



Gdański Uniwersytet Medyczny

Rozprawa doktorska

**Rola czynników naczyniowych w patogenezie otępienia w chorobie
Parkinsona**

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Serdecznie dziękuję wszystkim, którzy przyczynili się do powstania niniejszej pracy, w szczególności:

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I. WYKAZ PRAC WCHODZĄCYCH W SKŁAD ROZPRAWY DOKTORSKIEJ

1. Praca poglądowa

Kwaśniak-Butowska Magdalena, Dulski Jarosław, Pierzchlińska Anna, Białecka Monika, Wieczorek Dariusz, Sławek Jarosław

Cardiovascular dysautonomia and cognition in Parkinson's Disease - a possible relationship.

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IF 2,223 | MNiSW 100 | Q 4

2. Praca poglądowa

Pierzchlińska Anna, Kwaśniak-Butowska Magdalena, Sławek Jarosław, Drożdżik Marek, Białecka Monika

Arterial Blood Pressure Variability and Other Vascular Factors Contribution to the Cognitive Decline in Parkinson's Disease.

Molecules. 2021 Mar 10;26(6):1523.

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IF 4,927 | MNiSW 140 | Q 2

3. Praca oryginalna

Kwaśniak-Butowska Magdalena, Konkel Agnieszka, Skrzypkowska Agnieszka, Wieczorek Dariusz, Wąż Piotr, Tomczyk Marta, Białecka Monika, Szurowska Edyta, Smoleński Ryszard Tomasz, Sławek Jarosław

The impact of short-term blood pressure variability on cognitive decline in Parkinson's disease patients without co-morbidities.

Journal of Neural Transmission (Vienna). 2025 Nov;132(11):1635-1644

doi: 10.1007/s00702-025-02950-y.

IF 4,0 | MNiSW 70 | Q 1

4. Praca oryginalna

Kwaśniak-Butowska Magdalena, Skrzypkowska Agnieszka, Konkel Agnieszka, Wieczorek Dariusz, Tomczyk Marta, Białecka Monika, Smoleński Ryszard Tomasz, Sławek Jarosław

Peripheral renin-angiotensin system and cognitive decline in Parkinson's disease patients without co-morbidities.

Parkinsonism&Relat Disorders. 2025 Dec;141:108073

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IF 3,4 | MNiSW 100 | Q 2

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Wyniki badania zostały zaprezentowane:

- w formie prezentacji ustnej pt. „Wpływ krótkookresowej zmienności ciśnienia tętniczego na rozwój otępienia w chorobie Parkinsona z oceną układu renina-angiotensyna-aldosteron” podczas XXV Zjazdu Polskiego Towarzystwa Neurologicznego w Białymstoku. Wystąpienie zostało wyróżnione nagrodą za najlepszą prezentację ustną. (2024)

- w formie plakatu pt. „The impact of short-term blood pressure variability on dementia in Parkinson's disease in relation to the renin-angiotensin system” podczas XXIX IAPRD World Congress on Parkinson's Disease and Related Disorders w Lizbonie. (2024)

II. WYKAZ STOSOWANYCH SKRÓTÓW

ABPM – *ambulatory blood pressure monitoring*, całodobowe monitorowanie ciśnienia tętniczego

ACE – *angiotensin converting enzyme*, enzym konwertujący angiotensynę

Ang II – angiotensyna II

AGT – angiotensynogen

ARO – aktywność reninowa osocza

ARV – *average real variability*, średnia rzeczywista zmienność

AT1R – *Angiotensin II Type 1 Receptor*, receptor typu 1 dla angiotensyny II

AT2R – *Angiotensin II Type 2 Receptor*, receptor typu 2 dla angiotensyny II

AUC – *area under the curve*, pole pod krzywą

BNT – *Boston Naming Test*, Bostoński Test Nazywania

BP – *blood pressure*, ciśnienie tętnicze

BPV – *blood pressure variability*, zmienność ciśnienia tętniczego

COWAT – *Controlled Oral Word Association Test*, Test fluencji słownej

CV – *Coefficient of Variation*, współczynnik zmienności

CVLT – *California Verbal Learning Test*, Kalifornijski Test Ucznienia się Językowego

DBP – *diastolic blood pressure*, rozkurczowe ciśnienie tętnicze

JOLO – Benton Judgment of Line Orientation

LEDD – *levodopa equivalent daily dose*, dobową dawkę równoważną lewodopy

MAF – *minor allele frequency*, częstość występowania rzadszego allelu

Δ MAP – spadek średniego ciśnienia tętniczego w godzinach nocnych w porównaniu do wartości z dnia wyrażony w %,

