UNIVERSIDADE FEDERAL DO RIO GRANDE DO SUL
FACULDADE DE MEDICINA
PROGRAMA DE PÓS-GRADUAÇÃO EM MEDICINA: CIÊNCIAS MÉDICAS

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Dissertação apresentada como requisito parcial para obtenção de título de Mestre em Medicina: Ciências Médicas, da Universidade Federal do Rio Grande do Sul, Programa de Pós-Graduação em Medicina: Ciências Médicas.

Porto Alegre
2022

CIP - Catalogação na Publicação

Strelow, Matheus Zschornack
Associação entre sintomas motores e cognição em pacientes com doença de Parkinson / Matheus Zschornack Strelow. -- 2022.
68 f.
Orientador: Artur Francisco Schumacher Schuh.

Coorientadora: Maira Rozenfeld Olchik.

Dissertação (Mestrado) -- Universidade Federal do Rio Grande do Sul, Faculdade de Medicina, Programa de Pós-Graduação em Medicina: Ciências Médicas, Porto Alegre, BR-RS, 2022.

1. Doença de Parkinson. 2. Demência. 3. Cognição. I. Schumacher Schuh, Artur Francisco, orient. II. Olchik, Maira Rozenfeld, coorient. III. Título.

Elaborada pelo Sistema de Geração Automática de Ficha Catalográfica da UFRGS com os dados fornecidos pelo(a) autor(a).

DISSERTAÇÃO DE MESTRADO

Porto Alegre, 2022

“As paixões são os ventos que enfunam as velas dos barcos, elas fazem-nos naufragar, por vezes, mas sem elas, eles não poderiam singrar.”

Voltaire

AGRADECIMENTOS

À minha família, pelo que sou hoje

À Roberta pelo companheirismo, paciência e amor

Aos meus orientadores, Prof. Dr. Artur Schuh e Profa. Dra. Maira Olchik, por não desistirem de mim, pelo incentivo e pela excelência na orientação

RESUMO

Resumo

A doença de Parkinson (DP) é a segunda doença neurodegenerativa mais comum no mundo, afetando aproximadamente 6,1 milhões de pessoas, acometendo 1% das pessoas acima de 60 anos. Com o aumento da expectativa de vida da população, houve um aumento da prevalência da DP nas últimas duas décadas, acompanhado de aumento da incidência. Estudos projetam que a prevalência irá dobrar, atingindo cerca de 17 milhões em 2040.

A cognição pode ser impactada desde os estágios iniciais da DP, com substancial heterogeneidade entre domínios cognitivos, impactando predominantemente função executiva, atenção e função visuoespacial. Estudos demonstram que o declínio cognitivo e demência são mais associados com maior idade, menores escores cognitivos em avaliação inicial, depressão e alucinações. O declínio cognitivo impacta o risco de quedas, perda de independência e diminuição da qualidade de vida do paciente e do cuidador. O diagnóstico de declínio cognitivo depende de avaliação de rastreio. Estudos realizados na população brasileira demonstraram que o Mini-Exame do Estado Mental (MEEM) possui uma baixa sensibilidade, não sendo uma boa estratégia de rastreio quando comparado com o Montreal Cognitive Assessment (MoCA).

Vários estudos avaliaram a relação entre os sintomas motores e as alterações cognitivas na DP, com bradicinesia e instabilidade postural se associando com pior desempenho cognitivo e tremor se associando com melhor desempenho cognitivo.Este trabalho tem a proposta de investigar a cognição dos pacientes com Doença de Parkinson em relação aos sintomas e subtipos motores. Foi realizada uma avaliação cognitiva ampla e a avaliação da escala Unified Parkinson Disease Rating Scale (UPDRS).

Foram recrutados pacientes com doença de Parkinson idiopática em acompanhamento no Serviço de Neurologia do Hospital de Clínicas de Porto Alegre com idade de início dos sintomas após os 18 anos. Esses pacientes foram submetidos a um protocolo de avaliação clínica, com aplicação de escalas padronizadas. Com base no UPDRS, os escores motores foram somados por

sintoma. Com base na literatura prévia e nos nossos resultados, controlou-se os resultados dos testes cognitivos para escolaridade e idade.

Nosso estudo demonstrou uma correlação entre maiores escores de bradicinesia com piores resultados nas avaliações cognitivas nos testes de rastreio, linguagem, memória e função executiva. Maior presença de sintomas posturais e de marcha se associaram com piora nos testes de rastreio, linguagem e memória. Rigidez se correlacionou com a memória. Não houve correlação de tremor com escores cognitivos. Nosso estudo não encontrou relação entre subtipos motores com testes cognitivos, ou discinesia e flutuação motora com testes cognitivos.

A educação se correlacionou com todos os tipos de testes cognitivos realizados, cabendo destacar que pacientes com mais de 4 anos de escolaridade tiveram uma menor chance de declínio cognitivo, A idade se correlacionou com pior desempenho em função executiva. Não houve relação entre idade de início, tempo de doença, lado de início ou primeiro sintoma com alteração cognitiva. Não houve relação entre depressão e escores cognitivos.

Os resultados desta dissertação trazem informações para o melhor entendimento das alterações cognitivas da doença de Parkinson e dos seus mecanismos fisiopatológicos. Observamos uma relação direta da bradicinesia e da instabilidade postural com as alterações cognitivas, com influência relevante de fatores associados à reserva cognitiva, ao passo que a gravidade do tremor não se associou com pior performance cognitiva, sugerindo que estes pacientes apresentam uma doença mais delimitada em termos fisiopatológicos.

PALAVRAS-CHAVE: doença de Parkinson; demência; cognição.

ABSTRACT

Abstract

Parkinson's disease (PD) is the second most common neurodegenerative disease in the world, affecting approximately 6.1 million people, with a prevalence of 1% of people above 60 years old. The life expectancy growth induced an increase of PD prevalence in the last two decades, concomitant with an incidence increase. Studies project that the prevalence will rise to 17 million in 2040.

Cognition may be impacted even in the early stages of PD, with great heterogeneity between cognitive domains, mainly impacting executive function, attention and visuospatial function. Studies show that cognitive decline and dementia are more associated with older age, lower cognitive scores at baseline, depression and hallucinations. Cognitive decline impacts the risk of falls, loss of independence and decreased quality of life for the patient and caregiver. The diagnosis of cognitive decline depends on a screening assessment, such as Mini-Mental State Examination (MMSE) or Montreal Cognitive Assessment (MoCA). Studies carried out in the Brazilian population showed that the MMSE has a low sensitivity, not being a good screening strategy when compared to the MoCA.

Several studies have evaluated the relationship between motor symptoms and cognitive changes in PD, with bradykinesia and postural instability being associated with worse cognitive performance and tremor being associated with better cognitive performance. This work aims to investigate the cognition of patients with Parkinson's Disease in relation to symptoms and motor subtypes. A comprehensive cognitive assessment and the Unified Parkinson Disease Rating Scale (UPDRS) were performed.

Patients with idiopathic PD under follow-up at the Neurology outpatient clinic of the Hospital de Clínicas de Porto Alegre with age at onset of symptoms after 18 years were recruited. These patients underwent a clinical evaluation protocol, with the application of standardized scales. Based on the UPDRS, motor scores were summed by symptom. Based on the previous literature and our results, the results of the cognitive tests were controlled for schooling and age.

Our study demonstrated a correlation between higher bradykinesia scores and worse results in cognitive assessments in screening, language, memory and

executive function tests. Greater presence of postural and gait symptoms were associated with worsening in screening, language and memory tests. Rigidity correlated with memory. There was no correlation of tremor with cognitive scores. Our study found no relationship between motor subtypes with cognitive tests, or dyskinesia and motor fluctuation with cognitive tests.

Education was correlated with all types of cognitive tests performed, and it should be noted that patients with more than 4 years of schooling had a significantly lower chance of cognitive decline. Age was correlated with worse performance in executive function. There was no relationship between age at onset, disease duration, side of onset or first symptom with cognitive impairment. There was no relationship between depression and cognitive scores.

The results of this work provide information for a better understanding of the cognitive alterations of PD and its pathophysiological mechanisms. We observed a direct relationship between bradykinesia and postural instability with cognitive changes, with a relevant influence of factors associated with cognitive reserve, while tremor severity was not associated with worse cognitive performance, suggesting that these patients have a more limited disease in pathophysiological terms.

LISTA DE TABELAS

LISTA DE ABREVIATURAS

HCPA: Hospital de Clínicas de Porto Alegre.

UFRGS: Universidade Federal do Rio Grande do Sul.

UPDRS: Unified Parkinson's Disease Rating Scale.

MDS: Movement Disorders Society.

