conectam aos neurônios pós-

ganglionares da cadeia simpática. Os neurônios parassimpáticos pré-ganglionares se localizam em núcleos de nervos cranianos e no segmento sacral e se conectam aos neurônios pós-ganglionares em gânglios próximos aos tecidos-alvo. Fibras sensitivas viscerais aferentes se interligam com eferentes parassimpáticos no tórax, abdome e pelve. Fonte: Wehrwein, E.A. *et al* (2016). Traduzido pela autora.[1]

2.2.2 Desenvolvimento do sistema nervoso autonômico

O adequado desenvolvimento embrionário do sistema nervoso autonômico depende de uma perfeita regulação espacial e temporal de neurogênese, gliogênese, migração celular, direcionamento da inervação e formação de sinapses. Esses eventos são orquestrados por genes, moléculas de superfície específicas, fatores de transcrição, fatores de crescimento e moléculas da matriz extracelular; modificações em alguma das vias de sinalização celular podem levar a disfunções do sistema nervoso autonômico.[4]

Como já citado anteriormente, as células que vão compor o sistema nervoso autonômico periférico se originam na crista neural. Isso ocorre no momento em que as pregas neurais se fundem para formar o tubo neural, momento conhecido como neurulação. As células passam então por uma transição mesenquimal e se destacam do tubo neural, migrando através do embrião. Essa população de células origina toda a porção periférica do sistema nervoso autonômico, incluindo os neurônios, glia, gânglios simpáticos e parassimpáticos, córtex da adrenal, corpo carotídeo, sistema nervoso entérico, cadeia de gânglios da raiz dorsal e, além disso, melanócitos, estruturas esqueléticas do crânio e algumas partes do sistema cardíaco. Uma parte dessas células tem sua função pré-especificada mesmo antes de ocorrer a diferenciação e migração, mas a maior parte delas é multipotente e pode originar diversos tipos celulares. [4]

A migração das células é mediada por moléculas de atração e de repulsa e elas têm papel chave na adequada formação do sistema nervoso autonômico. Todas as células da crista neural expressam Sox10, um fator de transcrição – sua ausência causa falha na formação dos derivados da crista neural. A FoxD3 especifica as células que fazem a migração pela via ventral (as quais originam as linhagens simpática e adrenal e os gânglios da raiz dorsal), mas não as que fazem pela via dorsolateral (as

quais originam os melanócitos). As células de cada via também expressam diferentes fatores de transcrição – as da via ventral expressam Ascl1/Mash, enquanto as da via dorsolateral expressam neurogeninas. As células que migraram ventralmente para além do ponto de formação dos gânglios da raiz dorsal têm sua função simpatoadrenal determinada por uma rede de genes reguladores – a aorta dorsal secreta fatores de crescimento pertencentes à família TGF-beta, como BMP-4 e BMP-7, que, por sua vez, ativam a expressão de fatores de crescimento como Phox2b, Ascl1, Hand2 e GATA. Sua importância pode ser exemplificada a partir de modelos animais, em que, por exemplo, a deleção do gene do Phox2b leva à agenesia de todos os gânglios autonômicos. [4]

Além da crista neural, os placodes são outro grupo de estruturas fundamentais de onde se partem células que vão originar o sistema nervoso autonômico. Os placodes epibranquiais são espessamentos ectodérmicos na topografia da cabeça que são precursores dos neurônios sensitivos viscerais e da glia de alguns gânglios cranianos – geniculado (VII nervo craniano), petroso (IX nervo craniano) e nodoso (X nervo craniano). O Phox2b também é essencial para a sobrevivência dos neurônios dos gânglios autonômicos cranianos – a deleção do seu gene, à semelhança do que ocorre com os gânglios autonômicos provenientes da crista neural, leva à ausência de cerca de 90% dos neurônios dos gânglios petroso e nodoso, por exemplo – mas diversos outros fatores neurotrópicos também são fundamentais para a sua diferenciação e manutenção; entre eles, estão o BDNF, o NT-4 e o GDNF. Os neurônios desses gânglios cranianos originam receptores diversos, como barorreceptores, mecanorreceptores, quimiorreceptores e nociceptores. Os barorreceptores, por exemplo, expressam TrkB, o receptor para os fatores BDNF e NT-4 – sua deleção reduz a população de neurônios dos gânglios petroso e nodoso em 90%.[4]

Falando especificamente sobre a formação dos neurônios parassimpáticos, sabe-se que eles derivam, em sua maioria, da crista neural e já foi discutido em tópicos anteriores o fato de que seus gânglios encontram-se muito próximos aos seus órgãos-alvo. Para que a inervação ocorra de forma adequada, as fibras pré-ganglionares parassimpáticas funcionam como estradas para células-tronco (conhecidas como precursoras de células de Schwann - SCP) que, ao chegarem no alvo, proliferam e se

diferenciam em neurônios e células gliais dos gânglios respectivos influenciadas por fatores como Phox2b e Ascl1. As SCP expressam receptores ErbB2 e ErbB3 para neurorregulina1. Deleções tanto das fibras pré-ganglionares quanto da neurorregulina1 reduzem drasticamente a quantidade de neurônios e gânglios parassimpáticos. Depois que as fibras parassimpáticas passaram pelo processo de maturação e estão inervando seus tecidos-alvo, sua sobrevivência passa a ser dependente de GDNF. [4]

Já os neurônios simpáticos derivam inteiramente da crista neural, principalmente de um grupo de células que expressam o receptor CXCR4 para a quimiocina SDF1/CXCL12 expressa, por sua vez, no mesênquima periaórtico, onde se formarão os gânglios da cadeia paravertebral. A sobrevivência dos gânglios da cadeia simpática depende do GDNF. A migração de axônios pós-ganglionares até o tecido-alvo de inervação é mediada pelo BDNF secretado pelos axônios pré-ganglionares cujos receptores TrkB estão nos neurônios simpáticos. Phox2b e Ascl1 são fundamentais também na diferenciação e sobrevivência dos precursores de neurônios simpáticos. O fator de transcrição Hif1a é necessário durante o desenvolvimento das fibras tanto pré quanto pós-ganglionares simpáticas para que haja adequada inervação cardíaca. O BDNF, bem como NT-3 e NT-4 são homólogos de outro fator de crescimento, o NGF e são produzidos nos tecidos-alvo de neurônios simpáticos e são cruciais para sobrevivência dos axônios que atingem esses tecidos. [4]

O sistema nervoso entérico também é derivado da crista neural e tem uma população celular bastante variada – motora, sensitiva e interneurônios –, além de ter conexões com o sistema vagal, gânglios da raiz dorsal e fibras simpáticas pós-ganglionares. Os fatores BMP-2 e BMP-4 têm papel na migração, diferenciação e maturação dos gânglios entéricos. O GDNF e seus receptores Ret e Gfra1 são essenciais para a sobrevivência (bem como os receptores de tirosina-quinase ErbB3), proliferação (assim como a via da endotelina3/EdnrB) e migração das células entéricas provenientes da crista neural; deleções do fator ou dos seus receptores levam à aganglionose colorretal, marco da doença de Hirschprung. Recentemente, foi identificada, em modelos animais, uma população de células precursoras de

neurônios entéricos capazes de gerar novos neurônios e sua utilidade clínica ainda está em estudo. [4]

Além do componente genético e das cascatas de sinalização, não se pode deixar de levar em conta a influência de fatores ambientais tanto maternos quanto fetais no desenvolvimento do sistema nervoso autonômico, inclusive no período neonatal, tendo em vista que o término da maturação ocorre após o nascimento, como por exemplo a integração autonômica periférica com o tronco e com centros corticais superiores. Fatores como desnutrição fetal e materna, diabetes materna, hipóxia perinatal, infecções e prematuridade sabidamente impactam o sistema nervoso autonômico não só de forma óbvia (como no controle de resposta cardiovascular) como também através do desenvolvimento neuropsicomotor e comportamental; correlações já foram estabelecidas entre o adequado desenvolvimento autonômico e neuropsicomotor.[5]

2.3 DOENÇA DE PARKINSON

2.3.1 Conceitos, diagnóstico e patologia

A DP foi descrita em 1817 pelo inglês James Parkinson no famoso “Essay on the shaking palsy”. Mais de 200 anos depois, é a segunda doença neurodegenerativa mais frequente, atrás apenas da demência de Alzheimer. Tem uma prevalência de 0,3% na população geral e, em consonância com o fato de que seu principal fator de risco é a idade avançada, chega a 3% em idosos com mais de 80 anos.[6] Desde sua descrição inicial, inúmeras nuances foram descobertas, tanto clínicas quanto fisiopatológicas e, atualmente, sabe-se sobre a riqueza de sintomas motores e não-motores que compõem seu quadro clínico. O relato inicial traz os sintomas motores como características predominantes, mas já faz menção à presença de sintomas como constipação, hiperssalivação e DCSREM.[7]

Ao longo das últimas três décadas, diversos critérios diagnósticos foram propostos, todos com base em achados essencialmente clínicos e valendo-se da presença de sintomas motores. Entretanto, a exuberância de sintomas não-motores

que se apresentam na DP trouxe à tona a necessidade de revisão destes critérios diagnósticos. Neste contexto, em 2015, a Sociedade Internacional de Parkinson e Distúrbios do Movimento publicou os critérios MDS-PD (Tabela 1). Para o diagnóstico da DP, o primeiro passo é definir a presença de uma síndrome parkinsoniana e, aqui, a presença de sintomas motores é mandatória e se define por bradicinesia associada a pelo menos um dentre: tremor de repouso com frequência de 4-6 Hz e rigidez. Clinicamente, pode-se dividir os pacientes em duas formas motoras – predominantemente tremulante ou predominantemente rígido-acinética. A partir disto, foram elencados alguns sinais que corroboram o diagnóstico, chamados de critérios de suporte. Também foi elaborada uma lista de critérios de exclusão que inclui sinais e sintomas sugestivos de diagnósticos alternativos à DP, além de uma lista de sinais de alarme, os quais não necessariamente excluem a possibilidade, mas listam achados clínicos não usualmente vistos na DP. O diagnóstico pode ser então de DP clinicamente estabelecida ou provável. Com a presença de dois critérios de suporte e sem nenhum sinal de alarme, temos DP clinicamente estabelecida; se houver qualquer critério de exclusão ou mais de dois sinais de alarme, o diagnóstico de DP não pode ser feito; se houver dois ou menos sinais de alarme, desde que haja número igual de critérios de suporte, o diagnóstico é de DP provável.[8,9]

TABELA 1 – CRITÉRIOS DIAGNÓSTICOS DA DOENÇA DE PARKINSON

Após o diagnóstico clínico de parkinsonismo:
Doença de Parkinson clinicamente estabelecida
1. Ausência de critérios de exclusão; 2. Pelo menos dois critérios de suporte; 3. Ausência de sinais de alarme.
Doença de Parkinson clinicamente provável
1. Ausência de critérios de exclusão; 2. Sinais de alarme contrabalanceados por critérios de suporte: a. Se houver um sinal de alarme, pelo menos um critério de suporte é necessário; b. Se houver dois sinais de alarme, pelo menos dois critérios de suporte são necessários; c. A presença de mais do que dois sinais de alarme não permite o diagnóstico de doença de Parkinson.

Critérios de exclusão
1. Anormalidades cerebelares inequívocas; 2. Paralisia supranuclear do olhar vertical para baixo ou lentificação seletiva das sacadas verticais para baixo; 3. Diagnóstico provável de variante comportamental de demência frontotemporal ou afasia primária progressiva nos primeiros 5 anos de doença; 4. Sinais de parkinsonismo restritos aos membros inferiores por mais de 3 anos; 5. Tratamento com um bloqueador de receptor da dopamina ou com um agente depletor de dopamina em um período de tempo consistente com o diagnóstico de parkinsonismo induzido por drogas; 6. Ausência de resposta observável a doses altas de levodopa a despeito de severidade pelo menos moderada da doença; 7. Perda sensitiva cortical inequívoca, clara apraxia ideomotora ou afasia progressiva; 8. Neuroimagem funcional normal do sistema dopaminérgico pré-sináptico; 9. Documentação de um diagnóstico alternativo sabidamente causador de parkinsonismo e plausível ao caso do paciente ou avaliação de um expert que considera que um diagnóstico alternativo à doença de Parkinson é mais provável.
Sinais de alarme
1. Rápida progressão de distúrbio da marcha exigindo uso de cadeira-de-rodas nos primeiros 5 anos da doença; 2. Ausência completa de progressão de sinais ou sintomas por 5 anos ou mais, exceto se esta estabilidade for relacionada ao tratamento; 3. Disfunção bulbar (disfagia, disartria ou disfonia severas) nos primeiros 5 anos da doença; 4. Disfunção inspiratória (estridor inspiratório noturno ou diurno ou suspiros frequentes); 5. Disfunção autonômica severa nos primeiros 5 anos da doença (hipotensão ortostática ou incontinência/retenção urinária – em homens, a retenção não pode ser associada a doença prostática e deve ser acompanhada de disfunção erétil); 6. Quedas recorrentes (>1/ano) por desequilíbrio nos primeiros 3 anos da doença; 7. Anterocolis ou contraturas de mãos/pés desproporcionais nos primeiros 10 anos da doença; 8. Ausência de sintomas não-motores comuns após 5 anos de doença (distúrbios do sono, disfunção autonômica, hiposmia, distúrbios psiquiátricos); 9. Sinais piramidais não justificados, como fraqueza piramidal ou hiperreflexia (exceto mínima assimetria de reflexos ou reflexo cutâneo plantar extensor isolado); 10. Parkinsonismo bilateral simétrico.

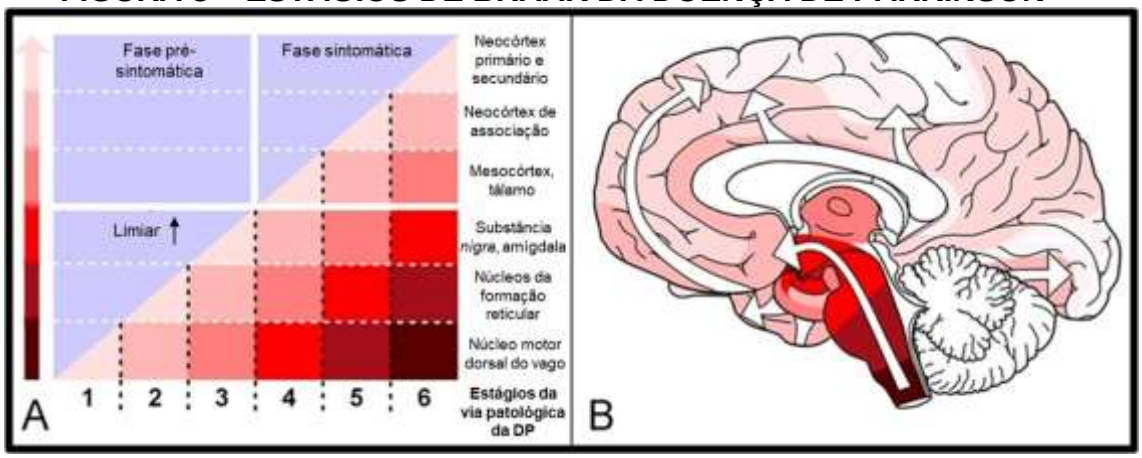
Critérios de suporte
1. Clara e dramática resposta à terapia dopaminérgica; 2. Discinesia induzida por levodopa; 3. Tremor de repouso em um membro documentado ao exame; 4. Presença de perda olfatória ou denervação cardíaca simpática à cintigrafia MBIG.

Fonte: Postuma *et al*. (2015). Traduzido e adaptado pela autora.[9]

Os sintomas motores são secundários ao déficit dopaminérgico decorrente da perda de neurônios da *substantia nigra pars compacta* e estima-se que, quando há o surgimento dos sintomas motores, já ocorreu uma perda de cerca de 50% destes neurônios.[10] Quando não houver uma síndrome parkinsoniana clinicamente definida, o diagnóstico pode ser uma DP prodrômica ou mesmo não ser DP. A ideia de uma DP prodrômica deriva de estudos das décadas de 1990 e 2000 realizados por diversos pesquisadores, especialmente por *Braak et al*. O depósito intraneuronal da proteína alfa-sinucleína, principalmente nos axônios e nos botões pré-sinápticos, é a característica patológica da DP. A alfa-sinucleína está normalmente presente em boa parte das células do sistema nervoso humano ligada à membrana de vesículas sinápticas ou a membranas ricas em fosfolipídios mas, no contexto patológico da DP, em alguns tipos celulares específicos, essa proteína perde a capacidade de ligação e passa a agregar-se e acumular-se com outras proteínas anormais formando os chamados corpúsculos de Lewy. Os estudos de *Braak et al* demonstraram de forma muito elegante, através de análises patológicas *post mortem*, que estes depósitos anormais de alfa-sinucleína iniciam décadas antes das manifestações motoras da DP e não estão restritas ao sistema nervoso central, mas encontram-se também nos sistemas nervosos autonômico e entérico, como por exemplo células pós-ganglionares intestinais (que são acometidas desde os primeiros estágios da doença) que fazem sinapse com núcleos do nervo vago no tronco encefálico (Figura 3).[11,12,13,14] Com estudos subsequentes, associaram-se evidências de que tais agregados anormais de alfa-sinucleína comportam-se de maneira priônica e que, desta forma, propagam-se célula a célula através de conexões interneurais; isso explica o fato de a DP ser muito mais do que uma doença de déficit dopaminérgico, mas que abarca também células glutamatérgicas, GABAérgicas, colinérgicas, serotoninérgicas,

adrenérgicas e noradrenérgicas ao longo de todo o sistema nervoso.[15] Mais recentemente, estudos questionaram alguns aspectos da teoria de Braak ao considerar que, em muitos casos, a teoria não pode ser aplicada tanto do ponto de vista patológico – por exemplo, relatos de pacientes com corpos de Lewy presentes em regiões compatíveis com estágios mais avançados de Braak (como na substância *nigra* e no *locus ceruleus*) mas ausentes em regiões compatíveis com estágios mais precoces – quanto do ponto de vista clínico – cerca de metade dos pacientes não apresentam DCSREM quando do início das manifestações motoras e sua prevalência aumenta com o decorrer da doença, por exemplo. Surge, assim, uma hipótese de que existam duas formas de desenvolvimento da doença, uma iniciada no sistema nervoso entérico (*body-first*) e outra iniciada no sistema nervoso central (*brain-first)*; as duas, entretanto, seriam indistinguíveis clinicamente nas fases moderada e avançada da doença.[16] Modelos animais corroboram essa teoria ao demonstrar que a propagação priônica de alfa-sinucleína é passível tanto de forma retrógrada quanto anterógrada. Nada, porém, exclui a possibilidade de processos central e periférico concomitantes de depósito de alfa-sinucleína.[17] Interessantemente, as doenças de corpos de Lewy (DP, demência por corpos de Lewy e falência autonômica pura) apresentam depósitos de alfa-sinucleína no corpo neuronal e extenso acometimento do sistema nervoso autonômico periférico, enquanto na atrofia de múltiplos sistemas, os depósitos de alfa-sinucleína ocorrem no citoplasma de oligodendrócitos e o envolvimento do sistema nervoso autonômico central é marcado, sendo irrelevante na periferia.[18]