MCI – *mild cognitive impairment*, łagodne zaburzenia poznawcze

MDS – *Movement Disorders Society*, Międzynarodowe Towarzystwo Zaburzeń Ruchowych i Choroby Parkinsona

MoCA – *Montreal Cognitive Assessment*, Montrealska Skala Oceny Funkcji Poznawczych

MRI – *Magnetic Resonance Imaging*, rezonans magnetyczny

NMSQ – *Non-Motor Symptoms Questionnaire*

OH – hipotonia ortostatyczna

PD – *Parkinson's disease*, choroba Parkinsona

PDD – *Parkinson's disease dementia*, otępienie w chorobie Parkinsona

PD-NC – grupa PD z prawidłowymi funkcjami poznawczymi

pkt. – punkt

PRA – *plasma renin activity*, aktywność reninowa osocza

RAA – układ renina-angiotensyna-aldosteron

SBP – *systolic blood pressure*, skurczowe ciśnienie tętnicze

SD - *standard deviation*, odchylenie standardowe

SH – *supine hypetension*, nadciśnienie w pozycji leżącej

SNP - *Single Nucleotide Polymorphism*, polimorfizm pojedynczego nukleotydu

TSH – hormon tyrotropowy

UPDRS – *Unified Parkinsons Disease Rating Scale*

VEGF – *Vascular Endothelial Growth Factor*, czynnik wzrostu śródbłónka naczyniowego

VOSP – *Visual Object and Space Perception Battery*, bateria percepcji wizualnej obiektów przestrzeni,

WAIS – *Wechsler Adult Intelligence Scale*, Skala Inteligencji Wechslera dla Dorosłych

WMH – *white matter hiperintensities*, zmiany hiperintensywne istoty białej

III. STRESZCZENIE W JĘZYKU POLSKIM

Choroba Parkinsona (PD) jest jedną z najczęściej występujących chorób neurodegeneracyjnych. Szacuje się, że dotyczy ona około 1% populacji >65 roku życia i zapadalność na nią wzrośnie dwukrotnie w ciągu najbliższej dekady. W wyniku nieprawidłowej agregacji α -synukleiny, dysfunkcji mitochondriów i lizosomów, zaburzeń transportu pęcherzykowego oraz synaptycznego, a także nasilonych procesów zapalnych dochodzi do obumierania i zaniku m.in. neuronów części zbitnej istoty czarnej. Prowadzi to do deficytu dopaminergicznego. Procesem chorobowym objęte są również inne obszary ośrodkowego i obwodowego układu nerwowego, co zaburza przekąźnictwo cholinergiczne, noradrenergiczne i serotoninericzne. Do objawów osiowych choroby należą bradykineza, sztywność oraz drżenie spoczynkowe. Istotny wpływ na jakość życia pacjentów mają także zaburzenia pozaruchowe. Do najczęściej występujących należą zaburzenia funkcji poznawczych i zaburzenia autonomiczne. Nie jest do końca jasne, czy jedynie ze sobą współwystępują czy wzajemnie wpływają na swój rozwój.

Celem pracy była ocena wpływu czynników naczyniowych, regulujących przepływ krwi w ośrodkowym układzie nerwowym, na funkcje poznawcze pacjentów z PD. W szczególności analizowano, czy krótkookresowa zmienność ciśnienia tętniczego (BPV), mierzona w ciągu 24 godzin oraz zaburzenia regulacji ciśnienia tętniczego: hipotonia ortostatyczna (OH), nadciśnienie w pozycji leżącej (SH), nieprawidłowy profil ciśnienia w nocy, są związane z występowaniem zaburzeń poznawczych w starannie wyselekcjonowanej grupie chorych, bez istotnych chorób współistniejących oraz bez stosowania terapii wpływających na układ sercowo-naczyniowy.

Zależność między obwodowym układem renina–angiotensyna–aldosteron (RAA), regulującym wysokość ciśnienia tętniczego, a funkcjami poznawczymi w PD pozostaje niejednoznaczna i opiera się głównie na pośrednich przesłankach. W badaniu oceniono również, czy aktywność RAA może przyczyniać się do zaburzeń poznawczych w PD. Dodatkowo przeanalizowano zależności między aktywnością RAA a nieprawidłowościami regulacji ciśnienia tętniczego oraz BPV.

Podjęto również próbę oceny wpływu stosowanego leczenia dopaminergicznego, wybranych czynników metabolicznych (stężenia homocysteiny, witaminy B12 czy kwasu foliowego) oraz wybranych czynników genetycznych związanych z aktywnością układu RAA na rozwój otępienia.