DP: Doença de Parkinson.

DDP: Demência na doença de Parkinson.

CCL: Comprometimento cognitivo leve.

AMS: Atrofia de Múltiplos Sistemas.

DCL: Demência de Corpos de Lewy.

DCSREM: Distúrbio comportamental do sono REM.

RC: Reserva cognitiva.

MEEM: Mini-Exame do Estado Mental.

MoCA: Montreal Cognitive Assessment.

Sumário

INTRODUÇÃO

A doença de Parkinson (DP) é a segunda doença neurodegenerativa mais comum no mundo, afetando aproximadamente 6,1 milhões de pessoas em 2016, acometendo entre 1 a 2% das pessoas acima de 65 anos. Com o aumento da expectativa de vida da população, houve um aumento da prevalência da DP nas últimas duas décadas, acompanhado de aumento da incidência. Estudos projetam que a prevalência irá dobrar, atingindo cerca de 12 milhões em 2040 (Dorsey, 2018), determinando um novo cenário para a Medicina e novas demandas para a saúde pública e assistência social.

É uma doença multifacetada com marcada heterogeneidade que pode afetar todos os sistemas, com manifestações motoras e não-motoras, gerando limitação funcional, diminuição de qualidade de vida e aumento da mortalidade. O parkinsonismo define a doença, ou seja, bradicinesia associada com tremor de repouso e/ou rigidez. As manifestações não-motoras mais comuns são alteração do olfato, distúrbio comportamental do sono REM, disfunção autonômica, depressão, constipação e alterações cognitivas (Bloem et al. 2021).

A fisiopatologia resulta na degeneração de neurônios produtores de dopamina da substância negra *pars compacta* e acúmulo de material proteico mal-dobrado nas células remanescentes (corpúsculos de Lewy) gerando uma redução de dopamina das vias de controle do movimento nos núcleos da base, o que provoca maior inibição dessas estruturas sobre o comportamento motor iniciado no córtex cerebral.

A cognição pode ser impactada desde os estágios iniciais da DP, com substancial heterogeneidade entre domínios cognitivos, impactando predominantemente a função executiva, a atenção e a função visuoespacial. Estudos demonstram que o declínio cognitivo e a demência estão mais associados com maior idade, menores escores cognitivos na avaliação inicial, depressão e alucinações. O declínio cognitivo pode ter significativo impacto na qualidade de vida do paciente e do cuidador, com aumento do risco de quedas e na perda de capacidade funcional.

Este trabalho se propõe a investigar a cognição dos pacientes com Doença de Parkinson em relação aos sintomas e subtipos motores, bem como explorar a relação da cognição com aspectos demográficos.

REVISÃO DE LITERATURA

Considerações sobre a doença de Parkinson

A Doença de Parkinson (DP) foi descrita em 1817 por James Parkinson em um artigo intitulado "*An Essay on the Shaking Palsy*" (Parkinson 2002), descrevendo a síndrome parkinsoniana. No final do século XIX, o neurologista Jean-Martin Charcot faz uma descrição clínica detalhada sobre a doença, argumentando contra o termo que vinha sendo utilizado - *paralysis agitans* - pelo fato de não haver paralisia verdadeira, e sim menor potência muscular, hoje conhecida como bradicinesia. Além disso, enfatizou que o tremor não ocorria em todos os pacientes, logo o termo "agitans" e "shaking" não seriam apropriados. Recomendou, então, que o termo utilizado fosse Doença de Parkinson. Fez também a primeira descrição das alterações cognitivas (Charcot 1872; Charcot 1877).

Nos dias atuais, a DP é a segunda doença neurodegenerativa mais comum, ficando atrás apenas da Doença de Alzheimer, e pode ocorrer em qualquer idade, com um pico de incidência em torno dos 60 anos de idade. O risco de desenvolver DP aumenta com a idade, com incidência de 1 em cada 15 indivíduos ao longo da vida (Dorsey et al. 2018a). Afeta aproximadamente 6,1 milhões de pessoas no mundo, acometendo entre 1 a 2% das pessoas acima de 65 anos. No Brasil, a prevalência foi de 3,3% em um estudo de base populacional (Barbosa et al. 2006; Roriz-Cruz, 2010). Estudos projetam que, com o aumento da expectativa de vida da população, a prevalência deve dobrar ao longo dos próximos 20 anos, determinando um novo cenário para a Medicina e novas demandas para a saúde pública e assistência social. A mortalidade ajustada para idade de pacientes com DP reduziu em 1,6 vezes após a introdução da levodopa (Yahr, 1976; Elbaz et al. 2003).

Os critérios diagnósticos atuais da DP foram publicados em 2015 pela Movement Disorders Society (Postuma et al. 2015) e se baseia em 3 níveis: o primeiro é o critério para diagnóstico de parkinsonismo, sendo definido pela presença de bradicinesia, combinado com rigidez e/ou tremor de repouso. A bradicinesia é definida pela lentidão do movimento associado com perda de amplitude e/ou velocidade conforme o movimento perpetua. A rigidez é avaliada

pelo movimento passivo das articulações com o paciente em posição relaxada; na presença de parkinsonismo, a rigidez é geralmente referida como “roda denteada”, ou seja, uma resistência velocidade-independente à movimentação passiva, não secundária à falha de relaxamento (paratonia/*gegenhalten* ou espasticidade). O tremor típico da DP é de 4-6 Hz, em repouso, podendo ocorrer na ação, principalmente na forma “reemergente”, ou seja, com pausa no tremor após a ação e reinício do tremor após a postura sustentada. O segundo nível para diagnóstico de DP é a ausência de critérios de exclusão (por exemplo, alterações cerebelares, paralisia do olhar supranuclear, uso de medicações bloqueadoras de dopamina, entre outros). O terceiro nível para diagnóstico é a presença de dois critérios de suporte, entre os quatro: 1) resposta clara e marcada à terapia dopaminérgica; 2) presença de discinesia induzida por levodopa; 3) tremor de repouso em membro; 4) hiposmia ou anosmia em teste complementar ou denervação simpática cardíaca em cintilografia com metaiodobenzilguanidina (MIBG).

Como observado, a doença se define pelas manifestações motoras, porém é crescente o reconhecimento da frequência e do impacto das manifestações não-motoras, sendo presentes em quase todos os pacientes (Barone et al. 2009). As manifestações não-motoras incluem depressão, fadiga, ansiedade, alterações urinárias, constipação, disautonomia (hipotensão postural e pós-prandial), dor, hiposmia/anosmia e distúrbio comportamental do sono REM (DCSREM) (J. Jankovic 2008). Cabe ressaltar também que é fundamental o seu reconhecimento visto que alguns sintomas não-motores proeminentes podem sugerir um diagnóstico alternativo, como a presença de demência precoce no curso da doença pode sugerir Demência de Corpos de Lewy (DCL), e disautonomia pode sugerir Atrofia de Múltiplos Sistemas (AMS).

Frequentemente, as manifestações não-motoras precedem a DP, sendo que hoje já existem critérios diagnósticos para DP prodrômica (DPP) com intuito de uso em pesquisa para identificar os pacientes antes da fase motora da doença(Berg et al. 2015). As manifestações cognitivas não estão incluídas nos critérios diagnósticos da DPP no momento, mas estudos indicam que podem ocorrer antes da DP, predominando alterações de função executiva (Fengler et al. 2017).

Em 1895, Brissaud (Brissaud, 1985) sugeriu que a substância negra (SN) poderia fazer parte do substrato anatômico da DP baseado em um relato de caso de parkinsonismo associado a um tuberculoma mesencefálico. Tretiakoff, em sua tese de doutorado em 1919 (Tretiakoff, 1919), estudou a SN de 54 casos de parkinsonismo, encontrando despigmentação, diminuição no número de células e gliose, além de descrever a presença de corpos de Lewy, previamente observados por Lewy (Lewy, 1914; Lewy, 1919). Corpos de Lewy são inclusões proteicas eosinofílicas no citoplasma do neurônio e hoje são reconhecidos como marca da DP, sendo encontrados também em gânglios autonômicos, nervos periféricos e células olfatórias nestes pacientes; semelhante aos corpos de Lewy, os neuritos de Lewy são alongados e se localizam preferencialmente nos prolongamentos neuronais (Del Tredici et al. 2010). Essas inclusões são formadas por acúmulo de material proteico de diversas origens, predominando a alfa-sinucleína. Os critérios atuais para definição patológica da DP incluem a presença de degeneração do sistema dopaminérgico nigroestriatal associada com acúmulo de corpos de Lewy e neuritos de Lewy (Dickson et al. 2009).