FIGURA 3 – ESTÁGIOS DE BRAAK DA DOENÇA DE PARKINSON



A. A fase pré-sintomática é marcada pelo surgimento de corpos de Lewy em cérebro de indivíduos assintomáticos. Na fase sintomática, o limiar neuropatológico individual é ultrapassado (seta preta). A ascendência e intensidade das cores abaixo da diagonal indicam gravidade crescente da patologia em regiões vulneráveis do cérebro (direita). A gravidade da patologia é indicada por tons mais escuros na seta colorida à esquerda. **B.** Diagrama mostrando o processo patológico ascendente (setas brancas). Os tons das áreas coloridas correspondem aos da imagem A. Fonte: Braak *et a.l* (2004). Traduzido pela autora[11]

A caracterização e identificação de sintomas previamente ao início das manifestações motoras da DP têm fundamental importância na busca de agentes modificadores de doença e, além disso, sintomas não-motores estão presentes na maior parte dos pacientes, às vezes dominando o quadro clínico e, muitas vezes, como a primeira manifestação da doença, de forma anatomicamente compatível com a progressão patológica descrita anteriormente[10]. Com isso em mente, além dos critérios para DP clinicamente definida da MDS-PD, foram postulados sinais de provável DP prodrômica – quando há sinais de neurodegeneração porém não suficientes para o diagnóstico clínico. Os sinais incluem sintomas motores leves (pontuação menor do que 6 na escala MDS-UPDRS – anexo 2), sintomas não-motores (DCSREM, disfunção olfatória, constipação, sonolência diurna excessiva, hipotensão ortostática sintomática, disfunção erétil ou urinária e depressão) e exames complementares (evidência de captação dopaminérgica pré-sináptica anormal do radiotraçador por SPECT ou PET)[8,9,15]. Estes achados foram utilizados para, em combinação com fatores de risco conhecidos e com a probabilidade geral da população de desenvolver DP, classificar indivíduos como tendo ou não DP prodrômica.[19] Este escore foi validado em coortes prospectivas com especificidade e valor preditivo positivo relativamente altos para conversão de provável DP prodrômica

para DP clinicamente definida e, mais recentemente, foi atualizada com revisão dos marcadores já incluídos e adição de novos (Tabela 2 – para orientações sobre o cálculo do risco, consulte a referência). O escore não tem validade para indivíduos sabidamente portadores de mutações de alta penetrância (consulte tópico 2.3.3 Genética na DP).[20] Tendo em vista a ausência de terapias neuroprotetoras ou modificadoras de doença até o presente momento, a utilidade principal de definirmos paciente com provável DP prodrômica se dá no contexto de pesquisas.[19]

TABELA 2 – MARCADORES PARA DOENÇA DE PARKINSON PRODRÔMICA

Marcadores prodrômicos	**LR+**	**LR-**
DCSREM evidenciado em polissonografia OU	130	0,65
Questionário positivo para DCSREM com especificidade >80%	2,80	0,89
PET/SPECT dopaminérgico anormal (<65% normal ou 2 desvios-padrão abaixo da média)	43,30	0,66
Parkinsonismo limítrofe (MDS-UPDRS <3, exceto tremor) OU	9,60	0,55
Testagem motora quantitativa anormal	3,50	0,60
Perda olfatória	6,40	0,40
Constipação	2,50	0,82
Sonolência diurna excessiva	2,70	0,86
Hipotensão ortostática neurogênica	18,50	0,88
Hipotensão ortostática sintomática	3,20	0,80
Disfunção erétil (homens)	3,40	0,87
Disfunção urinária	2,00	0,90
Depressão (+- ansiedade)	1,60	0,88
Déficit cognitivo global	1,80	0,88

Fonte: Berg *et al*. (2015). Traduzido e adaptado pela autora.[20]

2.3.2 Disautonomias na doença de Parkinson

Os sintomas não-motores da DP envolvem diversos sistemas e incluem hiposmia, distúrbios psiquiátricos, distúrbios do sono e disautonomias. Como já foi abordado anteriormente, eles podem se manifestar até mesmo décadas antes do início dos sintomas motores e continuam a se desenvolver durante todo o curso da doença; em média, pacientes com DP queixam-se de 8-13 sintomas não-motores, independentemente do estágio motor e do tempo de início dos sintomas motores. Como é possível observar na Tabela 2, alguns deles apresentam considerável valor preditivo positivo no período prodrômico. Ainda que as terapias atuais tenham foco principal no déficit dopaminérgico, há crescente reconhecimento e preocupação com os sintomas não-motores – eles são, comprovadamente, os principais determinantes da qualidade de vida e da necessidade de institucionalização dos pacientes com DP.[21]

Dentre os sintomas não-motores, as disautonomias são bastante frequentes e variadas, envolvendo diversos sistemas (Tabela 3) e a prevalência varia conforme o sintoma – 30% na hipotensão ortostática, 65% na constipação, por exemplo.[22] Essa variabilidade na prevalência, observada especialmente nas fases mais iniciais após o diagnóstico, pode ser explicada parcialmente dentro da teoria fisiopatológica *brain-first/body-first* discutida anteriormente;[16] entretanto, não se pode ignorar o impacto genético, que será trazido adiante. Como já exposto anteriormente, os sintomas autonômicos podem estar presentes muito precocemente no decorrer da patologia, mas tendem a aumentar significativamente em prevalência e gravidade nos primeiros 5 anos da doença. Existe associação entre sintomas autonômicos com prejuízo nas atividades diárias e com depressão, em especial sintomas cardiovasculares. Essa associação, interessantemente, não ocorre com os sintomas motores.[23] Além disso, disautonomia em pacientes com DP tem correlação com diagnóstico em idade mais avançada, progressão mais rápida, menor sobrevida, pior resposta ao uso de levodopa, envolvimento mais significativo da marcha.[18]

TABELA 3 – PRINCIPAIS SINTOMAS DISAUTONÔMICOS NA DOENÇA DE PARKINSON

Sintomas cardiovasculares
Hipotensão ortostática
Sintomas urogenitais
Urgência urinária Incontinência urinária Noctúria Hesitação urinária Esvaziamento vesical incompleto Disfunção erétil Anorgasmia
Sintomas gastrointestinais
Disfagia Perda de controle salivar Gastroparesia Constipação Incontinência fecal Náuseas e vômitos
Outros
Disfunção sudomotora com sudorese excessiva Disfunção pupilar com turvação visual

Fonte: desenvolvido pela autora.

O coração possui inervação simpática adrenérgica e noradrenérgica e parassimpática colinérgica e há disfunção do sistema cardiovascular em até 80% dos pacientes com DP. Tal disfunção pode levar, entre outros achados, à hipertensão supina (definida como pressão arterial sistólica >140mmHg ou pressão arterial diastólica >90mmHg quando em posição supina)[18], a qual está presente em cerca de 50% dos pacientes e tem associação com eventos cardio e cerebrovasculares, e à hipotensão ortostática (definida como queda da pressão sistólica >20mmHg ou da pressão diastólica >10mmHg comparando-se aferições em posição supina e após 3 minutos de ortostase, sem compensação com aumento da frequência cardíaca)[18,24], que está presente em 30-58% dos paciente e é fator de risco independente para mortalidade e para eventos coronarianos;[21] acredita-se que seja secundária à perda de neurônios do núcleo intermediolateral na medula e no núcleo dorsal do vago.[25] Apesar de a disautonomia cardiovascular estar associada à gravidade dos sintomas

motores, a um maior risco de quedas e ao declínio cognitivo, ela pode se manifestar desde o início da doença. [22] Tão relevante é a disautonomia cardiovascular na DP que o MBIG, um análogo da noradrenalina, pode ser utilizado através da cintigrafia como demonstrativo de denervação cardíaca simpática e servir como critério de suporte para o diagnóstico (Tabela 1); não se encoraja, entretanto, a realização do exame na intenção de completar critérios para o diagnóstico, ele é essencialmente clínico.[9]

A constipação, que é queixa relatada em até 80% dos pacientes,[16] e a gastroparesia afetam não só a qualidade de vida, mas também o tratamento medicamentoso, já que tanto a farmacocinética quanto a farmacodinâmica da levodopa são dependentes de absorção duodenal.[21] Fisiopatologicamente, o funcionamento gastrointestinal envolve múltiplos neurotransmissores e moduladores – acetilcolina, dopamina, serotonina, peptídeo intestinal vasoativo e óxido nítrico – e é provável que a disfunção na DP seja multifatorial. O controle autonômico tem por base o núcleo motor dorsal do nervo vago, que é um dos primeiros centros a ser afetado na patologia (Figura 3) e explica a precocidade dos sintomas gastrointestinais. Além do acometimento central, é consistente a presença de corpos de Lewy no sistema nervoso entérico em todos os níveis do trato digestivo.[21] Perda da capacidade de manejar saliva, além da correlação com depressão e isolamento social, aumenta o risco de disfagia e aspiração.[22]

Até 70% dos pacientes com DP apresentam sintomas urinários, sendo uma das disfunções autonômicas mais frequente.[26] A hiperatividade vesical pode contribuir para infecções urinárias e cutâneas, sendo uma das causas mais frequentes de internação hospitalar na DP, [26] além de interferir na qualidade do sono e aumentar o risco de quedas, especialmente os sintomas de noctúria e urgeincontinência urinárias.[22] A bexiga é inervada por impulsos colinérgicos muscarínicos e nicotínicos e também por impulsos adrenérgicos e noradrenérgicos e a micção é controlada por vias autonômicas sacrais, mas nenhuma alteração estrutural ou bioquímica foi evidenciada em pacientes com DP; há também influência central na micção – a contração tônica é facilitada pelo centro miccional pontino e o acúmulo, pelo hipotálamo, cerebelo, córtex frontal e pelos núcleos da base. Mais especificamente, globo pálido, estriado e caudado apresentam menores taxas de atividade em

pacientes com DP e disfunção vesical comparativamente aos que não apresentam disfunção vesical.[21]

A regulação térmica corporal é feita através de inervação simpática colinérgica muscarínica que controla sudorese e respostas vasomotoras cutâneas, com regência hipotalâmica. Cerca de 70% dos pacientes com DP apresentam queixas relacionadas à sudorese, habitualmente hiperidrose.[18]

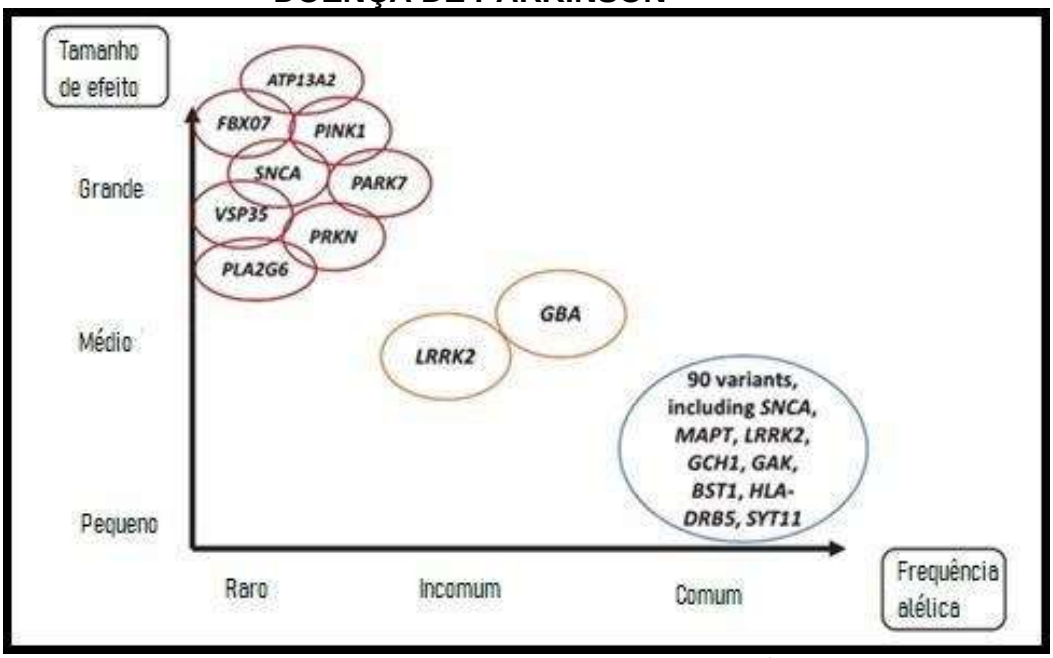
A avaliação das manifestações disautonômicas na DP é imprescindível e deve-se questionar ativamente em todas as consultas, tendo-se em vista que muitos pacientes não trazem espontaneamente tais queixas e existem inúmeras opções de tratamentos sintomáticos disponíveis que podem melhorar a qualidade de vida e até mesmo a sobrevida desses pacientes. Há duas formas principais de se avaliar objetiva e sistematicamente as queixas do sistema nervoso autonômico em pacientes com DP – através do SCOPA-AUT e do MDS-UPDRS. O SCOPA-AUT (Anexo 1) foi desenvolvido pela MDS em 2004[27] e validado para o português em 2010[28]; consiste em 21 questões gerais e mais 2 específicas diferentes para homens e mulheres com relação a sinais e sintomas de disfunção sexual. Já o MDS-UPDRS (Anexo 2) foi publicado em 2008[29] como uma revisão da escala anterior desenvolvida na década de 1980, o UPDRS, e consiste em uma ferramenta ampla de avaliação que aborda aspectos motores subjetivos, motores objetivos, complicações motoras e não-motores; com relação à versão anterior, o espectro não-motor da doença passou a incluir uma abordagem mais ampla, inclusive de sintomas disautonômicos – constipação, disfunção urinária, sensação cabeça vazia, salivação e deglutição.

2.3.3 Genética na doença de Parkinson

Na década de 1990, foi descrito o primeiro gene relacionado à DP de herança mendeliana, o gene da alfa-sinucleína (SNCA ou PARK1) e, desde então, mais de 20 formas monogênicas foram descritas e mais de 100 *loci* foram identificados como fator de risco para DP.[30] A nomenclatura adotada foi, inicialmente, dada pela ordem cronológica de identificação (PARK1, PARK2, por exemplo), mas muitos grupos consideraram tal metodologia confusa e, atualmente, se advoga pelo uso do nome do próprio gene (SNCA, por exemplo).[2] É importante salientar que a maioria dos estudos

genéticos na DP, utiliza coortes europeias, o que limita a aplicabilidade dos dados nas demais populações. [31]

FIGURA 4 – FREQUÊNCIA DE GENES E RISCO ASSOCIADO DE DOENÇA DE PARKINSON



Fonte: *Day et al*. Traduzido e adaptado pela autora.[31]

Entre 5 e 10% dos casos de DP são causados por mutações monogênicas.[32] Algumas formas mendelianas apresentam particularidades entre si e com relação à forma dita idiopática (esporádica); entretanto, muitas delas são clinicamente indistinguíveis da forma idiopática, especialmente em fases mais avançadas da doença. É interessante notar que as formas monogênicas são raras e com penetrância reduzida, enquanto há um número muito maior de variantes com menor tamanho de efeito, mas frequência muito maior na população (Figura 4).[31]

Mutações no gene Parkina (*PRKN* ou PARK2), que se localiza no cromossomo 6q25.2-27[33], representam a forma mais frequente de DP autossômica recessiva e heterozigotos compostos contabilizam mais da metade das doenças de Parkinson de início precoce. [30] A proteína Parkina é uma ubiquitina-ligase relacionada também à manutenção mitocondrial. [31] Clinicamente, há um quadro exuberante de início juvenil e com presença de distonia cervical, distonia de marcha, ataxia, neuropatia periférica, disautonomia e casos de hemiparkinsonismo-hemiatrofia.[34]

Entretanto, os sinais clássicos não-motores são menos frequentes em comparação à DP idiopática e a outras formas de DP de início precoce.[25] Há excelente resposta à levodopa, mas desenvolvimento precoce de discinesia medicamentosa.

O gene *LRRK2* (PARK8) se localiza no cromossomo 12q12-q13.1[34] e é a causa mais frequente de DP autossômica dominante, além de ser relacionada a formas esporádicas, com penetrância idade-dependente.[30] A proteína tem importância em transporte, autofagia e síntese proteica e é expressa em neurônios do estriado, entre outras células. A variante c.6055G>A (G2019S) é a mais frequente em termos gerais[31], sendo responsável não só pela forma familiar como por cerca de 2% dos casos esporádicos; *LRRK2* é especialmente frequente em etnias ibéricas, povos Berberes e judeus Ashkenazi,[30] sendo que a prevalência da variante p.G2019S nestas duas últimas populações chega a 41% e 26%, respectivamente.[31] Clinicamente, o início é tardio, simulando a forma idiopática, mas de curso mais benigno. Alguns achados atípicos incluem hipotensão ortostática marcada, demência, alucinações, síndrome corticobasal e afasia primária progressiva.[30] Interessantemente, pacientes com mutações na *LRRK2* e clínica indistinguível da DP idiopática podem não ter corpos de Lewy na avaliação patológica.[25]

O gene da *GBA* codifica a enzima que degrada glicocerebrosídeo em glicose e ceramidas, processo importante para a degradação de esfingolipídeos. [30] Além de doença de Gaucher, que é uma doença de depósito lisossomal e cujos pacientes têm risco aumentado de DP,[31] mutações heterozigotas, homozigotas e heterozigotas compostas no *GBA* são, de forma isolada, o maior fator de risco genético para DP na população em geral, ainda que não leve a um padrão de herança mendeliano.[30] Nesses casos, apresenta início mais precoce, maior limitação motora, maior prevalência de demência (e com maior envolvimento de funções executivas e habilidades visuoespaciais), além de maior frequência de anosmia e disautonomias.[32] Há 11 variantes *GBA*, em sua maioria missense, que, individualmente, aumentam o risco de DP. As mais frequentes são p.N370S (p.N409S), que é vista especialmente em populações de judeus Ashkenazi e aumenta o risco em 4 vezes, e p.L444P (p.L483P), que aumenta o risco de 12 vezes. Já as variantes p.E326K (p.E365K) e p.T369M (p.T408M), ainda que não causem doença de Gaucher, são mais frequentes em populações europeias e duplicam o risco de desenvolvimento de DP em

comparação com a população em geral, associado com maior risco de comprometimento cognitivo e progressão motora mais rápida. Até 15% dos pacientes europeus com DP apresentam alguma variante *GBA*, sendo o fator de risco genético mais significativo, como já destacado anteriormente.[31]

O gene SNCA (PARK1) se localiza no cromossomo 4q21.3; a DP ligada a ele é rara e tem herança autossômica dominante, podendo ser advinda de variantes missense, duplicação, triplicação e quadruplicação do gene – há correlação direta entre número de genes, início mais precoce, maior envolvimento cognitivo e disautonomia.[30,33] Especificamente a mutação p.G51D apresenta um fenótipo de DP sobreposta com características de AMS, com disfunção autonômica marcada e progressão rápida, porém com sinais piramidais e resposta considerável à levodopa.[33] Triplicações também apresentam fenótipo que se assemelha à AMS, com disautonomia precoce.[25] Além disso, há evidências de que polimorfismos no SNCA aumentam o risco de DP esporádica.