Oceniono także związek wymienionych wyżej zmiennych z nasileniem zmian hiperintensywnych istoty białej (WMH) w badaniu rezonansu magnetycznego mózgowia i ich wpływ na rozwój otępienia.

Do badania włączono 65 pacjentów z idiopatyczną PD leczonych w Poradni Neurologicznej Szpitala św. Wojciecha w Gdańsku. Kryteriami wyłączenia było stosowanie terapii zaawansowanych (infuzyjnych bądź głębokiej stymulacji mózgu), współistnienie chorób sercowo-naczyniowych (takich jak m.in. nadciśnienie tętnicze, cukrzyca typu 2, niewydolność serca, migotanie przedsionków), stosowanie leków wpływających na układ RAA, niewydolność nerek lub wątroby, istotne zaburzenia elektrolitowe. Dwóch chorych z powodu rozpoznania cukrzycy typu 2 już w trakcie trwania badania wyłączono z dalszych analiz.

Na podstawie badania neurologicznego w stanie ON, przy użyciu odpowiednich skal oceniono stopień nasilenia objawów (część III UPDRS, Shwab-England, NMSQ) i zaawansowania choroby (Hoehn-Yahr). Wszyscy chorzy przeszli badanie neuropsychologiczne oceniające funkcje poznawcze i nastrój. Na jego podstawie uczestnicy badania zostali zakwalifikowani do jednej z grup: w normie poznawczej (PD-NC), z łagodnymi zaburzeniami poznawczymi (MCI) oraz z otępieniem (PDD).

U wszystkich chorych zmierzono ciśnienie tętnicze w pozycji leżącej, wykonano próbę ortostatyczną oraz całodobowy pomiar ciśnienia tętniczego, z oceną jego profilu. Ocenianymi wskaźnikami BPV były: odchylenie standardowe (SD) oraz współczynnik zmienności (CV) ciśnienia skurczowego (SBP) i rozkurczowego (DBP) dla wartości z dnia, z nocy oraz z doby; średnia rzeczywista zmienność (ARV) dla SBP i DBP w ciągu doby.

U chorych oznaczono poziom glukozy, homocysteiny, witaminy B12, kwasu foliowego, reniny, angiotensyny II (Ang II), aldosteronu oraz aktywność reninową

osocza (ARO). Oceniono również morfologię krwi obwodowej oraz funkcję tarczycy, nerek i wątroby.

Zbadano także polimorfizmy pojedynczego nukleotydu (SNP) w genach angiotensynogenu (AGT: rs699 A>G, rs4762 G>T) i receptorów Ang II (AT1R: rs5186 A>C, AT2R: rs5194 A>G; rs1403543 A>G) oraz polimorfizm (insercja/delecja, I/D) w genie konwertazy angiotensyny (ACE).

Nasilenie WMH oceniano na podstawie badania rezonansu magnetycznego mózgowia wykonanego na 3T aparacie za pomocą skali Fazekas.

Pacjenci z otępieniem byli istotnie starsi i gorzej wykształceni, z bardziej nasilonymi objawami choroby niż pacjenci w normie poznawczej. Czas trwania choroby i stosowane leczenie dopaminergiczne nie różniły się istotnie między grupami.

Krótkookresowa zmienność ciśnienia tętniczego w badanej grupie była wyższa u chorych z otępieniem. Dodatkowo wyższe wartości SBP ARV korelowały z niższą punktacją w skali MoCA i gorszymi wynikami w zakresie funkcji wykonawczych i pamięci wzrokowo-przestrzennej. Wyższa wartość współczynnika SBP ARV zwiększała w analizie jednoczynnikowej ryzyko otępienia na poziomie trendu statystycznego. Analiza krzywych ROC wykazała umiarkowaną zdolność dyskryminacyjną wskaźników krótkookresowej BPV w predykcji otępienia, przy najwyższych wartościach AUC dla SBP ARV, DBP ARV oraz DBP SD i DBP CV obliczanych dla okresu dziennego. Nowe wskaźniki oceniające BPV, takie jak SBP ARV i DBP ARV, niezależne od dobowych wahań ciśnienia tętniczego, mogą mieć szczególną wartość kliniczną u chorych z zaburzeniami autonomicznymi. Podwyższona krótkookresowa BPV u chorych z PD może stanowić czynnik ryzyka rozwoju otępienia.

Krótkookresowa BPV nie wpływała na nasilenie WMH ocenianych w skali Fazekas. Nasilenie WMH w skali Fazekas, w badanej grupie pacjentów z PD (grupa z założenia bez towarzyszących chorób sercowo-naczyniowych), nie wiązało się ze zwiększonym ryzykiem występowania otępienia.