Os corpos de Lewy são encontrados na maioria dos pacientes com DP, porém alguns grupos fogem à regra, sendo presentes em apenas cerca de 2/3 dos pacientes com variante patogênica no gene *LRRK2* G2019S (Kalia et al. 2015), e raros em pacientes com variante patogênica no gene *PRKN* (Hattori et al. 2000). Desse modo, a presença de corpos de Lewy é achados patológicos confirmatórios para DP, mas sua presença não ocorre em todos os casos, e consequentemente não são patognomônicos para DP (Forno, 1982). Cabe destacar que estas alterações se correlacionam com as sinucleinopatias, grupo composto pela DP, AMS e DCL, sendo a DP a sua causa mais prevalente representante.

Braak et al (Braak et al. 2003) estudaram a presença de alfa-sinucleína em 41 autópsias de pacientes com DP e 69 de pacientes sem DP, mas com presença de corpos de Lewy, descrevendo um padrão de progressão de acúmulo de alfa-sinucleína e de corpos de Lewy que começava no núcleo olfatório e na região caudal do tronco (estágio 1); a rafe e o locus ceruleus seria o seguinte a ser envolvido (estágio 2); a SN a terceira (estágio 3); o mesocórtex

e o tálamo em seguida (estágio 4); e por fim, o neocórtex (estágio 5) e córtex motor primário e as áreas sensitivas (estágio 6). Este modelo foi reproduzido em outros estudos(Dickson et al. 2010), com algumas ressalvas em fases avançadas da doença, na correlação com os estágios de Hoehn-Yahr (Burke, Dauer, and Vonsattel 2008) e no achado de manifestações cognitivas associado com a ativação microglial cortical previamente ao estágio 5 e 6 (Brooks 2010), mas adequado para vários dos sintomas não-motores e sua frequente presença em fases prodrômicas ao diagnóstico de DP. Estudos (Savica, Rocca, and Ahlskog 2010; Lin et al. 2014) demonstraram que a constipação precede a DP, com a associação ocorrendo cerca de 20 anos antes da fase motora da doença. Alterações urinárias, hiposmia/anosmia e DCSREM também se correlacionaram com aumento de frequência na população que desenvolveu DP em relação ao grupo controle (Petrovitch et al. 2009; St Louis and Boeve 2017; Iranzo 2013; Ross et al. 2008).

A SN possui dopamina, com projeção para o neoestriado; na DP, a sua lesão gera uma queda do conteúdo de dopamina na SN e no estriado, afetando concomitantemente a inervação do putâmen (Nandhagopal et al. 2009). Essa cascata é o principal mecanismo fisiopatogênico dos sintomas motores da DP, com a perda de dopamina estriatal se relacionando principalmente com bradicinesia e rigidez. Outras monoaminas são envolvidas principalmente em sintomas não-motores; a hipotensão postural, por exemplo, é secundária à redução de catecolaminas, evidenciada pela redução de captação na cintilografia cardíaca com MIBG (Rascol and Schelosky 2009).

A etiologia da DP é incerta, tendo como hipótese vigente a ocorrência de múltiplos impactos contribuindo para a neurodegeneração, sendo eles o estresse oxidativo, a disfunção mitocondrial, a inflação e a apoptose (Sulzer 2007).

Alterações cognitivas na doença de Parkinson

As alterações cognitivas na DP foram descritas pela primeira vez por Charcot em 1872. O entendimento da importância das alterações cognitivas foi crescente ao longo das últimas décadas. As alterações cognitivas podem ser evidentes mesmo nos estágios iniciais da DP, inclusive nas fases prodrômicas. Lee e Smith descreveram em 1983 que pacientes com DP com diagnóstico recente possuíam maior taxa de erros perseverativos em comparação com o grupo controle (Lees and Smith 1983). Levin et al. (1989) avaliou 41 pacientes com DP com diagnóstico recente pareados com grupo controle demonstrando que pacientes com DP tiveram piores desempenhos em tarefas visuoespaciais, de flexibilidade e abstração, além de um pior desempenho de memória (Levin, Llabre, and Weiner 1989).

As alterações cognitivas são comuns na DP e, baseadas em diferentes critérios dos estudos, comprometimento cognitivo leve (CCL) é presente em 10-40% dos pacientes no diagnóstico de DP. Entre os pacientes que possuem cognição preservada ao diagnóstico, cerca de 50% desenvolve CCL após 6 anos. (Monastero et al. 2018; Pedersen et al. 2017; Santangelo et al. 2015; Weintraub et al. 2015; Yarnall et al. 2014; D. Aarsland et al. 2009; Poletti et al. 2012).

As alterações cognitivas são associadas com múltiplos mecanismos etiopatogênicos como fatores de risco genético (presença do alelo ε4 do gene da *APOE,* variantes no gene GBA e *SNCA)*; redução da atividade dopaminérgica mesolímbica e cortical, redução da atividade colinérgica, serotoninérgica e noradrenérgica. Ainda, outros fatores são hipotetizados, como fatores neutrofílicos, inflamatórios e disfunção mitocondrial. Em nível anatomopatológico, existe evidência que a presença de corpos de Lewy no sistema límbico e no córtex se correlaciona com demência na doença de Parkinson (DDP), com significativa contribuição de β-amiloide e proteína tau (Dag Aarsland et al. 2017).

Os domínios cognitivos mais afetados são classicamente associados ao lobo frontal, com pior desempenho em fluência verbal e memória de trabalho (Cooper et al. 1991). Existe grande heterogeneidade nas manifestações cognitivas, podendo impactar qualquer domínio cognitivo, mas predominantemente em função executiva, visuaespacial e atenção (Barone et al. 2011).

Tradicionalmente, se atribui estas alterações cognitivas à disfunção no sistema frontoestriatal, com as alterações cognitivas em outros domínios, como memória e linguagem, sendo secundários ao prejuízo da função executiva (Barone et al. 2011). Isto é fundamentado em diversos estudos que demonstraram que, quanto à memória declarativa, as alterações de aprendizado e evocação seriam secundárias ao prejuízo na codificação da informação e das estratégias de evocação (Stefanova et al. 2001; Troster, 1995). Porém, estudos recentes demonstraram que as alterações de memória declarativa não são dependentes apenas da disfunção executiva, com pacientes mantendo o prejuízo mesmo com pistas para evocação (Beyer et al. 2013; Higginson et al. 2005; Whittington, Podd, and Stewart-Williams 2006).

Evidências oriundas de neuroimagem sugerem também que as alterações cognitivas não são explicadas apenas pela alteração do sistema frontoestriatal. Pacientes que possuem maior alteração na função visuoespacial e fluência semântica possuem marcada disfunção cortical posterior e de lobo temporal (Kehagia, Barker, and Robbins 2013), com evolução para demência mais rapidamente (Alves et al. 2006). Estudos de imagem morfológica e funcional em pacientes com DP demonstraram a presença de atrofia global já em fases precoces da doença, se relacionando clinicamente também com escores motores e redução na captação FP-CIT, um biomarcador do transportador dopaminérgico, pelo estriado (Zeighami et al. 2015). A atrofia em estudo de ressonância magnética (RM) se correlacionou também com pior prognóstico motor, cognitivo e global (Zeighami et al. 2019). Estudos em pacientes com DDP relacionaram que a atrofia ocorre com maior frequência no hipocampo, tálamo e cíngulo anterior em relação ao grupo controle saudável (Summerfield et al. 2005), com outro estudo demonstrando maior grau de atrofia no hipocampo, uncus e giro parahipocampal em relação a pacientes com DP sem demência (Gee et al. 2017). volume hipocampal é o achado na neuroimagem que mais prediz desenvolvimento de alteração cognitiva (Kandiah et al. 2014).

Diversos autores hipotetizaram sobre os mecanismos fisiológicos envolvidos nas alterações cognitivas da DP. Kehagia et al. (2013) propôs que as alterações cognitivas envolvem duas síndromes distintas. Uma mediada pela depleção dopaminérgica, se associando com disfunção executiva, e outra como síndrome demencial, com diversas monoaminas envolvidas, com predomínio de alterações

visuoespaciais (Kehagia, Barker, and Robbins 2013). A função executiva é intensamente correlacionada com o sistema dopaminérgico mesocortical, cuja aferência vem da área tegmental ventral, e se projeta para áreas neocorticais. Nos pacientes com DP com diagnóstico recente, há hiperatividade neocortical de áreas que dependem de dopamina, na tentativa de compensar o déficit dopaminérgico (Gratwicke, Jahanshahi, and Foltynie 2015). A segunda síndrome é causada por outras monoaminas que podem estar alteradas na DP, predominantemente as alterações do sistema noradrenérgico e colinérgico (Gratwicke, Jahanshahi, and Foltynie 2015). Estudos demonstraram a importância da conectividade cortical do núcleo basal de Meynert (NBM) na DP como principal fonte de aferência colinérgica para o córtex, destacando-se a área motora suplementar, o giro parahipocampal e o giro lingual, afetando a atividade motora, a plasticidade neuronal e as funções cognitivas de memória, atenção e visuoespacial (Oswal et al. 2021).