O gene PLA2G6 (PARK14), localizado no cromossomo 22q13.1, codifica enzimas que participam da produção de ácidos graxos livres e de fosfolipídeos, importantes para a homeostase da membrana celular e na transdução de sinal celular, sendo que perda da sua função pode levar à disfunção mitocondrial. Mutações nesse gene foram relacionadas inicialmente com distrofia infantil neuroaxonal (INAD) e neurodegeneração com acúmulo cerebral de ferro (NBIA), mas duas mutações em homozigose foram descritas em pacientes com parkinsonismo-distonia responsivo à levodopa, sinais piramidais, atrofia cerebelar e cerebral, sintomas cognitivos e psiquiátricos e sem depósitos de ferro nos núcleos da base. Além disso, diversas variantes foram relatadas em associação a DP e distonia-parkinsonismo de início precoce, com envolvimento da marcha, espasticidade, mioclonias, disfunção autonômica e crises convulsivas.[33]

Mutações em homozigose e mutações heterozigotas compostas identificadas no gene VPS13C (PARK23), localizado no cromossomo 15q22.2, foram identificadas em pacientes com parkinsonismo típico de início precoce boa resposta à levodopa que, entretanto, se perde rapidamente com a progressão, associada a declínio cognitivo precoce, sintomas axiais, disautonomia e perda da resposta à levodopa. Deficiência de VPS13C leva à redução do potencial de membrana mitocondrial.[33]

Na população brasileira, apesar de dados epidemiológicos escassos nessa área, uma metanálise identificou 5 genes associados com DP monogênica: *PRKN*, *LRRK2*, PINK1, ATP13A2 e DNAJC6.[35]

Mais recentemente, com o advento do GWAS, puderam ser identificadas diversas variantes gênicas relacionadas a maior risco de desenvolvimento de DP. Como ilustrado na figura 4, o tamanho de efeito isolado de cada uma das variantes é pequeno, mas através de análises pós-GWAS e escores de risco poligênico, é possível estimar o risco individual de cada paciente somando-se o impacto de múltiplas variantes presentes; entretanto, estima-se que a identificação dessas múltiplas variantes corresponde a apenas 16-36% da herdabilidade da DP. Além disso, em termos de impacto em tomada de decisões, o uso de GWAS e análises de escores de risco poligênico ainda é limitado.[31]

A descoberta de variantes de suscetibilidade e de formas monogênicas da DP tem permitido novos olhares e novos *insights* a respeito da etiologia da doença,[36] como por exemplo a implicação de disfunção mitocondrial levando à degeneração preferencial de neurônios dopaminérgicos e evidência de neuroinflamação contribuindo para a agregação da alfa-sinucleína.[37] Sob essa perspectiva, esse conhecimento é relevante não apenas para melhor entendimento em termos clínicos e fisiopatológicos, mas também abre novas oportunidades terapêuticas. Em termos de tratamentos sintomáticos, há evidências, ainda que escassas, de que nas formas monogênicas a resposta às terapias dopaminérgicas é semelhante comparando-se as diversas mutações entre si e mesmo com a forma esporádica da doença. Duas exceções seriam SNCA e DJ1 que parecem responder de forma um pouco mais pobre à levodopa.[37] A despeito disso, especialmente nos últimos anos, terapias neuroprotetoras, modificadoras da doença e terapias individualizadas têm sido pesquisadas e a identificação de fatores de transcrição, fatores de sobrevivência celular e rotas de sinalização específicas são fundamentais na busca de alvos para essas terapias. Um exemplo é o GDNF que, desde a sua descoberta na década de 1990, vem sendo utilizado em diversos *trials* inclusive como terapia gênica com vetor viral, mas ainda com resultados conflitantes.[38]

2.4 PARKINSON'S PROGRESSION MARKERS INITIATIVE

2.4.1 Definição

O PPMI é um estudo longitudinal, observacional, multicêntrico, financiado pela Michael J. Foxx Foundation e que busca acompanhar a história natural da DP em termos de achados clínicos, desfechos de imagem e marcos biológicos e genéticos através das fases da doença, desde o prodrômico até fases moderadas. Atualmente, há cerca de 4000 participantes recrutados em acompanhamento em 50 centros pelo mundo.

2.4.2 Dados do PPMI na literatura

Sendo um banco que permite acesso a pesquisadores mediante autorização, diversos estudos já foram conduzidos com base no banco de dados do PPMI. Encontramos na revisão da literatura alguns estudos que abordam disautonomias nesta população. Alguns de seus resultados reforçam a grande importância da disfunção autonômica na DP sob vários aspectos. Demonstrou-se que as disautonomias são as maiores preditoras da progressão clínica; DCSREM estão intimamente ligados a disautonomias e atuam como preditores da progressão clínica. Em geral, pacientes com disautonomias e DCSREM tendem a apresentar maior gravidade de sintomas motores e não-motores, possivelmente por maior deposição de alfa-sinucleína. Entretanto, o efeito de diferentes sintomas não-motores na conversão clínica (de prodrômico para DP estabelecida) e na progressão da doença parece ser o mesmo na amostra do PPMI, achado diferente do já relatado na literatura anteriormente.[40] Outro estudo direcionado especificamente para disfunção autonômica gastrointestinal demonstrou correlação com a disponibilidade de transportador da dopamina, avaliada através de SPECT, correlação não observada com sintomas urinários e hipotensão ortostática.[41] Comparação de pontuações do SCOPA-AUT entre 414 pacientes com DP, 60 pacientes sem sinais de déficit dopaminérgico em estudos de imagem (SWEDD) e 170 indivíduos hígidos foi feita em um caso-controle na amostra de indivíduos do PPMI. Este estudo demonstrou que o

grupo de pacientes com DP apresentou menor gravidade de disautonomia do que os pacientes sem evidência de déficit dopaminérgico; estes achados foram avaliados conjuntamente com biomarcadores liquóricos e observou-se que sintomas termorregulatórios têm correlação com níveis de alfa-sinucleína no grupo sem déficit dopaminérgico e sintomas gastrointestinais se correlacionaram com níveis de beta-amiloide1-42 no grupo com DP. Níveis liquóricos de tau total e tau-fosforilada 181 se correlacionaram com sintomas urinários em pacientes com DP e em indivíduos hígidos.[42] Um estudo longitudinal com 226 pacientes avaliados no *baseline,* após 24 meses e após 60 meses demonstrou que modificações em sintomas autonômicos é um preditor significativo de modificações em atividades de vida diária, especialmente sintomas cardiovasculares. Essa associação é mediada parcialmente por sintomas depressivos.[43]

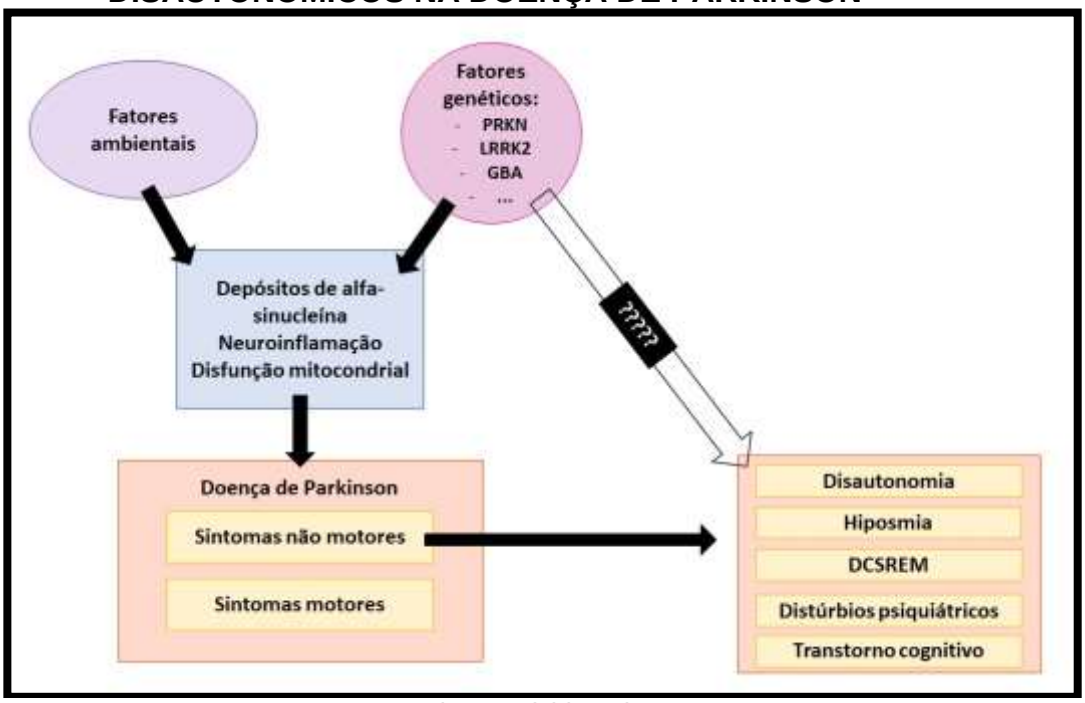
3. MARCO CONCEITUAL

Fatores de risco ambientais e fatores genéticos sabidamente coexistem para a o desenvolvimento de depósitos de alfa-sinucleína, processos de neuroinflamação e disfunção mitocondrial que, ao longo do tempo, são, atualmente os marcos conhecidos da fisiopatologia da DP.[11, 30, 31, 33, 37]

No quadro clínico, a DP se apresenta com sintomas motores e sintomas não motores; apesar de o diagnóstico e o tratamento sintomático basearem-se nos sintomas motores,[8,9] os sintomas não motores são proeminentes e, dentro destes, as disautonomias tem impacto significativo em depressão, escores de qualidade de vida, progressão da doença e mortalidade, porém com prevalência bastante variável dentre os pacientes.[18,20,23]

Dentre as formas da DP, as formas monogênicas secundárias a mutações no gene *LRRK2* e no gene *PRKN* são as mais comuns de herança autossômica dominante e recessiva, respectivamente. Além delas, mutações no gene *GBA* são um fator de risco relevante para formas genéticas não-monogênicas da DP. Compreender o impacto da sintomatologia disautonômica nos pacientes com tais mutações apresenta relevância clínica e epidemiológica.

FIGURA 5 - MARCO CONCEITUAL DA GENÉTICA DOS SINTOMAS DISAUTONÔMICOS NA DOENÇA DE PARKINSON



Fonte: desenvolvido pela autora.

4. JUSTIFICATIVA

A DP é uma das doenças neurodegenerativas mais frequentes e com previsões de crescimento ainda maior da sua prevalência nas próximas décadas. Seu impacto é enorme em diversos aspectos do próprio indivíduo – qualidade de vida, independência para atividades de vida diária, depressão e mortalidade – e em aspectos sociais – síndrome do cuidador, utilização de recursos de saúde e redução do tempo de vida laborativa.

A fisiopatologia envolve a perda de neurônios dopaminérgicos, aspecto este que é conhecido há algumas décadas. Entretanto, a identificação de genes relacionados ao desenvolvimento da DP, inclusive formas monogênicas, trouxe à luz outras vias fisiopatológicas possíveis – disfunção mitocondrial, estresse oxidativo e neuroinflamação, por exemplo. Esse conhecimento, levanta questões como a possibilidade de tratarem-se de espectros diferentes de doença.

Dado o significativo impacto dos sintomas não-motores, em especial os disautonômicos, um melhor entendimento a respeito de sua apresentação em pacientes com DP de etiologia genética possibilita abordagens mais individualizadas e otimização da qualidade de vida, além de avanço na compreensão a respeito do espectro clínico e fisiopatológico da DP em suas diversas formas (genéticas monogênicas, genéticas não-monogênicas e esporádicas).

5. OBJETIVOS

5.1 OBJETIVO PRIMÁRIO

Comparar a magnitude dos sintomas disautonômicos em pacientes com DP forma genética por mutações nos genes *PRKN*, *LRRK2* e *GBA* com pacientes com DP forma esporádica.

5.2 OBJETIVOS SECUNDÁRIOS

Traçar perfil demográfico dos grupos *PRKN*, *LRRK2*, *GBA* e esporádico.

Verificar se há diferenças entre esses grupos com relação a algumas variáveis:

- Subgrupo de sintoma disautonômico (cardiovascular, urogenital, gastrointestinal, sudomotor e pupilar);
- Etnia e descendência;
- Padrão de herança familiar (materna x paterna).

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7. ARTIGO

COMPARATIVE STUDY OF AUTONOMIC DISFUNCITION BETWEEN PARKINSON'S DISEASE WITH *LRRK2*, *PRKN* AND *GBA* MUTATIONS

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7.1 ABSTRACT

It has been suggested that patients with Parkinson's disease (PD) carrying variants in the glucocerebrosidase (*GBA*) gene (*GBA*-PD) suffer from autonomic dysfunction more frequently than idiopathic PD patients.

The present study aims to assess dysautonomic symptoms profiles in three groups of subjects with genetic PD – carrying mutations in *GBA, LRRK2* and *PRKN* genes – compared to those with idiopathic PD. A case-control observational study was performed, with a sample of 742 patients (485 in the sporadic group, 165 in the *LRRK2* group, 85 in the *GBA* group and 9 in the *PRKN* group). The data sample was obtained from Parkinson's Progression Markers Initiative (PPMI) with prior authorized access.

Regarding dysautonomia, evaluated by the Scales for Outcomes in Parkinson's Disease – Autonomic Dysfunction (SCOPA-AUT) score, only the *GBA* group showed significantly higher scores for dysautonomic features compared to the sporadic group, after controlling for potential confounders such as disease duration and Levodopa equivalent daily dose (LEDD). The *LRRK2* group also exhibited more dysautonomic features than the sporadic group, but this difference disappeared when considering the potential confounders. Subgroup of symptoms were also analyzed and revealed differences on the *GBA* and *LRRK2* groups. These findings could improve

the approach to patients in clinical practice and broaden the understanding about genetic forms of PD.

Key words: dysautonomia, Parkinson's disease, SCOPA-AUT, genetic

7.2 INTRODUCTION

The non-motor symptoms are the main determinants of quality of life and institutionalization of patients with PD.[1] Among these symptoms, dysautonomias are quite frequent, affecting between 30-65% of the patients[2], with prevalence varying with disease duration and increasing significantly within the first 5 years after diagnosis. In addition to their impact on quality of life, dysautonomias are associated with depression, impairment of independence for daily living activities,[3] increased mortality, and a poorer response to levodopa treatment, among other effects.[4]

The importance of non-motor symptoms resides not only on their impact but also because they can manifest early on the pathological process. In recent decades, there has been increased attention to these symptoms, including the observation of their presence many years prior to the onset of motor symptoms (and, hence, the clinical diagnosis and chance of treatment). This observation walks together with disruptive findings on the pathophysiology of PD by Braak *et al.*[5] and led to the development of a list of markers for prodromic PD, which currently holds significance primarily for research purposes.[6]

The discovery of genetic bases in the 90's expanded our understanding of the underlying pathological mechanisms involved in the loss of dopamine and other neurotransmitters in PD. In addition to monogenic forms of PD, which account for 5-10% of the patients,[7] there have been numerous pathogenic genetic variants described that confer an increased risk of developing PD, albeit in a non-Mendelian pattern, often with reduced penetrance or small effect sizes.[8] Besides the well-known alpha-synuclein deposition pathophysiology, those genes (both the monogenic and non-monogenic ones) act in different pathways like mitochondrial disfunction and neuroinflammation.[9,10] These findings challenge the notion that protein deposition alone is the sole pathogenic mechanism in PD and raise the question of whether genetic forms represent distinct entities.

Considering this point of view and the impact of dysautonomic features, the main goal of this study is to investigate differences in the magnitude of dysautonomic symptoms between subjects with sporadic and those with genetic forms of PD. The aim is to provide more personalized care for patients and seek for new insights into their clinical and epidemiological profiles. There are three genes of special interest – *PRKN* gene, located at 6q25.2-27,[11] which is associated with mitochondrial maintenence[8] and the most common mutation in autosomal recessive PD;[12] *LRRK2*, located at 12q12-q13.1[13], the most frequent cause of autosomal dominant PD and also implicated in sporadic forms with age-dependent penetrance,[12] functioning in transport and protein synthesis;[8] and *GBA*, the gene that codes the enzyme glucocerebrosidase, essential for the sphingolipids degradation pathway,[12] and which mutations are related not only to Gaucher disease but also to an increased risk of PD, although not in a Mendelian pattern, making it the main genetic risk factor.[8] Previous studies have suggested a link between *GBA* mutations and impact cognitive impairment in PD,[14] while recent clinical observations have indicated a potential association between GBA and more severe dysautonomic symptoms. A few studies evaluated this aspect showing specifically more marked cardiovascular autonomic disfunction.[15] Furthermore, this study intend to trace a profile regarding some relevant clinical and sociodemographic features.

7.3 METHODS

A cross-sectional observational case-control study was performed. The data sample was obtained from PPMI with prior authorized access. PPMI is a longitudinal, observational, multi-center natural history study sponsored by Michael J. Foxx Foundation which assesses progression of clinical features, imaging outcomes, biological and genetic markers across different stages of PD, from prodromal to moderate disease. Currently, it counts with approximately 4000 participants enrolled at around 50 sites worldwide.