Hipotonia ortostatyczna korelowała z pogorszeniem pamięci werbalnej i wzrokowo-przestrzennej oraz funkcji językowych i wykonawczych. Nadciśnienie w pozycji leżącej oraz zaburzenia dobowego profilu ciśnienia tętniczego (niewielki spadek lub wzrost w godzinach nocnych) korelowały z obecnością otępienia i w analizie jednoczynnikowej istotnie zwiększały ryzyko jego wystąpienia.

Stężenia badanych składowych układu RAA nie różniły się między grupami. Niemniej, wyższy poziom reniny i większa ARO wiązały się z lepszymi wynikami w skalach oceniających wybrane funkcje poznawcze (m.in. wzrokowo-przestrzenne czy językowe). Wyższe stężenia Ang II wpływały negatywnie na bezpośrednią i odroczoną pamięć słowną oraz na planowanie. Układ RAA nie wpływał bezpośrednio na oceniane zaburzenia regulacji ciśnienia tętniczego ani na krótkookresową BPV, poza ujemną korelacją między stężeniem reniny i ARO a SBP ARV oraz między stężeniem reniny a ortostatycznym spadkiem DBP. Analiza mediacji wykazała, że SBP ARV pośredniczyła w wpływie reniny i ARO na m.in. globalne funkcje poznawcze. Najwyższy poziom reniny i ARO był w grupie chorych z najbardziej nasilonymi WMH w badanej grupie (Fazekas 2).

Ilość przyjmowanych leków dopaminergicznych ocenianych łącznie (LEDD) oraz dawka lewodopy korelowały jedynie z wysokością spadku DBP w próbie ortostatycznej. Stosowane leczenie dopaminergiczne nie wpływało na krótkookresową BPV i SH, obwodowy układ RAA oraz nie zwiększało ryzyka wystąpienia otępienia i WMH.

Poziom witaminy B12, kwasu foliowego, TSH, glukozy nie różnił się między grupami. Wyższy poziom homocysteiny na poziomie trendu występował u chorych z otępieniem i korelował z wyższą dawką przyjmowanej lewodopy.

Monitorowanie ciśnienia metodą ABPM, jako prosta i tania procedura, powinno stanowić element rutynowej opieki nad pacjentami z PD, przy zachowaniu standaryzacji pomiarów. Wczesne rozpoznanie i leczenie zaburzeń regulacji ciśnienia tętniczego może zmniejszać ryzyko rozwoju zaburzeń poznawczych, co wymaga potwierdzenia w badaniach prospektywnych.

IV. STRESZCZENIE W JĘZYKU ANGIELSKIM

The influence of vascular factors on the pathogenesis of dementia in Parkinson's disease

Parkinson's disease (PD) is one of the most common neurodegenerative disorders, affecting approximately 1% of population over 65 years of age, with its incidence projected to double within the next decade. The pathological process involves abnormal aggregation of α -synuclein, mitochondrial and lysosomal dysfunction, impaired vesicular and synaptic transport, and enhanced neuroinflammatory processes, which lead to degeneration of, among others, dopaminergic neurons in the substantia nigra pars compacta. This results in striatal dopamine deficiency. The disease process also affects other regions of the central and peripheral nervous systems, disrupting cholinergic, noradrenergic, and serotonergic neurotransmission. The cardinal motor features of PD include bradykinesia, rigidity and resting tremor. However, also non-motor symptoms, particularly cognitive impairment and cardiovascular dysautonomia, significantly impair patients' quality of life. It remains unclear whether the relationship is causative or associative.

The aim of the study was to evaluate the impact of vascular factors regulating cerebral blood flow on cognitive function in PD patients. We investigated whether short-term blood pressure variability (BPV), assessed over 24 hours, and abnormalities in blood pressure (BP) regulation, such as orthostatic hypotension (OH), supine hypertension (SH), and altered nocturnal BP profile, were associated with cognitive impairment in a selected group of PD patients without comorbidities and not receiving medications affecting the cardiovascular system.

The relationship between the peripheral renin–angiotensin–aldosterone system (RAA, a regulator of blood pressure), and cognitive function in PD remains inconclusive and largely based on indirect evidence. We additionally assessed whether RAA activity contributes to cognitive impairment in this group. We also examined associations between RAA activity and BP dysregulation as well as short-term BPV.

Furthermore, we assessed the potential influence of dopaminergic treatment, metabolic factors (homocysteine, vitamin B12, and folate levels), and genetic polymorphisms related to RAA activity on the development of dementia. The relationship between these variables and the severity of white matter hyperintensities (WMH) on brain magnetic resonance imaging (MRI), as well as their contribution to dementia risk, were also assessed.