Em pacientes com DP que desenvolvem demência, corpos de Lewy são vistos no córtex cerebral e no sistema límbico, predominantemente no hipocampo, em virtualmente todos os casos (Hall et al. 2014). Copatologia é frequente, com 20 a 33% dos pacientes apresentando patologia Alzheimer, associando-se com o desenvolvimento de DDP em estudos com biomarcores *in vivo* (Siderowf et al. 2010); (Jack et al. 2018). Também é encontrada maior taxa de beta-amiloide estriatal em pacientes com o diagnóstico de DCL em comparação com DDP (Kalaitzakis et al. 2011), sugerindo que a copatologia é fator relevante para o fenótipo da doença neurodegenerativa. Semelhante ao que ocorre na Doença de Alzheimer, um estudo demonstrou que o acúmulo de tau se correlacionou com o grau das alterações cognitivas, não sendo encontrado relação entre acúmulo de beta-amiloide e status cognitivo (Smith et al. 2019). Um estudo recente demonstrou relação da carga beta-amiloide com pior função executiva, porém sem associação com alteração motora ou alteração cognitiva global, nem atrofia temporal (Garon et al. 2021). Estes achados indicam que a presença de beta-amiloide contribui com a fisiopatogenia das alterações cognitivas, mas pode não ser determinante para isto.

Existe um *continuum* da doença, com a progressão de queixa cognitiva subjetiva, para comprometimento cognitivo leve e, após, demência (Saredakis et al. 2019). O declínio cognitivo e o surgimento de demência se associam com maior idade, piores escores cognitivos ao início da doença, depressão, presença de

alucinações (Marinus et al. 2018), e a severidade do acometimento do olfato (Fang et al. 2021).

Os fatores de risco gerais na população também influenciam no risco de demência na DP. A presença de hipersinal T2/FLAIR em substância branca (HSB) se associou com piores escores motores, atrofia hipocampal e alterações cognitivas em pacientes com DP, incluindo um fator de risco para desenvolvimento de DPP (Dadar et al. 2020; González-Redondo et al. 2012; Kandiah et al. 2014). A presença de HSB na região temporal pode predizer declínio na memória verbal (Chahine et al. 2019). O HSB é presumivelmente de origem vascular, associa-se com a idade e é atribuídos à dano de origem isquêmica, inflamatório e deposição proteica, com a hipertensão arterial sistêmica e o diabete melito fortemente associado com este achado, não sendo mais frequente em pacientes com DP do que em grupo controle (Dadar et al. 2020). Foi demonstrado também que as alterações de sono se correlacionam com o congelamento de marcha e com piora na cognição (de Almeida et al. 2021), sendo a polissonografia útil como preditor de piora cognitiva em pacientes com DP (Bugalho, Ladeira, et al. 2021). A redução das ondas lentas de sono, a perda de atonia durante sono REM e o maior índice de movimentação periódica de membros associou-se com pior prognóstico cognitivo. Outros estudos também encontraram a associação de DCSREM com piora cognitiva na DP (Bugalho, Magriço, et al. 2021).

As alterações cognitivas podem se iniciar desde as fases prodrômicas da doença. O declínio cognitivo sutil, sem critérios para CCL ou demência, foi evidenciado até 7 anos antes do diagnóstico da DP (Dag Aarsland et al. 2017; Darweesh et al. 2017). Os atuais critérios da *Movement Disorders Society* (MDS) definem CCL como declínio cognitivo gradual, sem impacto funcional significativo, sendo definido por critérios clínicos, cognitivos e funcionais. É um transtorno heterogêneo, podendo ser classificado em amnéstico ou não amnéstico (Litvan et al. 2011; Goldman et al. 2018). O CCL se correlaciona com aumento de risco de desenvolvimento de DDP (Pigott et al. 2015; Pedersen et al. 2013; Hobson and Meara 2015).

Os critérios clínicos atuais da MDS definem DDP como prejuízo cognitivo em mais de um domínio que afeta a funcionalidade do paciente (Emre et al. 2007). Em um estudo, 10% dos pacientes desenvolveram DDP após 3,5 anos de tempo médio

da doença (Williams-Gray et al. 2007). Outro estudo demonstrou que 48% dos pacientes desenvolveram demência com 15 anos de doença (Hely et al. 2005), e 83% aos 20 (Hely et al. 2008). Alguns autores acreditam que todos os pacientes desenvolvem demência ao longo do tempo se viverem tempo o suficiente para isto (Bock and Tanner 2022; Joseph Jankovic et al. 2021). Porém, cabe ressaltar que nem todos estudos associaram tempo de doença com pior performance cognitiva (Nicoletti et al. 2019; Almeida et al., 2019).

A DDP se diferencia da DCL por um critério arbitrário que define que na DCL os sintomas cognitivos se iniciam antes ou em até 1 ano após o parkinsonismo (I. G. McKeith et al. 2017) e com a DDP o parkinsonismo ocorrendo geralmente anos antes do estágio demencial. Este critério foi definido para diferenciar na prática clínica e para pesquisas clínicas e desenvolvimento de terapias modificadoras de doença. Evidências, porém, sugerem que são doenças semelhantes com substrato patológico semelhantes, marcadas pelo acúmulo de alfa-sinucleína(Lindström et al. 2014).

O diagnóstico das alterações cognitivas se faz com base em um exame de rastreio. Os testes mais comumente utilizados são o Mini-Exame do Estado Mental (MEEM), o Montreal Cognitive Assessment (MoCA) e o Scales for Outcomes In Parkinson's Disease-COGnition (SCOPA-COG). Estes testes avaliam vários domínios cognitivos e são úteis para identificar alterações. Além da avaliação cognitiva, o paciente deve ser avaliado quanto às possíveis causas clínicas e medicamentosas de alterações cognitivas, como hipotireoidismo, hipovitaminose B12 e uso de medicações anticolinérgicas. Após a exclusão de causas sintomáticas de demência, o diagnóstico de demência por etiologia neurodegenerativa pode ser feito (Emre et al. 2007).

A avaliação cognitiva de rastreamento mais útil é MoCA, sendo mais sensível que o MEEM. Estudos realizados na população brasileira demonstraram que o Mini-Exame do Estado Mental (MEEM) possui uma baixa sensibilidade, não sendo uma boa estratégia de rastreio quando comparado com o Montreal Cognitive Assessment (MoCA) (Gill, 2008; Sobreira et al., 2015; Almeida et al., 2019; Oliveira et al., 2015). Um estudo com pacientes com DP na população coreana encontrou sensibilidade e especificidade semelhantes entre os testes, sugerindo que o MoCA também seja inapropriado para o diagnóstico de CCL (Kim et al. 2016).

É possível que os diferentes resultados entre os estudos que avaliaram a cognição dos pacientes possam ter sofrido interferência do teste utilizado, considerando as demandas que cada teste possui. Por exemplo, pacientes com DP de início recente apresentaram testes de função executiva visuoespacial normal (Owen et al. 1995), enquanto outros estudos com DP de início recente demonstraram função executiva alterada, particularmente envolvendo processamento espacial (Bradley, Welch, and Dick 1989; Postle, Locascio, et al. 1997; Postle, Jonides, et al. 1997). A inconsistência dos resultados pode decorrer de erros ao acaso ou de falta de poder estatístico, porém deve ser considerada a capacidade do teste cognitivo escolhido para avaliar cada domínio nos pacientes com DP.

Não existe tratamento modificador de doença para DP, inclusive das suas manifestações cognitivas (Sun and Armstrong 2021). Também não existe tratamento medicamentoso com evidência suficiente para recomendação de uso clínico para melhora de desfechos cognitivos ou funcionais em pacientes com queixas cognitivas ou CCL (Goldman et al. 2018). O foco do tratamento para as alterações cognitivas associadas a DP deve ser voltado para o manejo do sintoma que impacta na qualidade de vida, como por exemplo tratamento de transtorno do humor e do sono (Sun and Armstrong 2021). Para pacientes com DDP, existem evidências do uso de inibidores de acetilcolinesterase com benefício na apatia, ansiedade, delírios e alucinações (I. McKeith et al. 2000; D. Aarsland et al. 2002; Ravina et al. 2005). Um estudo clínico controlado, multicêntrico sugeriu benefício do uso de rivastigmina para melhora da demência em pacientes com DP (Emre et al. 2004). Memantina foi superior ao placebo em dois pequenos estudos (Aarsland 2009, Leroi 2009). Uma revisão sistemática da Cochrane avaliou a evidência do uso de inibidores da acetilcolinesterase demonstrando benefício nas avaliações globais dos pacientes com DDP, com aumento significativo nos efeitos adversos, sem aumento em eventos adversos graves (Rolinski et al. 2012).