The “case” group consisted of subjects with stablished diagnosis of PD with mutations in the *PRKN*, *LRRK2* or *GBA* genes. The “control” group, on the other hand, was composed by subjects with confirmed diagnosis of sporadic PD. Exclusion criteria were absence of clinical criteria for PD, even if gene mutations were identified. While

the original study is a cohort, the current analysis was conducted as a case-control study, utilizing data collected at a specific time point – the enrollment assessment, which took place between 2010 and 2022.

The sociodemographic features examined were age, gender, ethnicity, ancestry and family history. The clinical condition of the participants was assessed using variables such as disease duration, Hoehn&Yahr scale and LEDD. Dysautonomic symptoms were specifically assessed using SCOPA-AUT and specific questions from the Movement Disorders Society – Unified Parkinson's Disease Rating Scale (MDS-UPDRS) that address those manifestations (1.10, 1.11 and 1.12).

Statistical tests were selected according to the distribution of the variables, as determined by the Shapiro-Wilk test of normality. The quantitative variables (age, disease duration, LEDD, Hoehn&Yahr scale, SCOPA-AUT Scale and the selected MDS-UPDRS questions) exhibited a non-parametrical distribution. They were described using median, minimum and maximum values. They were analyzed using Kruskall-Wallis test and the methods for comparison between groups were multiple linear regression while controlling for potential confounders, Mann-Whitney and pairwise comparisons.

Qualitative variables were analyzed using the Chi-Square test, utilizing Pearson Chi-Square or Fisher's Exact Test as necessary. Results were presented in a frequency and percentage table, and comparisons were made using adjusted residuals (significant adjusted residuals < -1.96 or >1.96). The data handling was performed using RStudio 2022.12.0 for Windows and Excel Office 16 for Windows. IBM SPSS Statistics 24 was used for the statistical analysis, and GraphPad Prism 9.5.1 was utilized for generating the graphs. Statistical significance was defined as $p<0.05$.

7.4 RESULTS

A total of 1,172 individuals were initially considered eligible for the study. Among them, 420 were excluded because they had mutations in one of the genes of interest but did not meet criteria for PD diagnosis at enrollment. These individuals were part of a prodromal cohort being followed in the PPMI. Additionally, 10 were excluded due to missing of essential data. The final sample size for analysis consisted of 742

subjects – 485 in the sporadic group, 163 in the *LRRK2* group, 83 in the *GBA* group and 9 in the *PRKN* group.

The sociodemographic and some clinical data are presented in the table 1. Gender was categorized as “female” and “male”. The Pearson Chi-Square test revealed a significance of <0.001. The *GBA* and the *PRKN* group were found to be homogeneous (adjusted residual of 1.8 and -1.0 in the Chi-Square test, respectively), while the *LRRK2* group showed heterogeneity (4.7 adjusted residual for “female” and the sporadic group, 5.1 for “male”). Family history was considered as history of PD or parkinsonism in the parents or grandparents. The Fisher’s Exact Test yielded a significance of 0.004, with significant adjusted residuals for the maternal inheritance in the *LRRK2* (AR: 3.8) and *GBA* (AR: -2.4) groups, and for concomitant maternal and paternal inheritance in the *PRKN* group (AR: 3.6). The absence of known family history showed significant AR for the *LRRK2* (-2.1) and *GBA* (2.0) groups. Ethnicity was divided into some categories and those represented in our sample were de following: Asian, Black, White or American Indian/Alaska Native, demonstrating homogeneity between the groups (Fisher’s Exact Test: 0.572). Ancestry categories present in this sample consisted of African Berber, Ashkenazi Jewish, Basque, Hispanic/Latino and mixed ancestry. The Fisher’s Exact Test for this variable was 0.001, with significant AR for the Ashkenazi Jewish, Hispanic/Latino and Ashkenazi Jewish + Basque descents, all of them in the *GBA* group (3.3, -3.3 and 3.1 respectively).

The age, disease duration, Hoehn&Yahr and LEDD data were assessed using Kruskall-Wallis Independent Samples Test. Statistically significant differences between groups were analyzed through pairwise comparisons, with the significance adjusted by the Bonferroni correction for multiple tests. Regarding age, the Kruskall-Wallis significance was <0.001. Pairwise comparisons indicated a statistical difference in age between the *LRRK2* group when compared to *PRKN* and sporadic groups, with adjusted significances of 0.020 and 0.031, respectively. Disease duration also differed significantly between groups (Kruskal-Wallis significance: <0.001). Pairwise comparisons showed an adjusted significance of <0.001 when comparing the sporadic with *LRRK2* and *GBA* groups, and of 0.001 when comparing the sporadic and *PRKN* groups. The Hoehn&Yahr scale also demonstrated a Kruskall-Wallis significance <0.001 with differences observed between the sporadic and *LRRK2* groups (adjusted

significance: <0.001), and between the sporadic and *GBA* groups (adjusted significance: 0.003). The LEDD did not show significant differences between groups (Kruskall-Wallis: 0.447).

TABLE 1 – SOCIODEMOGRAPHIC AND CLINICAL FEATURES OF SUBJECTS ACCORDING TO THEIR GENETIC STATUS

	Sporadic	***GBA***	***LRRK2***	***PRKN***	***p-value***
Women/Men	153/332 (%31,5/68,5)	39/44 (%47/53)	88/75 (%54/46)	2/7 (%22/78)	< 0.001**††
Family history					
Father	50 (10,3%)	13 (15,7%)	25 (15,3%)	1 (11,1%)	
Mother	38 (7,8%)	5 (6%)	42 (25,7%)	0	
Father/Mother	4 (0,8%)	0	1 (0,6%)	1 (11,1%)	0.004†††‡‡§§
No family history	135 (27,8%)	42 (50,6%)	71 (43,6%)	3 (33,3%)	
No data	258 (53,2%)	23 (27,7%)	24 (14,8%)	4 (44,4%)	
Ethnicity					
Asian	10 (2,1%)	0	1 (0,6%)	0	
Black	7 (1,4%)	1 (1,2%)	0	0	
White	457 (94,2%)	82 (98,8%)	160 (98,2%)	9 (100%)	0.572
Am Indian/Alaska	2 (0,4%)	0	0	0	
No data	9 (1,9%)	0	2 (1,2%)	0	
Ancestry					

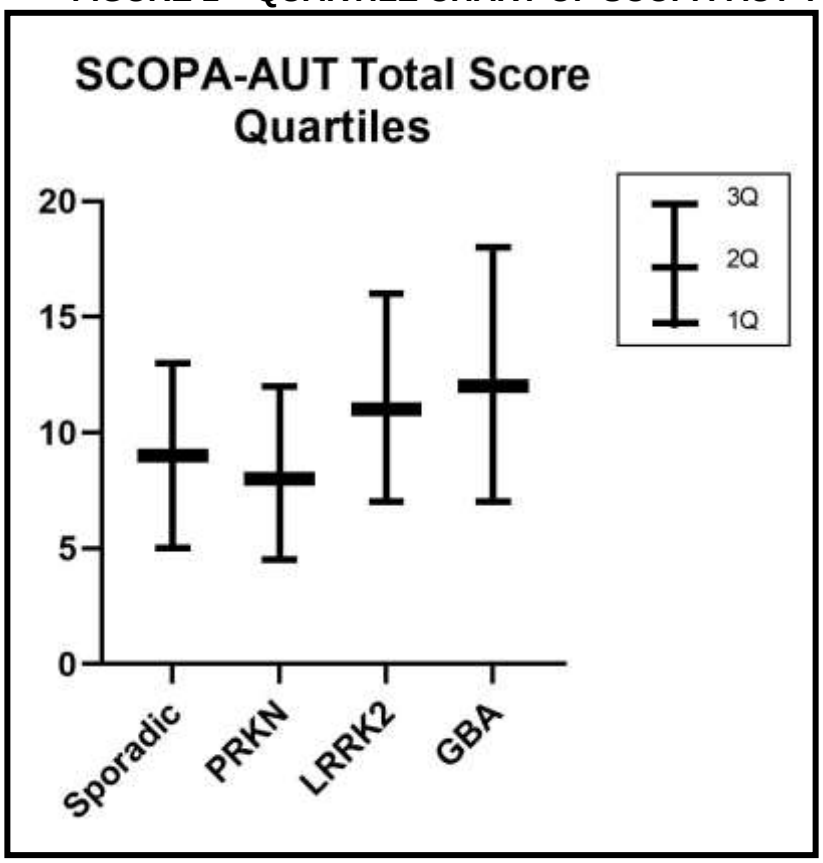
African Berber	0	0	2 (1,2%)	0	
Ashkenazi Jewish	37 (7,6%)	33 (39,8%)	71 (43,5%)	0	
Basque	1 (0,2%)	0	6 (3,7%)	0	
Hispaninc/Latino	19 (3,9%)	1 (1,2%)	28 (17,2%)	1 (11,1%)	0.001‡‡
AJ + HL	2 (0,4%)	0	1 (0,6%)	0	
AJ + B	0	2 (2,4%)	0	0	
AJ + B + HL	0	0	1 (0,6%)	0	
AB + HL	1 (0,2%)	0	0	0	
No data	425 (87,6%)	47 (56,6%)	54 (33,2%)	8 (88,9%)	
Age at evaluation (years)	62.70 (33.70 - 84.90)	64.60 (23.30 - 80.60)	65.40 (33.70 - 85.20)	56.30 (29.30 - 78.80)	0.003†‡
Disease duration (years)	1.00 (0 - 4)	3.00 (0 - 11)	3.00 (0 - 8)	4.00 (0 - 11)	<0.001†II*
Hohen&Yahr	2.00 (1 - 3)	2.00 (0 - 3)	2.00 (0 - 3)	2.00 (1 - 2)	<0.001†II
LEDD	300 (80 - 2172)	600 (50 - 3082)	520 (52 - 2847)	400 (52 - 1050)	0.447

Abbreviations: AJ = Ashkenazi Jewish; HL = Hispanic/Latino; B = Berber; AB = African Berber. ** Significant difference in the sporadic group; †† Significant difference in the *LRRK2* group; ‡‡ Significant difference in the *GBA* group; §§Significant difference in the *PRKN* group; † Significant differences between sporadic and *LRRK2* groups; ‡ Significant differences between *PRKN* and *LRRK2* groups; II Significant differences between sporadic and *GBA* groups; * Significant differences between sporadic and *PRKN* groups.

Dysautonomic features were evaluated using the SCOPA-AUT and specific questions from the MDS-UPDRS scale pertaining to the autonomic nervous system (1.10 for urinary symptoms, 1.11 for constipation, and 1.12 for lightheadedness). The total SCOPA-AUT score showed significant difference between groups (Kruskall-

Wallis test: <0.001). Pairwise comparisons revealed that this difference was between the sporadic and *LRRK2* groups, as well as between the sporadic and *GBA* groups, with adjusted significances of 0.002 and 0.004, respectively. A quartile chart (figure 1) illustrates the SCOPA-AUT total score data.

FIGURE 1 – QUARTILE CHART OF SCOPA-AUT TOTAL SCORE



The SCOPA-AUT scale consists of questions about symptoms categorized into systems such as gastrointestinal, urinary, cardiovascular, thermoregulatory, pupillomotor and sexual disfunction. Comparisons between each genetic group with the sporadic group were conducted, and the results are the presented in table 2.

TABLE 2 – MANN-WHITNEY *P-VALUES* FOR DYSAUTONOMIC FEATURES ARRANGED BY SYSTEM FOR EACH GROUP OF GENETIC PD COMPARED TO SPORADIC PD

	PRKN	***LRRK2***	***GBA***
Gastrointestinal	0.782	0.007	0.125
Urinary	0.413	0.092	0.152
Cardiovascular	0.507	0.011	0.007
Thermoregulatory	0.321	<0.001	0.006
Pupillomotor	0.892	0.413	0.234
Sexual disfunction	0.611	0.511	0.341

Significant statistical differences were observed in the gastrointestinal, cardiovascular and thermoregulatory groups of symptoms when comparing sporadic and *LRRK2* groups. Similarly, significant differences were observed in the cardiovascular and thermoregulatory categories when comparing sporadic and *GBA* groups. No statistical differences were found between the sporadic and *PRKN* groups. The summation of each part of the scale, grouped by genetic category, is presented in figure 2.

Table 3 presents the results of analyzing individual questions from the SCOPA-AUT scale. Some questions demonstrated significant differences, as described below. Questions that did not show significant differences in the Kruskal-Wallis test are also included in the table 3, along with their descriptive statistics.

Question 2, about dribbling saliva out of the mouth in the past month, yielded a Kruskall-Wallis significance of 0.027. Pairwise comparison revealed an adjusted significance of 0.025 between the *LRRK2* and *GBA* groups.

Question 4, regarding feeling full very quickly during a meal in the past month, exhibited a Kruskall-Wallis test significance of <0.001. Differences were observed in the comparison between the sporadic and *GBA* groups (adjusted significance: 0.05) and between the sporadic and *LRRK2* groups (adjusted significance: 0.01).

Question 5, that address presence of constipation in the past month, showed a Kruskall-Wallis test significance of 0.001. Differences were found in the pairwise comparisons between the sporadic and *GBA* groups (adjusted significance: 0.048) and between the sporadic and *LRRK2* groups (adjusted significance: 0.008).

Question 6, about the need to strain hard to pass stools in the past month, resulted in a Kruskall-Wallis significance of 0.019. However, the pairwise comparisons did not yield any adjusted significance within the statistically significant range; all the adjusted significances were >0.05.

Question 8 pertains to difficulty retaining urine in the past month and had a Kruskall-Wallis test with significance of 0.012. Pairwise comparison showed an adjusted significance of 0.026 between the sporadic and *LRRK2* groups.

Question 14 was about potential orthostatic hypotension in the past month (including symptoms like feeling lightheaded, not being able to see properly, or not being able to think clearly when standing up). It showed a Kruskall-Wallis significance of 0.019. However, similarly to the question 6, the pairwise comparisons did not yield any adjusted significances within the statistically significant range; all the adjusted significances were >0.05.

Questions 17 and 18 address excessive perspiration in the past month during the day and during the night, respectively. Both questions showed a Kruskall-Wallis significance of <0.001. Pairwise comparison revealed adjusted significance of <0.001 between the sporadic and *LRRK2* groups.

Question 21 pertains to trouble tolerating heat in the past month. It exhibited a Kruskall-Wallis significance of <0.001. Pairwise comparisons showed adjusted significances of 0.001 when comparing the sporadic and *LRRK2* groups, and 0.007 when comparing the sporadic and *GBA* groups.

About the MDS-UPDRS selected questions, the 1.10, that addresses urinary control problems, and the 1.11, regarding constipation, did not demonstrate significant differences between groups in the Kruskall-Wallis test and are listed in the table 3, along with its descriptive statistics. The question 1.12, that approaches potential symptoms of orthostatic hypotension, showed a Kruskall-Wallis significance of 0.012. Pairwise comparison between the sporadic and *GBA* groups had an adjusted significance of 0.005.

FIGURE 2 – SUM OF SCOPA-AUT BY SYSTEMS

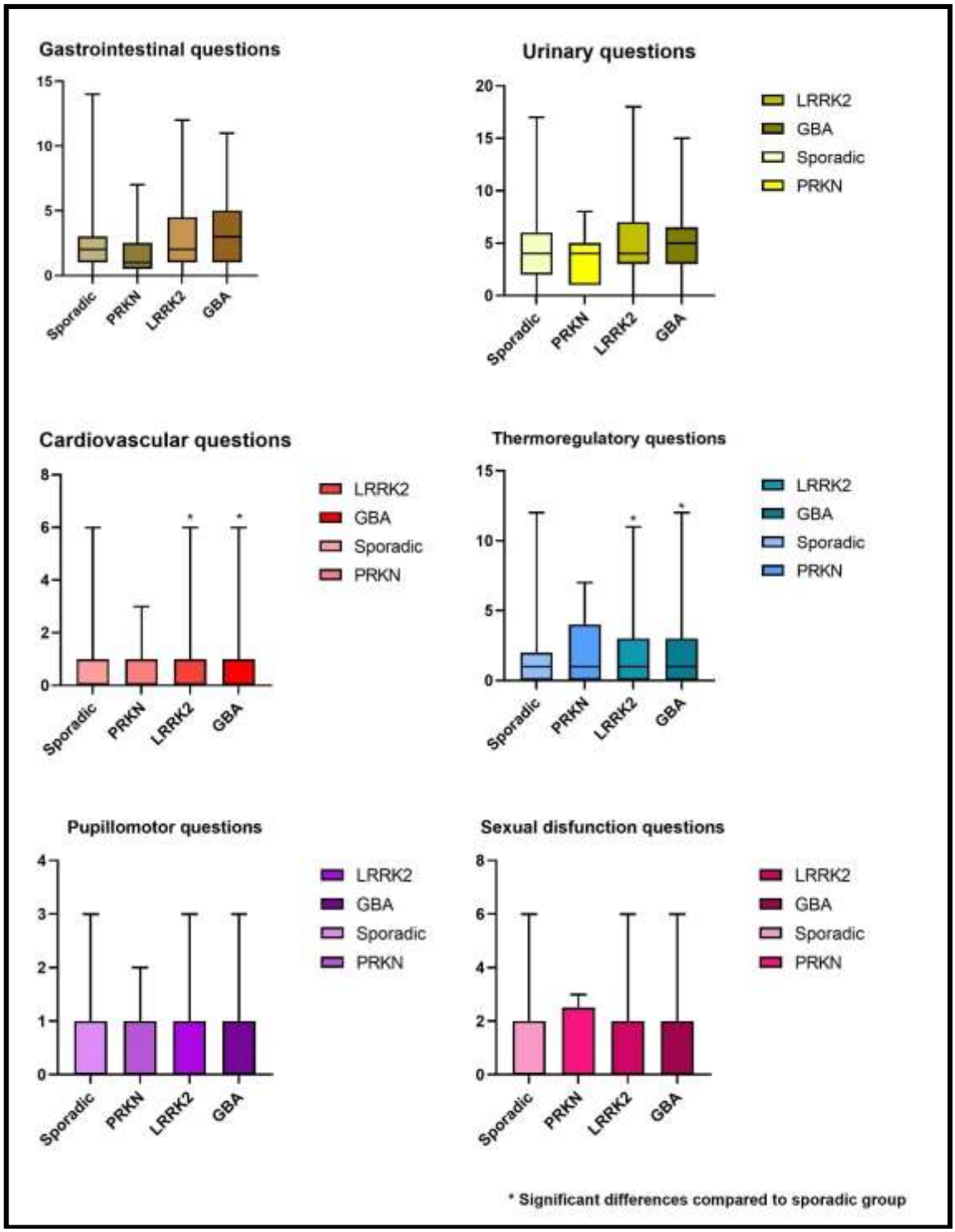


TABLE 3 – DYSAUTONOMIC FEATURES OF PD PATIENTS USING SCOPA-AUT AND MDS-UPDRS ACCORDING TO THE GENETIC STATUS

	Sporadic	*GBA*	*LRRK2*	*PRKN*	*p-value*
Gastrointestinal					
SCAU1	0 (0 - 3)	0 (0 - 2)	0 (0 - 3)	0 (0 - 2)	0.731
SCAU 2	0 (0 - 3)	0 (0 - 3)	0 (0 - 3)	0 (0 - 1)	0.027*
SCAU 3	0 (0 - 3)	0 (0 - 2)	0 (0 - 3)	0 (0 - 2)	0.243
SCAU 4	0 (0 - 3)	0 (0 - 3)	0 (0 - 3)	0 (0 - 1)	<0.001†‖
SCAU 5	0 (0 - 3)	0 (0 - 3)	0 (0 - 3)	0 (0 - 1)	<0.001†‖
SCAU 6	1.00 (0 - 3)	1.00 (0 - 3)	1.00 (0 - 3)	0 (0 - 1)	0.019
SCAU 7	0 (0 - 2)	0 (0 - 1)	0 (0 - 3)	0 (0 - 1)	0.571
Urinary					
SCAU 8	0 (0 - 3)	0 (0 - 3)	0 (0 - 3)	0 (0 - 1)	0.012†
SCAU 9	0 (0 - 3)	0 (0 - 3)	0 (0 - 3)	0 (0 - 1)	0.125
SCAU 10	0 (0 - 3)	1.00 (0 - 3)	0 (0 - 3)	0 (0 - 2)	0.665
SCAU 11	0 (0 - 3)	0 (0 - 3)	0 (0 - 3)	0 (0 - 1)	0.972
SCAU 12	1.00 (0 - 3)	1.00 (0 - 3)	1.00 (0 - 3)	1.00 (0 - 2)	0.525
SCAU 13	1.00 (0 - 3)	1.00 (0 - 3)	1.00 (0 - 3)	2.00 (0 - 2)	0.789
Cardiovascular					
SCAU 14	0 (0 - 3)	0 (0 - 3)	0 (0 - 3)	0 (0 - 2)	0.019
SCAU 15	0 (0 - 3)	0 (0 - 3)	0 (0 - 3)	0 (0 - 1)	0.182

SCAU 16	0 (0 - 2)	0 (0 - 1)	0 (0 - 1)	0 (0 - 2)	0.561
Sudomotor					
SCAU 17	0 (0 - 3)	0 (0 - 3)	0 (0 - 3)	0 (0 - 2)	<0.001†
SCAU 18	0 (0 - 3)	0 (0 - 3)	0 (0 - 3)	0 (0 - 2)	<0.001†
SCAU 20	0 (0 - 3)	0 (0 - 3)	0 (0 - 3)	0 (0 - 3)	0.524
SCAU 21	0 (0 - 3)	0 (0 - 3)	0 (0 - 3)	0 (0 - 3)	<0.001†II
Pupillomotor					
SCAU 19	0 (0 - 3)	0 (0 - 3)	0 (0 - 3)	0 (0 - 2)	0.472
Genital - men					
SCAU 22	0 (0 - 3)	1.00 (0 - 3)	0 (0 - 3)	0 (0 - 2)	0.234
SCAU 23	0 (0 - 3)	0 (0 - 3)	0 (0 - 3)	0 (0 - 2)	0.962
Genital - women					
SCAU 24	0 (0 - 3)	0 (0 - 3)	0 (0 - 3)	0 (0 - 3)	0.555
SCAU 25	0 (0 - 3)	0 (0 - 2)	1.00 (0 - 3)	1.00 (0 - 3)	0.683
Total SCAU	9.00 (0 - 43)	12 (0 - 29)	11.00 (0 - 39)	8 (3 - 25)	<0.001†II
MDS 1.10 URIN	1.00 (0 - 4)	1.00 (0 - 3)	0 (0 - 4)	0 (0 - 2)	0.288
MDS 1.11 CSTP	0 (0 - 4)	0 (0 - 4)	0 (0 - 3)	0 (0 - 1)	0.103
MDS 1.12 OH	0 (0 - 3)	0 (0 - 2)	0 (0 - 3)	0 (0 - 1)	0.012II

Abbreviations: SCAU = question of the SCOPA-AUT; MDS = MDS-UPDRS Scale; URIN = urinary symptoms; CSTP = constipation; OH = orthostatic hypotension.
* Significant differences between *LRRK2* and *GBA* groups; † Significant differences between sporadic and *LRRK2* groups; II Significant differences between sporadic and *GBA* groups

Finally, a linear regression was performed, and the results are summarized in table 4. In the test comparing the *GBA* with the sporadic group regarding the total SCOPA-AUT score, a B value of -2.926 was obtained with significance of <0.001. When controlling for disease duration and LEDD, the B value changed to -4.668, and the *p-value* was 0.050. The significance of each controlled variable of 0.966 for LEDD and 0.498 for disease duration.

The same regression was conducted with *LRRK2* group, and the obtained B value was -2.690 with a significance of <0.001. However, when controlling for the same confounding factors, the B value became -3.105, and the significance was 0.189. The significance of each controlled factor in this case was 0.039 for disease duration and 0.134 for LEDD.

In the case of the *PRKN* group regression, the results were non- significant even before the controlling, with a of B value of 0.306 and a significance of 0.892.

TABLE 4 - TOTAL SCOPA-AUT COMPARISON VALUES BETWEEN GENETIC AND SPORADIC GROUPS USING LINEAR REGRESSION

Variables	B	*p*
GBA*	-4.668	0.050
LRRK2*	-3.105	0.189
PRKN	0.306	0.892

*Controlled by LEDD and disease duration

7.5 DISCUSSION

The present study shows that the risk of autonomic dysfunction in PD is variable depending on genetic pattern.

The analysis of the total score of SCOPA-AUT score indicates that being in the sporadic group is associated with a decrease of 4.67 points in the mean dysautonomia compared to the *GBA* group (B = -4.668; p 0.05), after controlling for

potential confounders such as disease duration and LEDD. Furthermore, when examining specific subgroups of symptoms, the *GBA* group presents with more cardiovascular and thermoregulatory symptoms (p 0.007 and 0.006, respectively). Assessing each question from SCOPA-AUT individually, and the selected questions of the MDS-UPDRS related to dysautonomic features, the *GBA* group demonstrates higher rates of constipation, feeling full very quickly during a meal, trouble tolerating heat, and symptoms of orthostatic hypotension compared to the sporadic group.

When comparing the sporadic with the *LRRK2* group, there is a mean difference of 2.69 points in the total SCOPA-AUT score, indicating a lower dysautonomia burden in the sporadic group (B= -2.690; p <0.001). However, this significance is lost when controlling for potential confounders (B= -3.105; p 0.189). In this case, the disease duration emerges as a significant factor influencing dysautonomia (p 0.039). Analyzing the subgroups of symptoms, *LRRK2* group presents with more gastrointestinal, thermoregulatory, and cardiovascular manifestations (p 0.007, <0.001 and 0.011, respectively). When evaluating specific questions from the SCOPA-AUT and the selected MDS-UPDRS questions, the *LRRK2* group exhibits significantly higher rates of constipation, feeling full quickly early during a meal, urinary incontinence, excessive perspiration during both day and night, and trouble tolerating heat compared to the sporadic group.

The *PRKN* group did not show a significant influence on the dysautonomia when compared to the sporadic group, as indicated by the total SCOPA-AUT score (B= 0.306; p 0.892). This lack of significance was also observed when analyzing the subgroups of symptoms and the specific questions from both the SCOPA-AUT and MDS-UPDRS.

In terms of sociodemographic variables, the *PRKN* group did not show gender, ethnicity, ascendency or age predominancies. However, there was a predominance of concomitant maternal and paternal inheritance, which is consistent with the known autosomal recessive Mendelian pattern associated with *PRKN* mutations.

The *LRRK2* group did not show any predominant ethnicity or ascendency patterns. There was a higher proportion of females and the *LRRK2* group tended to be older compared to the sporadic and *PRKN* groups. Maternal inheritance also appeared to be more common in this group.

The *GBA* group did not exhibit gender, ethnicity, or age differences. There was a predominance of Ashkenazi Jewish ascendency, either in isolation or in combination with Basque ascendency. In terms of inheritance pattern, a lack of family history was predominant in this group, which is not surprising given the non-Mendelian pattern of inheritance associated with *GBA* mutations.

In terms of clinical aspects, all genetic groups had longer disease duration compared to the sporadic group. The Hoehn&Yahr score was significantly higher in the *LRRK2* and *GBA* groups compared with sporadic group. However, there were no significant differences in the LEDD between the four groups.

Specially in the *GBA* group, the findings are consistent with previous studies, but our study performed a detailed evaluation of each specific symptom. These findings, including the lack of differences in the *PRKN* group, suggest a genetic influence on all aspects of PD and may lead us to consider as different disorders based on genetic subtypes. These findings emphasize the need for further exploration of these genetic pathways, the importance of genetic testing and individualized care for patients in daily practice (particularly in relation to autonomic symptoms) and may result in more effective approaches to patients symptoms.

Also, it is important to acknowledge the limitations of the study, especially in the *PRKN* group due to its small sample size. Generalizing the findings to their respective groups can be done, but more homogenic groups in sociodemographic aspects would strengthen the results. Additionally, two important aspects that were not assessed in the study are prodromal profile of patients with those mutations and potential differences among different variants of each gene. Our sample counts with at least five different variants in the *GBA* group and three in the *LRRK2* group, and separate analysis of these variants could reveal intragroup differences and provide further insights.

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8. CONSIDERAÇÕES FINAIS

Este estudo buscou avaliar as manifestações disautonômicas em indivíduos com DP genético com três mutações específicas – *PRKN*, *LRRK2* e *GBA* – na forma de caso-controle, sendo que o grupo controle era composto por indivíduos com DP esporádica. Os instrumentos de avaliação utilizados foram o SCOPA-AUT e o MDS-UPDRS.

Alguns estudos recentes avaliaram especificamente indivíduos com DP e mutações no *GBA* com relação a manifestações disautonômicas cardiovasculares, com resultados que sugerem uma maior gravidade de sintomas nos pacientes com mutações *GBA*. Estes estudos tiveram como base uma impressão clínica de maior frequência de queixas disautonômicas nesse grupo de pacientes.

Os resultados obtidos no presente estudo traçam um perfil sociodemográfico dessa amostra e corroboram a hipótese de uma presença de maior gravidade de disfunção autonômica geral em pacientes com mutações no *GBA* e, mais especificamente, com relação a sintomas cardiovasculares e termorregulatórios. Já os indivíduos com mutações no gene *LRRK2* também apresentam um perfil de maior gravidade de sintomas disautonômicos, neste caso envolvendo manifestações gastrointestinais, cardiovasculares e termorregulatórias; neste grupo de indivíduos, entretanto, a significância observada se perde quando controlamos as análises para potenciais confundidores. Já os indivíduos do grupo *PRKN*, não apresentam diferenças significativas em comparação aos do grupo esporádico em termos de disfunção autonômica.

Assim, os objetivos deste estudo – comparar a magnitude de sintomas disautonômicos em indivíduos com DP por mutações nos genes *PRKN*, *LRRK2* e *GBA* com indivíduos com DP esporádica; traçar perfil demográfico destes pacientes, verificar a diferença entre os grupos de disfunção autonômica por subgrupo de sintomas, de etnia e descendência e de padrão de herança familiar foram satisfeitos.

Com estes resultados, espera-se reforçar a necessidade de uma abordagem individualizada de pacientes, especialmente do ponto de vista disautonômicos, levando em consideração impacto na mortalidade e na qualidade de vida dos pacientes e seus cuidadores.

9. PERSPECTIVAS FUTURAS

Os sintomas não-motores estão cada vez mais em foco no espectro da DP. Além disso, nas últimas décadas, o avanço vertiginoso das técnicas de análise genética e maior facilidade de acesso a elas permitiram a descoberta de uma face até então desconhecida da DP e diversas formas genéticas tem sido descritas desde então. Isso trouxe consigo muitos questionamentos, tanto clínicos quanto fisiopatológicos a respeito da DP. O estudo aqui desenvolvido, trouxe alguns esclarecimentos a respeito das manifestações disautonômicas e corroborou impressões advindas da prática clínica e de outros estudos. Entretanto, uma análise mais aprofundada de subgrupos com diferentes variantes de cada gene pode trazer *insights* ainda maiores a respeito de potenciais vias alternativas ou acessórias da fisiopatologia clássica da alfa-sinucleína na DP.

A principal limitação observada no nosso estudo, diz respeito especificamente ao tamanho da amostra de indivíduos com mutações no gene *PRKN* que, tendo um padrão de herança autossômico recessivo, tem uma prevalência muito menor na população em comparação a outros padrões de herança.

10. ANEXOS E/OU APÊNDICES

10.1 SCOPA-AUT

SCOPA

SCOPA-AUT

By means of this questionnaire, we would like to find out to what extent in the past month you have had problems with various bodily functions, such as difficulty passing urine, or excessive sweating. Answer the questions by placing a cross in the box which best reflects your situation. If you wish to change an answer, fill in the 'wrong' box and place a cross in the correct one. If you have used medication in the past month in relation to one or more of the problems mentioned, then the question refers to how you were while taking this medication. You can note the use of medication on the last page.

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1. In the past month, have you had difficulty swallowing or have you choked?

☐ never ☐ sometimes ☐ regularly ☐ often

2. In the past month, has saliva dribbled out of your mouth?

☐ never ☐ sometimes ☐ regularly ☐ often

3. In the past month, has food ever become stuck in your throat?

☐ never ☐ sometimes ☐ regularly ☐ often

4. In the past month, did you ever have the feeling during a meal that you were full very quickly?

☐ never ☐ sometimes ☐ regularly ☐ often

5. *Constipation is a blockage of the bowel, a condition in which someone has a bowel movement twice a week or less.*
In the past month, have you had problems with constipation?

☐ never ☐ sometimes ☐ regularly ☐ often

6. In the past month, did you have to strain hard to pass stools?

☐ never ☐ sometimes ☐ regularly ☐ often

SCOPA

7. In the past month, have you had involuntary loss of stools?

☐ never ☐ sometimes ☐ regularly ☐ often

Questions 8 to 13 deal with problems with passing urine. If you use a catheter you can indicate this by placing a cross in the box "*use cathether*".

---

8. In the past month, have you had difficulty retaining urine?

☐ never ☐ sometimes ☐ regularly ☐ often ☐ *use catheter*

9. In the past month, have you had involuntary loss of urine?

☐ never ☐ sometimes ☐ regularly ☐ often ☐ *use catheter*

10. In the past month, have you had the feeling that after passing urine your bladder was not completely empty?

☐ never ☐ sometimes ☐ regularly ☐ often ☐ *use catheter*

11. In the past month, has the stream of urine been weak?

☐ never ☐ sometimes ☐ regularly ☐ often ☐ *use catheter*

12. In the past month, have you had to pass urine again within 2 hours of the previous time?

☐ never ☐ sometimes ☐ regularly ☐ often ☐ *use catheter*

13. In the past month, have you had to pass urine at night?

☐ never ☐ sometimes ☐ regularly ☐ often ☐ *use catheter*

SCOPA

14. In the past month, when standing up have you had the feeling of either becoming lightheaded, or no longer being able to see properly, or no longer being able to think clearly?

☐ never ☐ sometimes ☐ regularly ☐ often

15. In the past month, did you become light-headed after standing for some time?

☐ never ☐ sometimes ☐ regularly ☐ often

16. Have you fainted in the past 6 months?

☐ never ☐ sometimes ☐ regularly ☐ often

17. In the past month, have you ever perspired excessively during the day?

☐ never ☐ sometimes ☐ regularly ☐ often

18. In the past month, have you ever perspired excessively during the night?

☐ never ☐ sometimes ☐ regularly ☐ often

19. In the past month, have your eyes ever been over-sensitive to bright light?

☐ never ☐ sometimes ☐ regularly ☐ often

20. In the past month, how often have you had trouble tolerating cold?

☐ never ☐ sometimes ☐ regularly ☐ often

21. In the past month, how often have you had trouble tolerating heat?

☐ never ☐ sometimes ☐ regularly ☐ often

SCOPA

The following questions are about sexuality. Although we are aware that sexuality is a highly intimate subject, we would still like you to answer these questions. For the questions on sexual activity, consider every form of sexual contact with a partner or masturbation (self-gratification). An extra response option has been added to these questions. Here you can indicate that the situation described has not been applicable to you in the past month, for example because you have not been sexually active. Questions 22 and 23 are intended specifically for **men**, 24 and 25 for **women**.

The following 3 questions are only for men

22. In the past month, have you been impotent (unable to have or maintain an erection)?

☐ never ☐ sometimes ☐ regularly ☐ often ☐ *not applicable*

23. In the past month, how often have you been unable to ejaculate?

☐ never ☐ sometimes ☐ regularly ☐ often ☐ *not applicable*

23a. In the past month, have you taken medication for an erection disorder? (If so, which medication?)

☐ no ☐ yes: _____

Proceed with question 26

The following 2 questions are only for women

24. In the past month, was your vagina too dry during sexual activity?

☐ never ☐ sometimes ☐ regularly ☐ often ☐ *not applicable*

25. In the past month, have you had difficulty reaching an orgasm?

☐ never ☐ sometimes ☐ regularly ☐ often ☐ *not applicable*

The following questions are for everyone

The questions below are about the use of medication for which you may have or have not needed a doctor's prescription. If you use medication, also give the name of the substance.

26. In the past month, have you used medication for:

a. constipation?	☐ no	☐ yes: _____
b. urinary problems?	☐ no	☐ yes: _____
c. blood pressure?	☐ no	☐ yes: _____
d. other symptoms *(not symptoms related to Parkinson's disease)*	☐ no	☐ yes: _____

_____

10.2 MDS-UPDRS

Part I: Non-Motor Aspects of Experiences of Daily Living (nM-EDL)

Overview: This portion of the scale assesses the non-motor impact of Parkinson's disease (PD) on patients' experiences of daily living. There are 13 questions. Part IA is administered by the rater (six questions) and focuses on complex behaviors. Part IB is a component of the self-administered Patient Questionnaire that covers seven questions on non-motor experiences of daily living.