Relação entre manifestações motoras e alterações cognitivas

Vários estudos demonstraram a relação entre as manifestações motoras e as alterações cognitivas na DP. Alguns estudos demonstraram que a alteração motora à direita se associava com pior performance em testes verbais, enquanto a alteração motora à esquerda se associava com pior performance em testes visuoespaciais (Bentin, Silverberg, and Gordon 1981; Spicer, Roberts, and LeWitt 1988). Porém, relatos mais recentes não encontraram relação entre a lateralidade e a cognição (Katzen, Levin, and Weiner 2006; Poletti et al. 2013). A maioria dos estudos encontrou uma relação positiva entre bradicinesia e rigidez com prejuízo cognitivo, com relatos inconsistentes de relação negativa entre tremor e prejuízo cognitivo (Cooper et al. 1991; Zetusky and Jankovic 1985; Iwasaki et al. 1989 Portin 1989, Huber 1991). Esta dissociação entre cada um dos sintomas motores e a cognição tem importantes implicações fisiopatológicas.

Estudos demonstram que desde a fase inicial da DP a bradicinesia se associou com memória de trabalho e flexibilidade mental, com as manifestações axiais associadas com memória episódica e função visuoespacial; rigidez e tremor não se relacionaram com cognição quando controlados para idade, sexo e educação, numa população de alta escolaridade (Domellöf, Elgh, and Forsgren 2011). Em outro estudo de acompanhamento longitudinal desde fases precoces da doença, tempo de doença se correlacionou com bradicinesia, tremor, fala e sintomas posturais e de marcha, sem associação de tremor com performance cognitiva. Associação de sintomas axiais com função visuoespacial e memória (J. S. Schneider, Sendek, and Yang 2015).

Também foi descrito associação entre outros sintomas motores e alterações cognitivas na DP, com a presença de congelamento de marcha se associando com pior desempenho em diversos domínios cognitivos em um estudo (Scholl et al. 2021). Existe relação também entre discinesia induzida por levodopa e alterações cognitivas, com alteração de atenção e função cognitiva sendo um fator de risco para o desenvolvimento da discinesia, o que sugere uma relação fisiopatogênica entre ambas (Luca et al. 2021).

Diversas propostas de categorização dos pacientes foram realizadas na tentativa de criar subtipos clínicos que representassem as diferenças biológicas em

diferentes grupos de pacientes conforme suas avaliações motoras (Schiess et al. 2000; Spiegel et al. 2007). Uma das propostas foi feita por Jankovic (J. Jankovic et al. 1990) dividindo os pacientes em subtipos tremor dominante (TD), instabilidade postural/distúrbio de marcha (PIGD) e indeterminado. Após atualização da UPDRS para MDS-UPDRS, houve uma nova proposta realizada por Stebbins para adaptação conforme a escala (Stebbins et al. 2013). Vários estudos demonstraram diferenças cognitivas entre estes pacientes, com os pacientes classificados como TD com melhor prognóstico em relação aos pacientes classificados como PIGD (Williams-Gray et al. 2007; Alves et al. 2006; Burn et al. 2006). Estas classificações, porém, não se mostraram úteis clinicamente pelos diferentes fatores de confusão que influenciam na confiabilidade da classificação, com instabilidade longitudinal da categorização de subtipo de cada paciente, principalmente com uma proporção considerável de pacientes TD convertendo para PIGD com o tempo (Simuni et al. 2016; von Coelln et al. 2021; Lee et al. 2019).

A tentativa de categorização em subtipos ocorre há décadas no esforço de simplificar a heterogeneidade biológica e clínica DP, porém com deficiências de aplicabilidade. A cognição pode ser peça chave na categorização, mas as evidências atuais deixam claro que não é possível apenas com dados adquiridos com informações clínicas (Zeighami et al. 2019). É provável que biomarcadores liquóricos e sanguíneos possam contribuir com o entendimento biológico e da heterogeneidade, agregando informações genéticas, de neurodegeneração e de imagem (Mestre et al. 2021).

Concluindo, os estudos demonstram uma íntima relação entre a função motora e a cognição, com robustas evidências de que é difícil, senão impossível, separar a ação motora direcionada da cognição. A visão contemporânea se direciona para considerar o controle motor e o comportamento, mesmo que de tarefas solicitadas no exame físico de um paciente com DP, como ato completamente integrado com os processos cognitivos.

JUSTIFICATIVA

Justificativa

A DP é a segunda doença neurodegenerativa mais comum, com crescente aumento na prevalência e incidência. As alterações cognitivas são frequentes e com grande impacto na morbimortalidade e qualidade de vida. O melhor entendimento das alterações cognitivas e de fatores de risco na população brasileira com DP podem gerar novas hipóteses para o processo fisiopatológico e também é essencial para o planejamento de saúde estratégico e operacional em nível governamental e assistencial.

OBJETIVOS

Geral

Identificar associação entre alterações cognitivas e sintomas motores em uma amostra de pacientes com doença de Parkinson idiopática.

Específicos

− Identificar associação entre soma de escores de tremor e performance cognitiva

− Identificar associação entre soma de escores de bradicinesia e performance cognitiva

− Identificar associação entre soma de escores de rigidez e performance cognitiva

− Identificar associação entre soma de escores de marcha e postura e performance cognitiva

− Identificar associação entre lado de início de sintomas motores e performance cognitiva

− Identificar associação entre primeiro sintoma motor e performance cognitiva

− Avaliar como a educação e outras variáveis demográficas influenciam a cognição

− Identificar associação entre subtipos motores e performance cognitiva

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ARTIGO

Association between cognitive and motor scores in a sample of Brazilian Parkinson's disease patients

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Running title:

Key words: Parkinson's disease, Parkinson's disease dementia;

Financial support: The research was supported by grants from "Financiadora de Estudos e Projetos" (FINEP 01.08.01230.00), "Conselho Nacional de Desenvolvimento Científico e Tecnológico" (CNPq), and "Fundo de Incentivo à Pesquisa" (FIPE-HCPA).

Potential conflict of interest: Nothing to report.

Abstract

Introduction: Numerous studies have explored the association between motor impairment and cognition. The aim of our study was to investigate the association between cognitive performance and motor impairment in brazilian patients with Parkinson's disease.

Methods: A cross-sectional study with 80 PD patients followed in a southern Brazilian Movement Disorders Clinic. The evaluation consisted of a cognitive testing battery and Unified PD Rating Scale (UPDRS).

Results: The results showed the relevant association between motor scores and cognitive performance, with bradykinesia and postural instability/gait symptoms negatively associated with multidomain cognitive performance. As expected, education level was correlated with better performance in all cognitive tests.

Conclusions: Our study demonstrates that a lower cognitive performance among PD patients was associated with bradykinesia and postural instability/gait, but not with tremor. These findings could imply a common pathophysiology between some motor aspects and cognitive domains in this population.

1. Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disorder affecting approximately 6.1 million people in 2016 worldwide (GBD 2016 Neurology Collaborators 2019). Evidence shows that the incidence and prevalence of this disease have risen in the past two decades and studies projected to double over 12 million by 2040 (Dorsey and Bloem 2018). PD is a multifaceted disorder and has a marked heterogeneity in clinical features, with motor and non-motor impairment, such as cognitive impairment, REM sleep disorder, depression, hyposmia, urinary incontinence and pain (Armstrong and Okun 2020). These non-motor features contribute greatly to the disability of affected individuals, and also have profound consequences for caregivers (Macchi et al. 2020; Santos García et al. 2019).

Cognition impairment may cause a substantial burden of disease for the patient and the caregiver (A. Schrag, Jahanshahi, and Quinn 2000; Anette Schrag et al. 2006; D. Aarsland et al. 2007). Cognition may be impacted even in early stages of PD, with substantial heterogeneity across cognitive domains, predominantly impacting executive function, attention and visuospatial function (D. Aarsland et al. 2009; Kehagia, Barker, and Robbins 2010). Cognitive decline and Parkinson's disease dementia (PDD) are associated with higher age, lower baseline cognitive scores, depression and hallucinations (Bloem, Okun, and Klein 2021; Buter et al. 2008).