Part IA:
In administering Part IA, the examiner should use the following guidelines:

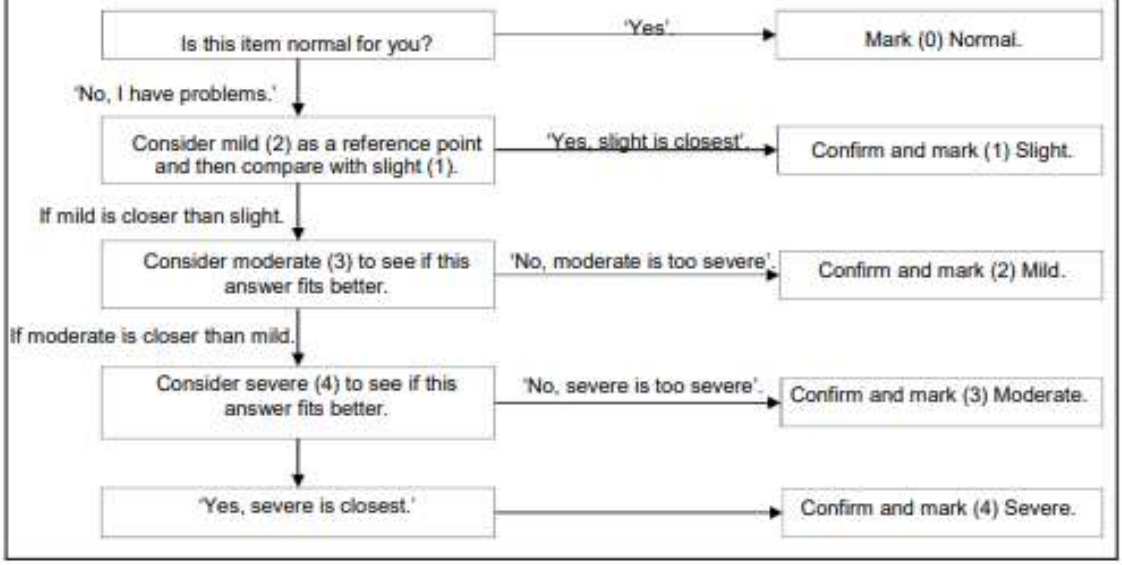
1. Mark at the top of the form the primary data source as patient, caregiver, or patient and caregiver in equal proportion.
2. The response to each item should refer to a period encompassing the prior week including the day on which the information is collected.
3. All items must have an integer rating (no half points, no missing scores). In the event that an item does not apply or cannot be rated (e.g., amputee who cannot walk), the item is marked **"UR"** for Unable to Rate.
4. The answers should reflect the usual level of function and words such as "usually," "generally," "most of the time" can be used with patients.
5. Each question has a text for you to read (Instructions to patients/caregiver). After that statement, you can elaborate and probe based on the target symptoms outlined in the Instructions to examiner. You should NOT READ the RATING OPTIONS to the patient/caregiver, because these are written in medical terminology. From the interview and probing, you will use your medical judgment to arrive at the best response.
6. Patients may have co-morbidities and other medical conditions that can affect their function. You and the patient must rate the problem as it exists and do not attempt to separate elements due to Parkinson's disease from other conditions.

EXAMPLE OF NAVIGATING THROUGH THE RESPONSE OPTIONS FOR PART IA

Suggested strategies for obtaining the most accurate answer:
After reading the instructions to the patient, you will need to probe the entire domain under discussion to determine normal vs. problematic: If your questions do not identify any problem in this domain, record 0 and move on to the next question.

If your questions identify a problem in this domain, you should work next with a reference anchor at the mid-range (option 2 or Mild) to find out if the patient functions at this level, better or worse. You will not be reading the choices of responses to the patient as the responses use clinical terminology. You will be asking enough probing questions to determine the response that should be coded.

Work up and down the options with the patient to identify the most accurate response, giving a final check by excluding the options above and below the selected response.



Patient Name or Subject ID	Site ID	(mm-dd-yyyy) Assessment Date	Investigator's Initials

MDS UPDRS
Part I: Non-Motor Aspects of Experiences of Daily Living (nM-EDL)

Part IA: Complex behaviors: [completed by rater]

Primary source of information:

☐ Patient ☐ Caregiver ☐ Patient and Caregiver in Equal Proportion

To be read to the patient: I am going to ask you six questions about behaviors that you may or may not experience. Some questions concern common problems and some concern uncommon ones. If you have a problem in one of the areas, please choose the best response that describes how you have felt MOST OF THE TIME during the PAST WEEK. If you are not bothered by a problem, you can simply respond NO. I am trying to be thorough, so I may ask questions that have nothing to do with you.

1.1 COGNITIVE IMPAIRMENT — **SCORE**

Instructions to examiner: Consider all types of altered level of cognitive function including cognitive slowing, impaired reasoning, memory loss, deficits in attention and orientation. Rate their impact on activities of daily living as perceived by the patient and/or caregiver.

Instructions to patient [and caregiver]: Over the past week have you had problems remembering things, following conversations, paying attention, thinking clearly, or finding your way around the house or in town? [If yes, examiner asks patient or caregiver to elaborate and probes for information.]

0: Normal:	No cognitive impairment.	
1: Slight:	Impairment appreciated by patient or caregiver with no concrete interference with the patient's ability to carry out normal activities and social interactions.	☐
2: Mild:	Clinically evident cognitive dysfunction, but only minimal interference with the patient's ability to carry out normal activities and social interactions.	
3: Moderate:	Cognitive deficits interfere with but do not preclude the patient's ability to carry out normal activities and social interactions.	
4: Severe:	Cognitive dysfunction precludes the patient's ability to carry out normal activities and social interactions.	

	SCORE
1.2 HALLUCINATIONS AND PSYCHOSIS Instructions to examiner: Consider both illusions (misinterpretations of real stimuli) and hallucinations (spontaneous false sensations). Consider all major sensory domains (visual, auditory, tactile, olfactory, and gustatory). Determine presence of unformed (for example sense of presence or fleeting false impressions) as well as formed (fully developed and detailed) sensations. Rate the patient's insight into hallucinations and identify delusions and psychotic thinking. *Instructions to patient [and caregiver]: Over the past week have you seen, heard, smelled, or felt things that were not really there?* [If yes, examiner asks patient or caregiver to elaborate and probes for information.] 0: Normal: No hallucinations or psychotic behavior. 1: Slight: Illusions or non-formed hallucinations, but patient recognizes them without loss of insight. 2: Mild: Formed hallucinations independent of environmental stimuli. No loss of insight. 3: Moderate: Formed hallucinations with loss of insight. 4: Severe: Patient has delusions or paranoia.	☐
1.3 DEPRESSED MOOD Instructions to examiner: Consider low mood, sadness, hopelessness, feelings of emptiness, or loss of enjoyment. Determine their presence and duration over the past week and rate their interference with the patient's ability to carry out daily routines and engage in social interactions. *Instructions to patient [and caregiver]: Over the past week have you felt low, sad, hopeless, or unable to enjoy things? If yes, was this feeling for longer than one day at a time? Did it make it difficult for you carry out your usual activities or to be with people?* [If yes, examiner asks patient or caregiver to elaborate and probes for information.] 0: Normal: No depressed mood. 1: Slight: Episodes of depressed mood that are not sustained for more than one day at a time. No interference with patient's ability to carry out normal activities and social interactions. 2: Mild: Depressed mood that is sustained over days, but without interference with normal activities and social interactions. 3: Moderate: Depressed mood that interferes with, but does not preclude the patient's ability to carry out normal activities and social interactions. 4: Severe: Depressed mood precludes patient's ability to carry out normal activities and social interactions.	☐

	SCORE
1.4 ANXIOUS MOOD Instructions to examiner: Determine nervous, tense, worried, or anxious feelings (including panic attacks) over the past week and rate their duration and interference with the patient's ability to carry out daily routines and engage in social interactions. *Instructions to patient [and caregiver]: Over the past week have you felt nervous, worried, or tense? If yes, was this feeling for longer than one day at a time? Did it make it difficult for you to follow your usual activities or to be with other people?* [If yes, examiner asks patient or caregiver to elaborate and probes for information.] 0: Normal: No anxious feelings. 1: Slight: Anxious feelings present but not sustained for more than one day at a time. No interference with patient's ability to carry out normal activities and social interactions. 2: Mild: Anxious feelings are sustained over more than one day at a time, but without interference with patient's ability to carry out normal activities and social interactions. 3: Moderate: Anxious feelings interfere with, but do not preclude, the patient's ability to carry out normal activities and social interactions. 4: Severe: Anxious feelings preclude patient's ability to carry out normal activities and social interactions.	☐
1.5 APATHY Instructions to examiner: Consider level of spontaneous activity, assertiveness, motivation, and initiative and rate the impact of reduced levels on performance of daily routines and social interactions. Here the examiner should attempt to distinguish between apathy and similar symptoms that are best explained by depression. *Instructions to patient [and caregiver]: Over the past week, have you felt indifferent to doing activities or being with people?* [If yes, examiner asks patient or caregiver to elaborate and probes for information.] 0: Normal: No apathy. 1: Slight: Apathy appreciated by patient and/or caregiver, but no interference with daily activities and social interactions. 2: Mild: Apathy interferes with isolated activities and social interactions. 3: Moderate: Apathy interferes with most activities and social interactions. 4: Severe: Passive and withdrawn, complete loss of initiative.	☐

SCORE

1.6 FEATURES OF DOPAMINE DYSREGULATION SYNDROME

Instructions to examiner: Consider involvement in a variety of activities including atypical or excessive gambling (e.g. casinos or lottery tickets), atypical or excessive sexual drive or interests (e.g., unusual interest in pornography, masturbation, sexual demands on partner), other repetitive activities (e.g. hobbies, dismantling objects, sorting or organizing), or taking extra non-prescribed medication for non-physical reasons (i.e., addictive behavior). Rate the impact of such abnormal activities/behaviors on the patient's personal life and on his/her family and social relations (including need to borrow money or other financial difficulties like withdrawal of credit cards, major family conflicts, lost time from work, or missed meals or sleep because of the activity).

Instructions to patient (and caregiver): Over the past week, have you had unusually strong urges that are hard to control? Do you feel driven to do or think about something and find it hard to stop? [Give patient examples such as gambling, cleaning, using the computer, taking extra medicine, obsessing about food or sex, all depending on the patient.]

0: Normal:	No problems present.	☐
1: Slight:	Problems are present but usually do not cause any difficulties for the patient or family/caregiver.	
2: Mild:	Problems are present and usually cause a few difficulties in the patient's personal and family life.	
3: Moderate:	Problems are present and usually cause a lot of difficulties in the patient's personal and family life.	
4: Severe:	Problems are present and preclude the patient's ability to carry out normal activities or social interactions or to maintain previous standards in personal and family life.	

The remaining questions in Part I (Non-motor Experiences of Daily Living) [Sleep, Daytime Sleepiness, Pain and Other Sensation, Urinary Problems, Constipation Problems, Lightheadedness on Standing, and Fatigue] are in the **Patient Questionnaire** along with all questions in Part II [Motor Experiences of Daily Living].

Patient Questionnaire:

Instructions:

This questionnaire will ask you about your experiences of daily living.

There are 20 questions. We are trying to be thorough, and some of these questions may therefore not apply to you now or ever. If you do not have the problem, simply mark 0 for NO.

Please read each one carefully and read all answers before selecting the one that best applies to you.

We are interested in your average or usual function over the past week including today. Some patients can do things better at one time of the day than at others. However, only one answer is allowed for each question, so please mark the answer that best describes what you can do most of the time.

You may have other medical conditions besides Parkinson's disease. Do not worry about separating Parkinson's disease from other conditions. Just answer the question with your best response.

Use only 0, 1, 2, 3, 4 for answers, nothing else. Do not leave any blanks.

Your doctor or nurse can review the questions with you, but this questionnaire is for patients to complete, either alone or with their caregivers.

Who is filling out this questionnaire (check the best answer):

☐ Patient ☐ Caregiver ☐ Patient and Caregiver in Equal Proportion

Part I: Non-Motor Aspects of Experiences of Daily Living (nM-EDL)	
1.7 SLEEP PROBLEMS Over the past week, have you had trouble going to sleep at night or staying asleep through the night? Consider how rested you felt after waking up in the morning. 0: Normal: No problems. 1: Slight: Sleep problems are present but usually do not cause trouble getting a full night of sleep. 2: Mild: Sleep problems usually cause some difficulties getting a full night of sleep. 3: Moderate: Sleep problems cause a lot of difficulties getting a full night of sleep, but I still usually sleep for more than half the night. 4: Severe: I usually do not sleep for most of the night.	**SCORE** ☐
1.8 DAYTIME SLEEPINESS Over the past week, have you had trouble staying awake during the daytime? 0: Normal: No daytime sleepiness. 1: Slight: Daytime sleepiness occurs, but I can resist and I stay awake. 2: Mild: Sometimes I fall asleep when alone and relaxing. For example, while reading or watching TV. 3: Moderate: I sometimes fall asleep when I should not. For example, while eating or talking with other people. 4: Severe: I often fall asleep when I should not. For example, while eating or talking with other people.	☐

	SCORE
1.9 PAIN AND OTHER SENSATIONS Over the past week, have you had uncomfortable feelings in your body like pain, aches, tingling, or cramps? 0: Normal: No uncomfortable feelings. 1: Slight: I have these feelings. However, I can do things and be with other people without difficulty. 2: Mild: These feelings cause some problems when I do things or am with other people. 3: Moderate: These feelings cause a lot of problems, but they do not stop me from doing things or being with other people. 4: Severe: These feelings stop me from doing things or being with other people.	☐
1.10 URINARY PROBLEMS Over the past week, have you had trouble with urine control? For example, an urgent need to urinate, a need to urinate too often, or urine accidents? 0: Normal: No urine control problems. 1: Slight: I need to urinate often or urgently. However, these problems do not cause difficulties with my daily activities. 2: Mild: Urine problems cause some difficulties with my daily activities. However, I do not have urine accidents. 3: Moderate: Urine problems cause a lot of difficulties with my daily activities, including urine accidents. 4: Severe: I cannot control my urine and use a protective garment or have a bladder tube.	☐

	SCORE
1.11 CONSTIPATION PROBLEMS Over the past week have you had constipation troubles that cause you difficulty moving your bowels? 0: Normal: No constipation. 1: Slight: I have been constipated. I use extra effort to move my bowels. However, this problem does not disturb my activities or my being comfortable. 2: Mild: Constipation causes me to have some troubles doing things or being comfortable. 3: Moderate: Constipation causes me to have a lot of trouble doing things or being comfortable. However, it does not stop me from doing anything. 4: Severe: I usually need physical help from someone else to empty my bowels.	☐
1.12 LIGHT HEADEDNESS ON STANDING Over the past week, have you felt faint, dizzy, or foggy when you stand up after sitting or lying down? 0: Normal: No dizzy or foggy feelings. 1: Slight: Dizzy or foggy feelings occur. However, they do not cause me troubles doing things. 2: Mild: Dizzy or foggy feelings cause me to hold on to something, but I do not need to sit or lie back down. 3: Moderate: Dizzy or foggy feelings cause me to sit or lie down to avoid fainting or falling. 4: Severe: Dizzy or foggy feelings cause me to fall or faint.	☐

	SCORE
1.13 FATIGUE Over the past week, have you usually felt fatigued? This feeling is <u>not</u> part of being sleepy or sad. 0: Normal: No fatigue. 1: Slight: Fatigue occurs. However it does not cause me troubles doing things or being with people. 2: Mild: Fatigue causes me some troubles doing things or being with people. 3: Moderate: Fatigue causes me a lot of troubles doing things or being with people. However, it does not stop me from doing anything. 4: Severe: Fatigue stops me from doing things or being with people.	☐

Part II: Motor Aspects of Experiences of Daily Living (M-EDL)

2.1 SPEECH Over the past week, have you had problems with your speech? 0: Normal: Not at all (no problems). 1: Slight: My speech is soft, slurred or uneven, but it does not cause others to ask me to repeat myself. 2: Mild: My speech causes people to ask me to occasionally repeat myself, but not every day. 3: Moderate: My speech is unclear enough that others ask me to repeat myself every day even though most of my speech is understood. 4: Severe: Most or all of my speech cannot be understood.	☐

	SCORE
2.2 SALIVA AND DROOLING Over the past week, have you usually had too much saliva during when you are awake or when you sleep? 0: Normal: Not at all (no problems). 1: Slight: I have too much saliva, but do not drool. 2: Mild: I have some drooling during sleep, but none when I am awake. 3: Moderate: I have some drooling when I am awake, but I usually do not need tissues or a handkerchief. 4: Severe: I have so much drooling that I regularly need to use tissues or a handkerchief to protect my clothes.	☐
2.3 CHEWING AND SWALLOWING Over the past week, have you usually had problems swallowing pills or eating meals? Do you need your pills cut or crushed or your meals to be made soft, chopped, or blended to avoid choking? 0: Normal: No problems. 1: Slight: I am aware of slowness in my chewing or increased effort at swallowing, but I do not choke or need to have my food specially prepared. 2: Mild: I need to have my pills cut or my food specially prepared because of chewing or swallowing problems, but I have not choked over the past week. 3: Moderate. I choked at least once in the past week. 4: Severe: Because of chewing and swallowing problems, I need a feeding tube.	☐

	SCORE
2.4 EATING TASKS Over the past week, have you usually had troubles handling your food and using eating utensils? For example, do you have trouble handling finger foods or using forks, knives, spoons, chopsticks? 0: Normal: Not at all (no problems). 1: Slight: I am slow, but I do not need any help handling my food and have not had food spills while eating. 2: Mild: I am slow with my eating and have occasional food spills. I may need help with a few tasks such as cutting meat. 3: Moderate: I need help with many eating tasks but can manage some alone. 4: Severe: I need help for most or all eating tasks.	☐
2.5 DRESSING Over the past week, have you usually had problems dressing? For example, are you slow or do you need help with buttoning, using zippers, putting on or taking off your clothes or jewelry? 0: Normal: Not at all (no problems). 1: Slight: I am slow, but I do not need help. 2: Mild: I am slow and need help for a few dressing tasks (buttons, bracelets). 3: Moderate: I need help for many dressing tasks. 4: Severe: I need help for most or all dressing tasks.	☐

	SCORE
2.6 HYGIENE Over the past week, have you usually been slow or do you need help with washing, bathing, shaving, brushing teeth, combing your hair, or with other personal hygiene? 0: Normal: Not at all (no problems). 1: Slight: I am slow, but I do not need any help. 2: Mild: I need someone else to help me with some hygiene tasks. 3: Moderate: I need help for many hygiene tasks. 4: Severe: I need help for most or all of my hygiene tasks.	☐
2.7 HANDWRITING Over the past week, have people usually had trouble reading your handwriting? 0: Normal: Not at all (no problems). 1: Slight: My writing is slow, clumsy or uneven, but all words are clear. 2: Mild: Some words are unclear and difficult to read. 3: Moderate: Many words are unclear and difficult to read. 4: Severe: Most or all words cannot be read.	☐
2.8 DOING HOBBIES AND OTHER ACTIVITIES Over the past week, have you usually had trouble doing your hobbies or other things that you like to do? 0: Normal: Not at all (no problems). 1: Slight: I am a bit slow but do these activities easily. 2: Mild: I have some difficulty doing these activities. 3: Moderate: I have major problems doing these activities, but still do most. 4: Severe: I am unable to do most or all of these activities.	☐

	SCORE
2.9 TURNING IN BED Over the past week, do you usually have trouble turning over in bed? 0: Normal: Not at all (no problems). 1: Slight: I have a bit of trouble turning, but I do not need any help. 2: Mild I have a lot of trouble turning and need occasional help from someone else. 3: Moderate: To turn over I often need help from someone else. 4: Severe: I am unable to turn over without help from someone else.	☐
2.10 TREMOR Over the past week, have you usually had shaking or tremor? 0: Normal: Not at all. I have no shaking or tremor. 1: Slight: Shaking or tremor occurs but does not cause problems with any activities. 2: Mild: Shaking or tremor causes problems with only a few activities. 3: Moderate: Shaking or tremor causes problems with many of my daily activities. 4: Severe: Shaking or tremor causes problems with most or all activities.	☐
2.11 GETTING OUT OF BED, A CAR, OR A DEEP CHAIR Over the past week, have you usually had trouble getting out of bed, a car seat, or a deep chair? 0: Normal: Not at all (no problems). 1: Slight: I am slow or awkward, but I usually can do it on my first try. 2: Mild: I need more than one try to get up or need occasional help. 3: Moderate: I sometimes need help to get up, but most times I can still do it on my own. 4: Severe: I need help most or all of the time.	☐

	SCORE
2.12 WALKING AND BALANCE Over the past week, have you usually had problems with balance and walking? 0: Normal: Not at all (no problems). 1: Slight: I am slightly slow or may drag a leg. I never use a walking aid. 2: Mild: I occasionally use a walking aid, but I do not need any help from another person. 3: Moderate: I usually use a walking aid (cane, walker) to walk safely without falling. However, I do not usually need the support of another person. 4: Severe: I usually use the support of another person to walk safely without falling.	☐
2.13 FREEZING Over the past week, on your usual day when walking, do you suddenly stop or freeze as if your feet are stuck to the floor? 0: Normal: Not at all (no problems). 1: Slight: I briefly freeze, but I can easily start walking again. I do not need help from someone else or a walking aid (cane or walker) because of freezing. 2: Mild: I freeze and have trouble starting to walk again, but I do not need someone's help or a walking aid (cane or walker) because of freezing. 3: Moderate: When I freeze I have a lot of trouble starting to walk again and, because of freezing, I sometimes need to use a walking aid or need someone else's help. 4: Severe: Because of freezing, most or all of the time, I need to use a walking aid or someone's help.	☐

This completes the questionnaire. We may have asked about problems you do not even have, and may have mentioned problems that you may never develop at all. Not all patients develop all these problems, but because they can occur, it is important to ask all the questions to every patient. Thank you for your time and attention in completing this questionnaire.

Part III: Motor Examination

Overview: This portion of the scale assesses the motor signs of PD. In administering Part III of the MDS-UPDRS the examiner should comply with the following guidelines:

At the top of the form, mark whether the patient is on medication for treating the symptoms of Parkinson's disease and, if on levodopa, the time since the last dose.

Also, if the patient is receiving medication for treating the symptoms of Parkinson's disease, mark the patient's clinical state using the following definitions:

ON is the typical functional state when patients are receiving medication and have a good response.
OFF is the typical functional state when patients have a poor response in spite of taking medications.

The investigator should "rate what you see." Admittedly, concurrent medical problems such as stroke, paralysis, arthritis, contracture, and orthopedic problems such as hip or knee replacement and scoliosis may interfere with individual items in the motor examination. In situations where it is absolutely impossible to test (e.g., amputations, plegia, limb in a cast), use the notation "**UR**" for Unable to Rate. Otherwise, rate the performance of each task as the patient performs in the context of co-morbidities.

All items must have an integer rating (no half points, no missing ratings).

Specific instructions are provided for the testing of each item. These should be followed in all instances. The investigator demonstrates while describing tasks the patient is to perform and rates function immediately thereafter. For Global Spontaneous Movement and Rest Tremor items (3.14 and 3.17), these items have been placed purposefully at the end of the scale because clinical information pertinent to the score will be obtained throughout the entire examination.

At the end of the rating, indicate if dyskinesia (chorea or dystonia) was present at the time of the examination, and if so, whether these movements interfered with the motor examination.

3a Is the patient on medication for treating the symptoms of Parkinson's disease? ☐ No ☐ Yes

3b If the patient is receiving medication for treating the symptoms of Parkinson's disease, mark the patient's clinical state using the following definitions:

☐ ON: On is the typical functional state when patients are receiving medication and have a good response.

☐ OFF: Off is the typical functional state when patients have a poor response in spite of taking medications.

3c Is the patient on levodopa ? ☐ No ☐ Yes

3.C1 If yes, minutes since last levodopa dose: _____

	SCORE
3.1 SPEECH Instructions to examiner: Listen to the patient's free-flowing speech and engage in conversation if necessary. Suggested topics: ask about the patient's work, hobbies, exercise, or how he got to the doctor's office. Evaluate volume, modulation (prosody), and clarity, including slurring, palilalia (repetition of syllables), and tachyphemia (rapid speech, running syllables together). 0: Normal: No speech problems. 1: Slight: Loss of modulation, diction, or volume, but still all words easy to understand. 2: Mild: Loss of modulation, diction, or volume, with a few words unclear, but the overall sentences easy to follow. 3: Moderate: Speech is difficult to understand to the point that some, but not most, sentences are poorly understood. 4: Severe: Most speech is difficult to understand or unintelligible.	☐
3.2 FACIAL EXPRESSION Instructions to examiner: Observe the patient sitting at rest for 10 seconds, without talking and also while talking. Observe eye-blink frequency, masked facies or loss of facial expression, spontaneous smiling, and parting of lips. 0: Normal: Normal facial expression. 1: Slight: Minimal masked facies manifested only by decreased frequency of blinking. 2: Mild: In addition to decreased eye-blink frequency, masked facies present in the lower face as well, namely fewer movements around the mouth, such as less spontaneous smiling, but lips not parted. 3: Moderate: Masked facies with lips parted some of the time when the mouth is at rest. 4: Severe: Masked facies with lips parted most of the time when the mouth is at rest.	☐

3.3 RIGIDITY

SCORE

Instructions to examiner: Rigidity is judged on slow passive movement of major joints with the patient in a relaxed position and the examiner manipulating the limbs and neck. First, test without an activation maneuver. Test and rate neck and each limb separately. For arms, test the wrist and elbow joints simultaneously. For legs, test the hip and knee joints simultaneously. If no rigidity is detected, use an activation maneuver such as tapping fingers, fist opening/closing, or heel tapping in a limb not being tested. Explain to the patient to go as limp as possible as you test for rigidity.

0: Normal:	No rigidity.	
1: Slight:	Rigidity only detected with activation maneuver.	
2: Mild:	Rigidity detected without the activation maneuver, but full range of motion is easily achieved.	
3: Moderate:	Rigidity detected without the activation maneuver; full range of motion is achieved with effort.	
4: Severe:	Rigidity detected without the activation maneuver and full range of motion not achieved.	

☐ Neck

☐ RUE

☐ LUE

☐ RLE

☐ LLE

3.4 FINGER TAPPING

Instructions to examiner: Each hand is tested separately. Demonstrate the task, but do not continue to perform the task while the patient is being tested. Instruct the patient to tap the index finger on the thumb 10 times as quickly AND as big as possible. Rate each side separately, evaluating speed, amplitude, hesitations, halts, and decrementing amplitude.

0: Normal:	No problems.
1: Slight:	Any of the following: a) the regular rhythm is broken with one or two interruptions or hesitations of the tapping movement; b) slight slowing; c) the amplitude decrements near the end of the 10 taps.
2: Mild:	Any of the following: a) 3 to 5 interruptions during tapping; b) mild slowing; c) the amplitude decrements midway in the 10-tap sequence.
3: Moderate:	Any of the following: a) more than 5 interruptions during tapping or at least one longer arrest (freeze) in ongoing movement; b) moderate slowing; c) the amplitude decrements starting after the 1st tap.
4: Severe:	Cannot or can only barely perform the task because of slowing, interruptions, or decrements.

☐ R

☐ L

	SCORE
3.5 HAND MOVEMENTS Instructions to examiner: Test each hand separately. Demonstrate the task, but do not continue to perform the task while the patient is being tested. Instruct the patient to make a tight fist with the arm bent at the elbow so that the palm faces the examiner. Have the patient open the hand 10 times as fully AND as quickly as possible. If the patient fails to make a tight fist or to open the hand fully, remind him/her to do so. Rate each side separately, evaluating speed, amplitude, hesitations, halts, and decrementing amplitude. 0: Normal: No problems. 1: Slight: Any of the following: a) the regular rhythm is broken with one or two interruptions or hesitations of the movement; b) slight slowing; c) the amplitude decrements near the end of the task. 2: Mild: Any of the following: a) 3 to 5 interruptions during the movements; b) mild slowing; c) the amplitude decrements midway in the task. 3: Moderate: Any of the following: a) more than 5 interruptions during the movement or at least one longer arrest (freeze) in ongoing movement; b) moderate slowing; c) the amplitude decrements starting after the 1st open-and-close sequence. 4: Severe: Cannot or can only barely perform the task because of slowing, interruptions, or decrements.	☐ R ☐ L
3.6 PRONATION-SUPINATION MOVEMENTS OF HANDS Instructions to examiner: Test each hand separately. Demonstrate the task, but do not continue to perform the task while the patient is being tested. Instruct the patient to extend the arm out in front of his/her body with the palms down, and then to turn the palm up and down alternately 10 times as fast and as fully as possible. Rate each side separately, evaluating speed, amplitude, hesitations, halts, and decrementing amplitude. 0: Normal: No problems. 1: Slight: Any of the following: a) the regular rhythm is broken with one or two interruptions or hesitations of the movement; b) slight slowing; c) the amplitude decrements near the end of the sequence. 2: Mild: Any of the following: a) 3 to 5 interruptions during the movements; b) mild slowing; c) the amplitude decrements midway in the sequence. 3: Moderate: Any of the following: a) more than 5 interruptions during the movement or at least one longer arrest (freeze) in ongoing movement; b) moderate slowing; c) the amplitude decrements starting after the 1st supination-pronation sequence. 4: Severe: Cannot or can only barely perform the task because of slowing, interruptions, or decrements.	☐ R ☐ L

	SCORE
3.7 TOE TAPPING Instructions to examiner: Have the patient sit in a straight-backed chair with arms, both feet on the floor. Test each foot separately. Demonstrate the task, but do not continue to perform the task while the patient is being tested. Instruct the patient to place the heel on the ground in a comfortable position and then tap the toes 10 times as big and as fast as possible. Rate each side separately, evaluating speed, amplitude, hesitations, halts, and decrementing amplitude. 0: Normal: No problems. 1: Slight: Any of the following: a) the regular rhythm is broken with one or two interruptions or hesitations of the tapping movement; b) slight slowing; c) amplitude decrements near the end of the ten taps. 2: Mild: Any of the following: a) 3 to 5 interruptions during the tapping movements; b) mild slowing; c) amplitude decrements midway in the task. 3: Moderate: Any of the following: a) more than 5 interruptions during the tapping movements or at least one longer arrest (freeze) in ongoing movement; b) moderate slowing; c) amplitude decrements after the 1st tap. 4: Severe: Cannot or can only barely perform the task because of slowing, interruptions or decrements.	☐ R ☐ L
3.8 LEG AGILITY Instructions to examiner: Have the patient sit in a straight-backed chair with arms. The patient should have both feet comfortably on the floor. Test each leg separately. Demonstrate the task, but do not continue to perform the task while the patient is being tested. Instruct the patient to place the foot on the ground in a comfortable position and then raise and stomp the foot on the ground 10 times as high and as fast as possible. Rate each side separately, evaluating speed, amplitude, hesitations, halts and decrementing amplitude. 0: Normal: No problems. 1: Slight: Any of the following: a) the regular rhythm is broken with one or two interruptions or hesitations of the movement; b) slight slowing; c) amplitude decrements near the end of the task. 2: Mild: Any of the following: a) 3 to 5 interruptions during the movements; b) mild slowness; c) amplitude decrements midway in the task. 3: Moderate: Any of the following: a) more than 5 interruptions during the movement or at least one longer arrest (freeze) in ongoing movement; b) moderate slowing in speed; c) amplitude decrements after the 1st tap. 4: Severe: Cannot or can only barely perform the task because of slowing, interruptions, or decrements.	☐ R ☐ L

	SCORE
3.9 ARISING FROM CHAIR Instructions to examiner: Have the patient sit in a straight-backed chair with arms, with both feet on the floor and sitting back in the chair (if the patient is not too short). Ask the patient to cross his/her arms across the chest and then to stand up. If the patient is not successful, repeat this attempt up to a maximum of two more times. If still unsuccessful, allow the patient to move forward in the chair to arise with arms folded across the chest. Allow only one attempt in this situation. If unsuccessful, allow the patient to push off using his/her hands on the arms of the chair. Allow a maximum of three trials of pushing off. If still not successful, assist the patient to arise. After the patient stands up, observe the posture for item 3.13. 0: Normal: No problems. Able to arise quickly without hesitation. 1: Slight: Arising is slower than normal; or may need more than one attempt; or may need to move forward in the chair to arise. No need to use the arms of the chair. 2: Mild: Pushes self up from the arms of the chair without difficulty. 3: Moderate: Needs to push off, but tends to fall back; or may have to try more than one time using the arms of the chair, but can get up without help. 4: Severe: Unable to arise without help.	☐
3.10 GAIT Instructions to examiner: Testing gait is best performed by having the patient walking away from and towards the examiner so that both right and left sides of the body can be easily observed simultaneously. The patient should walk at least 10 meters (30 feet), then turn around and return to the examiner. This item measures multiple behaviors: stride amplitude, stride speed, height of foot lift, heel strike during walking, turning, and arm swing, but not freezing. Assess also for "freezing of gait" (next item 3.11) while patient is walking. Observe posture for item 3.13. 0: Normal: No problems. 1: Slight: Independent walking with minor gait impairment. 2: Mild: Independent walking but with substantial gait impairment. 3: Moderate: Requires an assistance device for safe walking (walking stick, walker) but not a person. 4: Severe: Cannot walk at all or only with another person's assistance.	☐

	SCORE
3.11 FREEZING OF GAIT Instructions to examiner: While assessing gait, also assess for the presence of any gait freezing episodes. Observe for start hesitation and stuttering movements especially when turning and reaching the end of the task. To the extent that safety permits, patients may NOT use sensory tricks during the assessment. 0: Normal: No freezing. 1: Slight: Freezes on starting, turning, or walking through doorway with a single halt during any of these events, but then continues smoothly without freezing during straight walking. 2: Mild: Freezes on starting, turning, or walking through doorway with more than one halt during any of these activities, but continues smoothly without freezing during straight walking. 3: Moderate: Freezes once during straight walking. 4: Severe: Freezes multiple times during straight walking.	☐
3.12 POSTURAL STABILITY Instructions to examiner: The test examines the response to sudden body displacement produced by a quick, forceful pull on the shoulders while the patient is standing erect with eyes open and feet comfortably apart and parallel to each other. Test retropulsion. Stand behind the patient and instruct the patient on what is about to happen. Explain that s/he is allowed to take a step backwards to avoid falling. There should be a solid wall behind the examiner, at least 1-2 meters away to allow for the observation of the number of retropulsive steps. The first pull is an instructional demonstration and is purposely milder and not rated. The second time the shoulders are pulled briskly and forcefully towards the examiner with enough force to displace the center of gravity so that patient MUST take a step backwards. The examiner needs to be ready to catch the patient, but must stand sufficiently back so as to allow enough room for the patient to take several steps to recover independently. Do not allow the patient to flex the body abnormally forward in anticipation of the pull. Observe for the number of steps backwards or falling. Up to and including two steps for recovery is considered normal, so abnormal ratings begin with three steps. If the patient fails to understand the test, the examiner can repeat the test so that the rating is based on an assessment that the examiner feels reflects the patient's limitations rather than misunderstanding or lack of preparedness. Observe standing posture for item 3.13. 0: Normal: No problems. Recovers with one or two steps. 1: Slight: 3-5 steps, but subject recovers unaided. 2: Mild: More than 5 steps, but subject recovers unaided. 3: Moderate: Stands safely, but with absence of postural response; falls if not caught by examiner. 4: Severe: Very unstable, tends to lose balance spontaneously or with just a gentle pull on the shoulders.	☐

	SCORE
3.13 POSTURE Instructions to examiner: Posture is assessed with the patient standing erect after arising from a chair, during walking, and while being tested for postural reflexes. If you notice poor posture, tell the patient to stand up straight and see if the posture improves (see option 2 below). Rate the worst posture seen in these three observation points. Observe for flexion and side-to-side leaning. 0: Normal: No problems. 1: Slight: Not quite erect, but posture could be normal for older person. 2: Mild: Definite flexion, scoliosis or leaning to one side, but patient can correct posture to normal posture when asked to do so. 3: Moderate: Stooped posture, scoliosis or leaning to one side that cannot be corrected volitionally to a normal posture by the patient. 4: Severe: Flexion, scoliosis or leaning with extreme abnormality of posture.	☐
3.14 GLOBAL SPONTANEITY OF MOVEMENT (BODY BRADYKINESIA) Instructions to examiner: This global rating combines all observations on slowness, hesitancy, and small amplitude and poverty of movement in general, including a reduction of gesturing and of crossing the legs. This assessment is based on the examiner's global impression after observing for spontaneous gestures while sitting, and the nature of arising and walking. 0: Normal: No problems. 1: Slight: Slight global slowness and poverty of spontaneous movements. 2: Mild: Mild global slowness and poverty of spontaneous movements. 3: Moderate: Moderate global slowness and poverty of spontaneous movements. 4: Severe: Severe global slowness and poverty of spontaneous movements.	☐
3.15 POSTURAL TREMOR OF THE HANDS Instructions to examiner: All tremor, including re-emergent rest tremor, that is present in this posture is to be included in this rating. Rate each hand separately. Rate the highest amplitude seen. Instruct the patient to stretch the arms out in front of the body with palms down. The wrist should be straight and the fingers comfortably separated so that they do not touch each other. Observe this posture for 10 seconds. 0: Normal: No tremor. 1: Slight: Tremor is present but less than 1 cm in amplitude. 2: Mild: Tremor is at least 1 but less than 3 cm in amplitude. 3: Moderate: Tremor is at least 3 but less than 10 cm in amplitude. 4: Severe: Tremor is at least 10 cm in amplitude.	☐ R ☐ L

3.16 KINETIC TREMOR OF THE HANDS

SCORE

Instructions to examiner: This is tested by the finger-to-nose maneuver. With the arm starting from the outstretched position, have the patient perform at least three finger-to-nose maneuvers with each hand reaching as far as possible to touch the examiner's finger. The finger-to-nose maneuver should be performed slowly enough not to hide any tremor that could occur with very fast arm movements. Repeat with the other hand, rating each hand separately. The tremor can be present throughout the movement or as the tremor reaches either target (nose or finger). Rate the highest amplitude seen.