The assessment of cognitive impairment depends upon a cognitive screening, such as the Mini-Mental State Examination (MMSE) and the Montreal Cognitive Assessment (MoCA). Studies demonstrate the MMSE has a low sensitivity for screening cognitive impairment in high educated level PD patients compared with MoCA (Hoops et al. 2009; Gill et al. 2008), which was replicated in one Brazilian study (Breder et al. 2017). MoCA was evaluated in the Brazilian population with high sensitivity and specificity to identify PDD (Almeida 2019). Other studies applied MMSE with a cutoff adjusted to education level with similar sensitivity and specificity to MoCA to screening PDD in Chinese population (Kim et al. 2016), implicating that educational level of the population may interfere in the applicability of MMSE.

Several studies demonstrated a relationship linking motor symptoms and cognition, most of them indicate a positive correlation between bradykinesia and rigidity with cognitive impairment, with inconsistent results between tremor and

cognition (Cooper et al. 1991; Zetusky and Jankovic 1985; Iwasaki et al. 1989) Portin 1989, Huber 1991). This association may implicate in the pathophysiological mechanism of distinct motor and cognitive impairment. The aim of our study was to investigate the association between cognitive performance and motor scores in a low educated level population with Parkinson's disease, along with other factors that may contribute to cognitive impairment.

2. Methods

2.1 Patients and data collection procedures

Patients with diagnosis of PD (Daniel and Lees 1993) that were in follow-up from 2006 to 2013 at the Movement Disorders Outpatient Clinic at the Hospital de Clínicas de Porto Alegre, a Brazilian southern city, were invited to participate if they were older than 18 years old and if they spontaneously consented to participate in the study. The exclusion criteria was the impossibility to be evaluated in neuropsychological tests such as severe sensorial deficit (hearing or sight), severe psychotic symptoms and impossibility to come to the medical appointment. Levodopa equivalent daily doses were calculated as previously proposed (Tomlinson et al. 2010).

The following standardized neuropsychological instruments testing multiple cognitive domains were used: mini-mental state examination (MMSE), Montreal Cognitive Assessment (MoCA), Scale for Outcomes in Parkinson's Disease - COGnition (SCOPA-COG), Frontal Assessment Battery (FAB), Verbal Fluency Test (semantic and phonology), Trail Making Test (TMT), Rey Auditory Verbal Learning Test (RAVLT). Depression was measured via the Beck's Depression Inventory (BDI). According to the recommendation for using the MoCA, when patients were 12 years of education or lower, 1 point was added to their final MoCA score.

Clinical stage of the disease was evaluated according to the Hoehn and Yahr (HY) and the clinical status was assessed by the Unified PD Rating Scale (UPDRS) (Martínez-Martín et al. 1994). All patients were assessed in "on status".

The study was approved by the Hospital Ethics Committee and all patients gave written informed consent to participate in the study.

2.1 Motor score sums

From the UPDRS part III scores, we grouped single questions to derive motor subscores to measure distinct clinical manifestations. Tremor subscore included rest tremor and action tremor questions. Postural instability and gait motor subscores included postural instability, posture and gait questions. Rigidity subscore included rigidity questions in all body segments evaluated. Bradykinesia subscore also included bradykinesia questions in all body segments.

2.3. Motor subtype classification

We classified patients by motor subtype as proposed by Jankovic et. al (Jankovic et al. 1990). The motor subtypes are tremor dominant (TD), mixed and postural instability and gait disorder (PIGD). It was calculated by the ratio of the mean UPDRS tremor scores to the mean postural instability and gait scores. The subtypes were defined according to the ratio; TD with a ratio ≥ 1.5, PIGD with a ratio ≤ 1.0, and mixed between 1.0 and 1.5.

2.4. Cognitive impairment definition

We defined cognitive impairment based on cut-off points of the Portuguese version of the MoCA, with cut-offs of 22 ≤ for PD-MCI and ≤ 17 for PDD (Almeida et al. 2015). For MMSE, we used previously defined cut-offs adjusted to educational level (Kochhan et al. 2010). Participants were divided into 3 groups according to MoCA scores, as mentioned before.

TMT was categorized into normal or altered according to previously defined cutoff points (Hamdam et al. 2009). BDI was used to define depression diagnosis according to previously defined cutoff points (Gorenstein et al. 1996). FAB was categorized as normative Brazilian data with cutoffs adjusted to education level (Beato et al. 2012). SCOPA-cog was categorized as cut-off determined in literature (Verbaan et al. 2011), adapted to the Brazilian population (Carod-Artal et al. 2008).

2.5. Statistical analyses

Comparisons between patients were made using independent-samples t-tests, Mann-Whitney U tests, or Wilcoxon tests for normally and non normally continuous variables, as appropriate (Shapiro-Wilk test for normality). Chi-square tests were used for categorical variables. Continuous variables were described by using means and SDs, and frequency with percentage was used for describing categorical variables.

We consider it acceptable to ignore 5% of missing data. Missing data were analyzed using MCAR test; nonsignificant results indicated that the missing items were missing at random across all scales items. We applied imputation by mode to categorical data and mean to quantitative data.

Univariate linear analyses were performed to test the relationship between motor scores and cognitive performance. Logistic regression was performed to test the relationship between subtypes and depression to cognitive performance. Regression analyses were performed in adjusted multivariate models with age and education as covariates.

A p value of ≤ 0.05 was considered to be statistically significant. All analyses were performed using Python version 3.6.9, and the modules Pandas v. 1.2.5 and SciPy v. 1.7.0.

3. Results

Eighty patients (44 men and 36 women) were enrolled in the study with mean age of 62.23 years old. Mean education level was 6.61 years (SD 3.99), with 25% of our population below 4 years of study, . The mean disease duration was 9.04 years (SD 5.29) and tremor was the first symptom in 51 patients (63.75%). See **Table 1** for more clinical and demographic characterization of the study population. The majority of our patients were classified as mild PD (HY 2 or 2.5), with 56.25% (53 patients) and moderate (HY 3) with 26.25% (21 patients). Advanced stage of PD (HY 4 or 5) was only 5% (four patients) of our patients and unilateral disease (HY 1) was only 2.5% (one patient). All patients were using levodopa with a mean levodopa equivalent dose of 980.6 (SD 473.70).

Table 1 - Demographic and clinical characteristics

Demographic (n = 80)		***SD / %***
Age	62.23	10.81
Sex (% male)	55%	
Ethnicity (% european ancestry)	90%	
Mean education (in years)	6.61	3.99
Less than 4 years of education (n)	20	25%
4-7 years of education (n)	29	36.25%
8-11 years of education (n)	25	31.25%
12 years or more of education (n)	6	7.5%
Clinical (n = 80)		
First symptom (% tremor)	63.75%	-
Side of onset (% right)	57.5%	
Disease duration (in years)	9.04	5.29
Levodopa equivalent dose (in mg)	980.6	473.70
HY (%)		
1	2.5%	
2 - 2.5	56.25%	
3	26.25%	
4 - 5	5%	
Motor subtype		
Tremor dominant	33.75%	
PIGD	11.25%	
Indetermined	55%	

MoCA, Montreal Cognitive Assessment; MMSE, Mini–Mental State Examination; SCOPA-Cog, Scales for Outcomes in Parkinson's Disease Cognition; FAB, Frontal Assessment Battery; FAS, phonemic verbal fluency assessment; FAS cat, categorical verbal fluency assessment; RVALT, Rey Auditory Verbal Learning Test; UPDRS, Unified Parkinson's Disease Rating Scale; REM SD, Rapid Eye Movement sleep disorder; BDI, Beck Depression Inventory; TD, tremor dominant; PIGD, postural instability and gait disorder

Motor and cognition performance description data are presented in **Table 2.** TMT A was altered in 53 patients (70.67%) and TMT B was altered in 56 patients (74.67%). Applying previous defined MoCA cutoffs, 60 patients (75%) of the patients were defined as cognitively impaired, with 34 (42,5%) defined as PDD. Using MMSE cutoff to PDD, 23 patients (28,75%) were screened as PDD. SCOPA-Cog was positive for cognitive impairment in 74 patients (92.5%).