0: Normal:	No tremor.	
1: Slight:	Tremor is present but less than 1 cm in amplitude.	R
2: Mild:	Tremor is at least 1 but less than 3 cm in amplitude.	
3: Moderate:	Tremor is at least 3 but less than 10 cm in amplitude.	
4: Severe:	Tremor is at least 10 cm in amplitude.	L

3.17 REST TREMOR AMPLITUDE

Instructions to examiner: This and the next item have been placed purposefully at the end of the examination to allow the rater to gather observations on rest tremor that may appear at any time during the exam, including when quietly sitting, during walking, and during activities when some body parts are moving but others are at rest. Score the maximum amplitude that is seen at any time as the final score. Rate only the amplitude and not the persistence or the intermittency of the tremor.
As part of this rating, the patient should sit quietly in a chair with the hands placed on the arms of the chair (not in the lap) and the feet comfortably supported on the floor for 10 seconds with no other directives. Rest tremor is assessed separately for all four limbs and also for the lip/jaw. Rate only the maximum amplitude that is seen at any time as the final rating.

Extremity ratings

0: Normal:	No tremor.	
1: Slight:	< 1 cm in maximal amplitude.	RUE
2: Mild:	≥ 1 cm but < 3 cm in maximal amplitude.	
3: Moderate:	≥ 3 cm but < 10 cm in maximal amplitude.	LUE
4: Severe:	≥ 10 cm in maximal amplitude.	
		RLE
		LLE

Lip/Jaw ratings

0: Normal:	No tremor.	
1: Slight:	< 1 cm in maximal amplitude.	
2: Mild:	≥ 1 cm but < 2 cm in maximal amplitude.	
3: Moderate:	≥ 2 cm but < 3 cm in maximal amplitude.	Lip/Jaw
4: Severe:	≥ 3 cm in maximal amplitude.	

3.18 CONSTANCY OF REST TREMOR

SCORE

Instructions to examiner: This item receives one rating for all rest tremor and focuses on the constancy of rest tremor during the examination period when different body parts are variously at rest. It is rated purposefully at the end of the examination so that several minutes of information can be coalesced into the rating.

0: Normal:	No tremor.
1: Slight:	Tremor at rest is present ≤ 25% of the entire examination period.
2: Mild:	Tremor at rest is present 26-50% of the entire examination period.
3: Moderate:	Tremor at rest is present 51-75% of the entire examination period.
4: Severe:	Tremor at rest is present > 75% of the entire examination period.

☐

DYSKINESIA IMPACT ON PART III RATINGS

A. Were dyskinesias (chorea or dystonia) present during examination? ☐ No ☐ Yes

B. If yes, did these movements interfere with your ratings? ☐ No ☐ Yes

HOEHN AND YAHR STAGE

0: Asymptomatic.

1: Unilateral involvement only.

2: Bilateral involvement without impairment of balance.

3: Mild to moderate involvement; some postural instability but physically independent; needs assistance to recover from pull test.

4: Severe disability; still able to walk or stand unassisted.

5: Wheelchair bound or bedridden unless aided.

☐

Part IV: Motor Complications

Overview and Instructions: In this section, the rater uses historical and objective information to assess two motor complications, dyskinesias and motor fluctuations that include OFF-state dystonia. Use all information from patient, caregiver, and the examination to answer the six questions that summarize function over the past week including today. As in the other sections, rate using only integers (no half points allowed) and leave no missing ratings. If the item cannot be rated, place **"UR"** for Unable to Rate. You will need to choose some answers based on percentages, and therefore you will need to establish how many hours the patient is generally awake and use this figure as the denominator for "OFF" time and dyskinesias. For "OFF dystonia", the total "OFF" time will be the denominator. Operational definitions for examiner's use.

Dyskinesias: Involuntary random movements:
Words that patients often recognize for dyskinesias include "irregular jerking", "wiggling", "twitching." It is essential to stress to the patient the difference between dyskinesias and tremor, a common error when patients are assessing dyskinesias.

Dystonia: Contorted posture, often with a twisting component:
Words that patients often recognize for dystonia include "spasms", "cramps", "posture."

Motor fluctuation: Variable response to medication:
Words that patients often recognize for motor fluctuation include "wearing out", "wearing off", "roller-coaster effect", "on-off", "uneven medication effects."

OFF: Typical functional state when patients have a poor response in spite of taking mediation or the typical functional response when patients are on NO treatment for parkinsonism. Words that patients often recognize include "low time", "bad time", "shaking time", "slow time", "time when my medications don't work."

ON: Typical functional state when patients are receiving medication and have a good response:
Words that patients often recognize include "good time", "walking time", "time when my medications work."

A. DYSKINESIAS [exclusive of OFF-state dystonia]

SCORE

4.1 TIME SPENT WITH DYSKINESIAS

Instructions to examiner: Determine the hours in the usual waking day and then the hours of dyskinesias. Calculate the percentage. If the patient has dyskinesias in the office, you can point them out as a reference to ensure that patients and caregivers understand what they are rating. You may also use your own acting skills to enact the dyskinetic movements you have seen in the patient before or show them dyskinetic movements typical of other patients. Exclude from this question early morning and nighttime painful dystonia.

Instructions to patient [and caregiver]: Over the past week, how many hours do you usually sleep on a daily basis, including nighttime sleep and daytime napping? Alright, if you sleep ___ hrs, you are awake ____ hrs. Out of those awake hours, how many hours in total do you have wiggling, twitching, or jerking movements? Do not count the times when you have tremor, which is a regular back and forth shaking or times when you have painful foot cramps or spasms in the early morning or at nighttime. I will ask about those later. Concentrate only on these types of wiggling, jerking, and irregular movements. Add up all the time during the waking day when these usually occur. How many hours ____ (use this number for your calculations).

0: Normal:	No dyskinesias.
1: Slight:	≤ 25% of waking day.
2: Mild:	26 - 50% of waking day.
3: Moderate:	51 - 75% of waking day.
4: Severe:	> 75% of waking day.

1. Total Hours Awake: _____
2. Total Hours with Dyskinesia: _____
3. % Dyskinesia = ((2/1)*100): _____

4.2 FUNCTIONAL IMPACT OF DYSKINESIAS — **SCORE**

Instructions to examiner: Determine the degree to which dyskinesias impact on the patient's daily function in terms of activities and social interactions. Use the patient's and caregiver's response to your question and your own observations during the office visit to arrive at the best answer.

Instructions to patient [and caregiver]: Over the past week, did you usually have trouble doing things or being with people when these jerking movements occurred? Did they stop you from doing things or from being with people?

0: Normal:	No dyskinesias or no impact by dyskinesias on activities or social interactions.
1: Slight:	Dyskinesias impact on a few activities, but the patient usually performs all activities and participates in all social interactions during dyskinetic periods.
2: Mild:	Dyskinesias impact on many activities, but the patient usually performs all activities and participates in all social interactions during dyskinetic periods.
3: Moderate:	Dyskinesias impact on activities to the point that the patient usually does not perform some activities or does not usually participate in some social activities during dyskinetic episodes.
4: Severe:	Dyskinesias impact on function to the point that the patient usually does not perform most activities or participate in most social interactions during dyskinetic episodes.

B. MOTOR FLUCTUATIONS

4.3 TIME SPENT IN THE OFF STATE

Instructions to examiner: Use the number of waking hours derived from 4.1 and determine the hours spent in the "OFF" state. Calculate the percentage. If the patient has an OFF period in the office, you can point to this state as a reference. You may also use your knowledge of the patient to describe a typical OFF period. Additionally you may use your own acting skills to enact an OFF period you have seen in the patient before or show them OFF function typical of other patients. Mark down the typical number of OFF hours, because you will need this number for completing 4.6.

Instructions to patient [and caregiver]: Some patients with Parkinson's disease have a good effect from their medications throughout their awake hours and we call that "ON" time. Other patients take their medications but still have some hours of low time, bad time, slow time, or shaking time. Doctors call these low periods "OFF" time. Over the past week, you told me before that you are generally awake ____ hrs each day. Out of these awake hours, how many hours in total do you usually have this type of low level or OFF function? ____ (use this number for your calculations).

0: Normal:	No OFF time.
1: Slight:	≤ 25% of waking day.
2: Mild:	26 - 50% of waking day.
3: Moderate:	51 - 75% of waking day.
4: Severe:	> 75% of waking day.

1. Total Hours Awake: _____
2. Total Hours OFF: _____
3. % OFF = ((2/1)*100): _____

	SCORE
4.4 FUNCTIONAL IMPACT OF FLUCTUATIONS Instructions to examiner: Determine the degree to which motor fluctuations impact on the patient's daily function in terms of activities and social interactions. This question concentrates on the difference between the ON state and the OFF state. If the patient has no OFF time, the rating must be 0, but if patients have very mild fluctuations, it is still possible to be rated 0 on this item if no impact on activities occurs. Use the patient's and caregiver's response to your question and your own observations during the office visit to arrive at the best answer. *Instructions to patient [and caregiver]: Think about when those low or "OFF" periods have occurred over the past week. Do you usually have more problems doing things or being with people than compared to the rest of the day when you feel your medications working? Are there some things you usually do during a good period that you have trouble with or stop doing during a low period?* 0: Normal: No fluctuations or no impact by fluctuations on performance of activities or social interactions. 1: Slight: Fluctuations impact on a few activities, but during OFF, the patient usually performs all activities and participates in all social interactions that typically occur during the ON state. 2: Mild: Fluctuations impact many activities, but during OFF, the patient still usually performs all activities and participates in all social interactions that typically occur during the ON state. 3: Moderate: Fluctuations impact on the performance of activities during OFF to the point that the patient usually does not perform some activities or participate in some social interactions that are performed during ON periods. 4: Severe: Fluctuations impact on function to the point that, during OFF, the patient usually does not perform most activities or participate in most social interactions that are performed during ON periods.	☐
4.5 COMPLEXITY OF MOTOR FLUCTUATIONS Instructions to examiner: Determine the usual predictability of OFF function whether due to dose, time of day, food intake, or other factors. Use the information provided by the patients and caregivers and supplement with your own observations. You will ask if the patient can count on them always coming at a special time, mostly coming at a special time (in which case you will probe further to separate slight from mild), only sometimes coming at a special time, or are they totally unpredictable? Narrowing down the percentage will allow you to find the correct answer. *Instructions to patient [and caregiver]: For some patients, the low or "OFF" periods happen at certain times during day or when they do activities like eating or exercising. Over the past week, do you usually know when your low periods will occur? In other words, do your low periods always come at a certain time? Do they mostly come at a certain time? Do they only sometimes come at a certain time? Are your low periods totally unpredictable?"* 0: Normal: No motor fluctuations. 1: Slight: OFF times are predictable all or almost all of the time (> 75%). 2: Mild: OFF times are predictable most of the time (51-75%). 3: Moderate: OFF times are predictable some of the time (26-50%). 4: Severe: OFF episodes are rarely predictable (≤ 25%).	☐

C. "OFF" DYSTONIA

4.6 PAINFUL OFF-STATE DYSTONIA

Instructions to examiner: For patients who have motor fluctuations, determine what proportion of the OFF episodes usually includes painful dystonia? You have already determined the number of hours of "OFF" time (4.3). Of these hours, determine how many are associated with dystonia and calculate the percentage. If there is no OFF time, mark 0.

Instructions to patient (and caregiver): In one of the questions I asked earlier, you said you generally have ____ hours of low or "OFF" time when your Parkinson's disease is under poor control. During these low or "OFF" periods, do you usually have painful cramps or spasms? Out of the total ____ hrs of this low time, if you add up all the time in a day when these painful cramps come, how many hours would this make?

0:	Normal:	No dystonia OR NO OFF TIME.
1:	Slight:	≤ 25% of time in OFF state.
2:	Mild:	26-50% of time in OFF state.
3:	Moderate:	51-75% of time in OFF state.
4:	Severe:	> 75% of time in OFF state.

☐

1. Total Hours OFF: _____
2. Total OFF Hours with Dystonia: _____
3. % OFF Dystonia = ((2/1)*100): _____

Summary statement to patient: READ TO PATIENT

This completes my rating of your Parkinson's disease. I know the questions and tasks have taken several minutes, but I wanted to be complete and cover all possibilities. In doing so, I may have asked about problems you do not even have, and I may have mentioned problems that you may never develop at all. Not all patients develop all these problems, but because they can occur, it is important to ask all the questions to every patient. Thank you for your time and attention in completing this scale with me.

Patient Name or Subject ID	Site ID	(mm-dd-yyyy) Assessment Date	Investigator's Initials
_____	___ ___ ___	_____ - _____ - _____	___ ___ ___

MDS UPDRS Score Sheet

1.A	Source of information	☐ Patient ☐ Caregiver ☐ Patient + Caregiver	3.3b	Rigidity– RUE	
			3.3c	Rigidity– LUE	
Part I			3.3d	Rigidity– RLE	
1.1	Cognitive impairment		3.3e	Rigidity– LLE	
1.2	Hallucinations and psychosis		3.4a	Finger tapping– Right hand	
1.3	Depressed mood		3.4b	Finger tapping– Left hand	
1.4	Anxious mood		3.5a	Hand movements– Right hand	
1.5	Apathy		3.5b	Hand movements– Left hand	
1.6	Features of DDS		3.6a	Pronation- supination movements– Right hand	
1.6a	Who is filling out questionnaire	☐ Patient ☐ Caregiver ☐ Patient + Caregiver	3.6b	Pronation- supination movements– Left hand	
			3.7a	Toe tapping– Right foot	
1.7	Sleep problems		3.7b	Toe tapping– Left foot	
1.8	Daytime sleepiness		3.8a	Leg agility– Right leg	
1.9	Pain and other sensations		3.8b	Leg agility– Left leg	
1.10	Urinary problems		3.9	Arising from chair	
1.11	Constipation problems		3.10	Gait	
1.12	Light headedness on standing		3.11	Freezing of gait	
1.13	Fatigue		3.12	Postural stability	
Part II			3.13	Posture	
2.1	Speech		3.14	Global spontaneity of movement	
2.2	Saliva and drooling		3.15a	Postural tremor– Right hand	
2.3	Chewing and swallowing		3.15b	Postural tremor– Left hand	
2.4	Eating tasks		3.16a	Kinetic tremor– Right hand	
2.5	Dressing		3.16b	Kinetic tremor– Left hand	
2.6	Hygiene		3.17a	Rest tremor amplitude– RUE	
2.7	Handwriting		3.17b	Rest tremor amplitude– LUE	
2.8	Doing hobbies and other activities		3.17c	Rest tremor amplitude– RLE	
2.9	Turning in bed		3.17d	Rest tremor amplitude– LLE	
2.10	Tremor		3.17e	Rest tremor amplitude– Lip/jaw	
2.11	Getting out of bed		3.18	Constancy of rest tremor	
2.12	Walking and balance			Were dyskinesias present?	☐ No ☐ Yes
2.13	Freezing			Did these movements interfere with ratings?	☐ No ☐ Yes
3a	Is the patient on medication?	☐ No ☐ Yes		Hoehn and Yahr Stage	
3b	Patient's clinical state	☐ Off ☐ On	**Part IV**		
3c	Is the patient on levodopa?	☐ No ☐ Yes	4.1	Time spent with dyskinesias	
3.C1	If yes, minutes since last dose:		4.2	Functional impact of dyskinesias	
Part III			4.3	Time spent in the OFF state	
3.1	Speech		4.4	Functional impact of fluctuations	
3.2	Facial expression		4.5	Complexity of motor fluctuations	
3.3a	Rigidity– Neck		4.6	Painful OFF-state dystonia	

10.3 STROBE Statement

STROBE Statement—Checklist of items that should be included in reports of ***case-control studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	51
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	51
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	52-53
Objectives	3	State specific objectives, including any prespecified hypotheses	52-53
Methods			
Study design	4	Present key elements of study design early in the paper	53-54
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	54
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls	54
		(*b*) For matched studies, give matching criteria and the number of controls per case	54
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	54
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	54
Bias	9	Describe any efforts to address potential sources of bias	54
Study size	10	Explain how the study size was arrived at	54
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	54
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	54
		(*b*) Describe any methods used to examine subgroups and interactions	54
		(*c*) Explain how missing data were addressed	54
		(*d*) If applicable, explain how matching of cases and controls was addressed	-
		(*e*) Describe any sensitivity analyses	-
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	55
		(b) Give reasons for non-participation at each stage	55
		(c) Consider use of a flow diagram	-
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	55-57
		(b) Indicate number of participants with missing data for each variable of interest	56-57 (table)
Outcome data	15*	Report numbers in each exposure category, or summary measures of exposure	55-57

Main results		16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	58-64
			(*b*) Report category boundaries when continuous variables were categorized	58
			(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	-
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses		-
Discussion				
Key results	18	Summarise key results with reference to study objectives		65-66
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias		66
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence		66
Generalisability	21	Discuss the generalisability (external validity) of the study results		66
Other information				
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based		53

*Give information separately for cases and controls.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.