Table 2 - Motor and cognitive scores

Motor scores (n = 80)		***SD***
Rigidity	5.24	4.25
Tremor	6.18	4.93
Bradykinesia	12.86	7.09
Postural/gait	6.18	4.55
Dyskinesia	1.84	2.39
UPDRS Part I	2.48	2.06
UPDRS Part II	13.74	7.12
UPDRS Part III	28.71	15.68
UPDRS Part IV	5.31	3.62
UPDRS total	50.24	22.71
Cognitive tests		**SD / %**
MoCA	17.67	6.41
MMSE	23.47	4.68
SCOPA-COG	13.17	5.27
FAB	10.98	3.98
FAS	21.44	13.56
FAScat	12.57	4.91
RVALT	23.27	5.27
TMT A - normal/altered (% altered)	23/57	71.25%
TMT B - normal/altered (% altered)	20/60	75.00%
Cognitive impairment (n = 80)	n	%
Cognitive impairment *defined by MoCA ≤ 23*	60	75%
PDD positive screening defined by MoCA ≤ 18	34	42.5%
PDD positive screening defined by MMSE adjusted to education level	23	28.75%
Cognitive impairment defined by SCOPA-Cog	74	92.5%
FAB cutoff	23	28.75%

MoCA, Montreal Cognitive Assessment; MMSE, Mini–Mental State Examination; SCOPA-Cog, Scales for Outcomes in Parkinson's Disease Cognition; FAB, Frontal Assessment Battery; FAS, phonemic verbal fluency assessment; FAS cat, categorical verbal fluency assessment; RVALT, Rey Auditory Verbal Learning Test; UPDRS, Unified Parkinson's Disease Rating Scale; REM SD, Rapid Eye Movement sleep disorder; BDI, Beck Depression Inventory; TD, tremor dominant; PIGD, postural instability and gait disorder

Table 3 demonstrates multivariate regression analysis. Years of education were independently associated with all cognitive tests. Age was only independently associated with FAB performance. In multiple regression, for each additional year of education, there was an increase of 0.73 points in the MoCA results ($p < 0.001$) and 0.44 in the MMSE results ($p < 0.001$). Bradykinesia correlated with worst performance in MoCA, SCOPA-COG, FAB and categorical FAS. Rigidity was only associated with worst performance in RVALT. Postural/gait impairment was associated with worst performance in MoCA, SCOPA-Cog, phonemical FAS, categorical FAS and RVALT. There was no correlation between disease duration, first symptom, side of onset and levodopa equivalent dose and cognition scores. There were no differences in gender, BDI score and disease duration between cognitive impairment.

Table 3 Multivariate linear regression*

	MoCA	MMSE	SCOPA COG	FAB	FAS	FAS cat	RVALT
Age	-0.07	-0.03	-0.07	**-0.10 (p < 0.01)**	-0.14	-0.08	-0.09
Education	**0.73 (p < 0.01)**	**0.44 (p < 0.01)**	**0.44 (p < 0.01)**	**0.26 (p 0.01)**	**1.78 (p < 0.01)**	**0.49 (p < 0.01)**	**0.80 (p < 0.01)**
Disease duration	-0.07	-0.04	0.05	-0.14	-0.05	-0.007	-0.11
Gender	-1.36	-1.08	-1.78	-0.50	-3.54	-0.52	2.01
First symptom	2.38	1.68	2.20	1.25	3.76	1.16	1.33
Onset side	1.32	0.92	0.61	0.66	5.30	1.79	1.68
REM SD	0.94	0.73	1.11	0.35	3.67	1.17	-2.01
Depression	-1.01	-1.26	-0.85	-0.43	-3.02	-0.8705	-1.49
BDI	-0.04	-0.07	-0.01	0.002	-0.001	0.00	-0.06
Smell	1.81	0.74	0.70	-1.29	0.85	0.8549	-1.60
Rigidity	-0.26	-0.12	-0.21	-0.10	-0.18	-0.2146	**-0.49 (p 0.03)**
Tremor	-0.18	-0.14	-0.19	-0.04	-0.01	-0.0634	-0.36
Bradykinesia	**-0.24 (p < 0.01)**	-0.12	**-0.20 (p < 0.01)**	**-0.20 (p < 0.01)**	-0.31	**-0.1899 (p < 0.01)**	**-0.44 (p < 0.01)**
Postural/gait	**-0.32 (p 0.02)**	**-0.24 (p 0.04)**	-0.29	-0.23	**-0.25 (p < 0.01)**	**-0.6099 (p 0.03)**	**0.23 (p 0.01)**

Table 3 Continuation

	MoCA	MMSE	SCOPA COG	FAB	FAS	FAS cat	RVALT
UPDRS dyskinesia	-0.23	-0.02	0.16	-0.23	-0.69	-0.1798	-0.003
UPDRS fluctuation	-0.10	0.023	0.27	-0.12	-0.36	-0.0616	0.09
UPDRS part I	-0.21	-0.30	-0.0669	-0.07	-0.49	-0.11	-0.47
UPDRS part II	-0.08	-0.07	-0.0148	-0.10	-0.22	-0.08	-0.19
UPDRS part III	**-0.11 (p < 0.01)**	-0.06	**-0.0977 (p < 0.01)**	**-0.07 (p < 0.01)**	-0.13	**-0.08 (p < 0.01)**	**-0.20 (p < 0.01)**
UPDRS part IV	-0.08	-0.01	0.2461	-0.09	-0.41	-0.03	0.11
UPDRS total	**-0.06 (p < 0.01)**	**-0.05 (p < 0.01)**	-0.0357	**-0.04 (p < 0.01)**	-0.10	-0.04	-0.09
TD	0.52	0.69	-0.3741	0.83	0.35	-0.04	0.69
PIGD	0.17	0.21	0.2344	-0.65	-2.44	0.18	0.21
Indeterminate	-1.58	-2.07	0.2512	-0.22	5.19	-0.33	-2.05

Bold values represent a significant level of association ($p < 0.05$)
MoCA, Montreal Cognitive Assessment; MMSE, Mini–Mental State Examination; SCOPA-Cog, Scales for Outcomes in Parkinson's Disease Cognition; FAB, Frontal Assessment Battery; FAS, phonemic verbal fluency assessment; FAS cat, categorical verbal fluency assessment; RVALT, Rey Auditory Verbal Learning Test; UPDRS, Unified Parkinson's Disease Rating Scale; REM SD, Rapid Eye Movement sleep disorder; BDI, Beck Depression Inventory; TD, tremor dominant; PIGD, postural instability and gait disorder

Multivariate regression analysis for categorized TMT is presented in **Table 4**, with only UPDRS total score significantly associated with altered TMT. There was no multicollinearity between covariables and other independent variables in each regression model.

Table 4 - Categorized Trail Making Test

	TMT A			***TMT B***		
	OR	***CI (95%)***	***p value***	***OR***	***CI (95%)***	***p value***
Education level	**0.75**	**0.63-0.89**	**<0.01**	**0.69**	**0.56-0.84**	**<0.01**
Age	1.06	1.0-1.13	0.07	1.08	1.0-1.17	0.05
Disease duration	1.1	0.96-1.26	0.18	1.08	0.93-1.26	0.30
Depression	1.44	0.4-5.26	0.58	5.47	0.89-33.45	0.07
Bradykinesia	1.1	0.99-1.24	0.08	1.12	0.99-1.28	0.08
Rigidity	1.12	0.94-1.33	0.19	1.05	0.88-1.27	0.58
Tremor	1.1	0.96-1.26	0.18	1.06	0.92-1.23	0.39
Dyskinesia	1.02	0.79-1.31	0.90	1.34	0.96-1.86	0.09
Postural and gait	1.1	0.93-1.29	0.27	1.18	0.95-1.47	0.14
UPDRS Part I	1.05	0.8-1.38	0.72	1.3	0.91-1.87	0.15
UPDRS Part II	1.03	0.94-1.13	0.58	1.1	0.97-1.24	0.14
UPDRS part III	1.06	1.0-1.12	0.05	1.06	0.99-1.13	0.09
UPDRS part IV	1.02	0.85-1.22	0.81	1.22	0.95-1.55	1.12
UPDRS total	1.03	0.99-1.06	0.11	**1.05**	**1.0-1.1**	**0.04**

TMT, Trail Making Test A and B; UPDRS, Unified Parkinson's Disease Rating Scale; REM SD, Rapid Eye Movement sleep disorder; BDI, Beck Depression Inventory; TD, tremor dominant; PIGD, postural instability and gait disorder

4. Discussion

The cognition on PD has a marked heterogeneity, including in cognitive impairment (Tremblay et al. 2013), with many factors implicating in it (Guo et al. 2019; Uc et al. 2009). The aim of this study was to assess the relationship between cognition and motor symptoms in Parkinson's Disease in a low level educated population and evaluate how it relates. The results showed the relevant association between motor scores and cognitive performance, with bradykinesia and postural instability/gait symptoms negatively associated with multidomain cognitive performance. As expected, education level was correlated with better performance in all cognitive tests.

Bradykinesia was associated with lower cognitive performance in several studies (Schneider, Sendek, and Yang 2015; Katzen, Levin, and Weiner 2006; Rabinowitz and Lavner 2014). Postural and gait symptoms are traditionally associated with attention and visuospatial function (Yogev-Seligmann, Hausdorff, and Giladi 2008; Stuart et al. 2016). In our study, bradykinesia correlated with worst performance in MoCA, SCOPA-Cog, FAB and categorical FAS, which implies that bradykinesia is not only associated with executive function, but also with memory. It is important to note that categorical FAS is intimately associated with executive function, and, apart from being a language domain, this impairment could be explained only by executive dysfunction (Aita et al. 2019). Postural/gait impairment was associated with worst performance in MoCA, SCOPA-Cog, phonemical FAS, categorical FAS and RVALT. This implies that bradykinesia, memory and executive function may be disrupted with the same circuit mechanism, but not along with rigidity or tremor; at the same time, postural/gait impairment may be disrupted with executive function, memory and language. Rigidity was associated with RVALT scores and tremor was not statistically associated with any cognitive performance. UPDRS part III (motor scores) correlated with worst performance in MoCA, SCOPA-Cog, FAB and FAS, which we attribute mostly to bradykinesia and postural/gait scores that were the motor parameters that encompasses most of the UPDRS part III. We demonstrated that motor and cognitive scores correlate within, but not with disease duration, and bradykinesia and postural and gait scores being related to worse cognition performance in multi domain cognitive tests.

Our study demonstrated higher prevalence of cognitive impairment than previous studies. A meta-analysis revealed that PD-MCI occurs in about a third of nondemented patients with PD (Baiano et al. 2020). A cohort demonstrated an incidence of PDD of 7.2% (Counsell et al. 2022), with great discrepancy with others studies (Baiano et al. 2020). We hypothesize that our higher prevalence of cognitive impairment is a consequence of a low cognitive reserve (CR) based on our low education level. CR is defined as the mechanism which enables some individuals to be more resilient to the pathological brain protein aggregation, such as synuclein, amyloid-β42 and tau. Education level is one of the known factors of CR (Bennett et al. 2003). Understanding the factors relatable to CR is key to target interventions in both public and scientific perspective, leading to targeted interventions and disease-modifying treatments.

We found a significant relationship between education level and cognitive performance, with lower level education associated with lower scores in all cognitive tests. Although age, gender, disease duration and level of education were reported as factors influencing MMSE and MoCA, regression analyses showed that the education level was the only non-motor factor associated with the score on both tests. In regression analyses, age was only associated with FAB, which was consistent with previous reports (Schneider et al. 2010).

Motor subtypes were not associated with cognitive performance. Motor subtyping has been challenged because of inconsistent reliability and confounding by disease stage (Zhang et al. 2019). Several studies demonstrated that TD is generally considered to have a more favorable prognosis than the postural and gait disorder phenotype(Jankovic 2008) including less likely to develop cognitive impairment (Williams-Gray et al. 2007; Alves et al. 2006; Burn et al. 2006), but this was not implicated with better longitudinal prognosis as demonstrated by Alves (2006). Fereshtehnejad (2017) demonstrated that motor Jankovic' subtype could not predict cognitive prognosis. In studying the incidence of dementia, Alves et. al (2006) found that the tremor-dominant subtype did not develop dementia until those patients converted to the PIGD subtype. Other studies demonstrated the relation between cognitive impairment with more severe motor symptomatology, with some heterogeneous results in motor subtype analysis. Since several studies have demonstrated that a high proportion of individuals with the TD phenotype will switch

to a PIGD phenotype over time (Simuni et al. 2016; von Coelln et al. 2021; Lee et al. 2019), motor subtype may not be helpful in clinical practice to predict prognosis.

The correlation of motor and cognitive performance implicates PD complex pathophysiology. Cognitive impairment in PD is attributed to multiple possible mechanisms such as multiple genetic risks factors such as APOE*ε4 allele, GBA mutations and SCNA mutations and triplications. In neurotransmitter level, evidences show that mesolimbic and mesocortical dopaminergic activity is associated with cognitive functioning, among others neurotransmitters such as cholinergic, serotonergic and noradrenergic; understanding these neurotransmitters in PD are key to understanding cognitive impairment in PD. And other factors such as neurotrophic factors, inflammation and mitochondrial dysfunction are implicated in cognitive impairment. Regarding the pathological level, good evidence from postmortem studies indicates that limbic and cortical Lewy body pathology is the main pathological correlate of dementia in PD, with a significant contributor of copathology with amyloid-β42 and tau (Dag Aarsland et al. 2017). Studies demonstrated the importance of cortical connectivity of the nucleus basalis of Meynert (NBM) in Parkinson's Disease and Lewy body dementias, as it is the principal source of cholinergic inputs to cortex, mainly to supplementary motor area, parahippocampal gyrus and lingual gyrus, implicating in motor function and plasticity, memory, attention and visual processing (Oswal et al. 2021). At the same time, the caudate nucleus is also related to cognitive function in PD patients, with lower functional connectivity of the caudate nucleus correlates with worse global cognition scores(Wright et al. 2020). Also, the striatum and its dopaminergic loss is linked to cognitive deficits in early-stage PD, although it does not affect cognitive prognosis (Chung et al. 2018).

Our research has some important limitations. First, patients were not evaluated about the standard diagnosis criteria of dementia at any point. This does not invalidate our inferences between cognitive impairment, as we based our cutoffs in previous studies in similar populations, and our findings strengthen the correlation between poor cognitive performance, low education level and motor symptoms. Second, our study did not evaluate patients longitudinally, which limits the power to make inferences on prognosis. Third, we did not evaluate each cognitive domain because of missing data in subparts of each test, making the analysis unfeasible;

but, in regard to that, our study had the power to define cognitively impaired patients and correlates with motor scores, without the need to evaluate each cognitive domain.

5. Conclusion

In conclusion, our study demonstrates the relationship between motor and cognitive performance in PD patients, which could imply in the pathophysiology of both. Poor cognitive performance was also correlated with lower educational level, but not with disease duration or consistently with age and depression. Our study contributes to demonstrating that cognition and motor function are intrinsically associated. Contemporary view is heading to consider motor control and behavior as an act integrated into cognitive processes.

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CONSIDERAÇÕES FINAIS E PERSPECTIVAS FUTURAS

A doença de Parkinson foi descrita há mais de 200 anos e o desenvolvimento da ciência auxiliou os pacientes que vivem com esta doença a terem melhor qualidade de vida. As alterações cognitivas fazem parte da complexa heterogeneidade clínica, porém ainda restam muitas lacunas de conhecimento a serem preenchidas.

O futuro das intervenções que trarão benefícios para os pacientes envolve terapias personalizadas que se adaptem a esta heterogeneidade da doença. O conhecimento das alterações cognitivas e de como elas se comportam em conjunto com os sintomas motores é peça chave para personalizar o tratamento.

Além disso, o conhecimento fisiopatológico das alterações cognitivas pode auxiliar a guiar a saúde pública para planejamento estratégico e operacional, com objetivo de um bem comum para a população. Cabe ressaltar que é crescente o conceito de reserva cognitiva e como o ambiente se relaciona com a doença, sendo a educação um dos mais importantes determinantes da reserva cognitiva.

O crescente conhecimento da doença de Parkinson ainda é escasso em países em desenvolvimento, com a maioria dos estudos avaliando a cognição em pacientes com alta escolaridade.

Os resultados desta dissertação mostram como a doença e o ambiente podem moldar a cognição, com esta se relacionando fortemente com bradicinesia e sintomas de instabilidade postural/marcha. O fato das alterações cognitivas não se correlacionarem com a idade ou o tempo de doença quando quando corrigido para escolaridade no nosso trabalho, mas se relacionarem com sintomas motores sugere um efeito fisiopatológico comum entre estes sintomas e a performance cognitiva.

ANEXO

Checklist STROBE

STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

	Item No	Recommendation
Title and abstract ✓	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/rationale ✓	2	Explain the scientific background and rationale for the investigation being reported
Objectives ✓	3	State specific objectives, including any prespecified hypotheses
Methods		
Study design ✓	4	Present key elements of study design early in the paper
Setting ✓	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants ✓	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants
Variables ✓	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
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
Bias ✓	9	Describe any efforts to address potential sources of bias
Study size ✓	10	Explain how the study size was arrived at
Quantitative variables ✓	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods ✓	12	(*a*) Describe all statistical methods, including those used to control for confounding
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) If applicable, describe analytical methods taking account of sampling strategy
		(*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
		(b) Give reasons for non-participation at each stage
		(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
		(b) Indicate number of participants with missing data for each variable of interest
Outcome data ✓	15	Report numbers of outcome events or summary measures
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
		(*b*) Report category boundaries when continuous variables were categorized
		(*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
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
Interpretation ✓	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability ✓	21	Discuss the generalisability (external validity) of the study results
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