Sixty-five patients with idiopathic PD recruited from the Outpatient Movement Disorder Clinic were enrolled. Exclusion criteria included advanced therapies (infusion therapies or deep brain stimulation), cardiovascular diseases (including hypertension, type 2 diabetes mellitus, heart failure, and atrial fibrillation), use of RAA-modulating drugs, renal or hepatic insufficiency and significant electrolyte disturbances. Two patients were subsequently excluded from further analyses due to diabetes mellitus diagnosed after initial evaluation.

Disease severity was assessed in the ON state using validated clinical scales (UPDRS part III, Hoehn and Yahr staging, Schwab–England scale, and NMSQ). All participants underwent neuropsychological examination of cognitive function and mood. Based on the results they were classified as cognitively normal (PD-NC), having mild cognitive impairment (MCI), or with dementia (PDD).

Supine BP measurement, an orthostatic test, and 24-hour ambulatory blood pressure monitoring (ABPM) with circadian profile assessment were performed in all patients. BPV indices included standard deviation (SD) and coefficient of variation (CV) of systolic (SBP) and diastolic blood pressure (DBP) for daytime, nighttime, and 24-hour periods, as well as average real variability (ARV) for SBP and DBP over 24 hours.

Laboratory assessments included glucose, homocysteine, vitamin B12, folate, renin, angiotensin II (AngII), aldosterone, and plasma renin activity (PRA). Complete blood count and thyroid, renal, and hepatic function tests were also performed. Single nucleotide polymorphisms (SNPs) in the angiotensinogen (AGT: rs699 A>G, rs4762 G>T) and Ang II receptor genes (AT1R: rs5186 A>C; AT2R: rs5194 A>G, rs1403543 A>G), as well as the insertion/deletion polymorphism in the angiotensin-converting enzyme (ACE) gene, were analyzed. WMH severity was assessed on 3T brain MRI using the Fazekas scale.

Patients with dementia were significantly older, less educated and had more advanced disease stage than PD-NC. Disease duration and dopaminergic therapy were similar across the groups.

Short-term BPV was higher in PDD. Higher SBP ARV correlated with lower MoCA scores and poorer executive and visuospatial memory performance. In univariate analysis, SBP ARV increased the risk of dementia at a trend level. The highest accuracy as predictors of dementia was observed for SBP ARV, DBP ARV, and daytime DBP SD and CV. Novel BPV indices such as SBP ARV and DBP ARV, independent of circadian BP fluctuations, may be of particular clinical value in patients with autonomic dysfunction. Increased short-term BPV may be associated with cognitive decline in PD.

Short-term BPV was not associated with WMH severity on the Fazekas scale. In this cohort of PD patients without cardiovascular comorbidities, WMH were not associated with an increased risk of dementia.

Orthostatic hypotension correlated with impaired verbal and visuospatial memory as well as language and executive dysfunction. Supine hypertension and abnormal nocturnal BP profile (non-dipping or nocturnal rise) were associated with dementia and significantly increased its risk in univariate analysis.

The total dopaminergic medication dose (calculated as levodopa equivalent daily dose, LEDD) and levodopa dose correlated only with the orthostatic DBP drop. Dopaminergic treatment did not affect short-term BPV, supine hypertension, peripheral RAA activity, or the risk of dementia and WMH.

Renin-angiotensin system component levels did not differ between the groups. However, higher renin levels and PRA were associated with better performance in visuospatial and language functions, whereas higher Ang II concentrations were negatively associated with immediate and delayed verbal memory and planning. Renin-angiotensin system did not directly influence BP dysregulation or short-term BPV, except for negative correlations between renin levels and SBP ARV, and orthostatic DBP drop. Mediation analysis indicated that SBP ARV mediated the relationship between renin and PRA and global cognitive

function. The highest levels of renin and ARO were observed in patients with the most severe WMH (Fazekas grade 2).

Vitamin B12, folate, TSH, and glucose levels did not differ between groups. Higher homocysteine levels showed a trend toward association with dementia and correlated with higher levodopa doses.

ABPM, as a simple and inexpensive tool, should be considered in monitoring of PD patients. The procedure needs to be standardized. Early identification and management of BP abnormalities may potentially mitigate further cognitive decline, what requires confirmation in prospective studies.

V. WPROWADZENIE

Choroba Parkinsona jest drugą, co do częstości, po chorobie Alzheimerera, chorobą neurozwyrodnieniową¹. Częstość jej występowania w Polsce wynosi około 269 chorych na 100 tysięcy mieszkańców². Akumulacja α -synukleiny w neuronach części zbitęj istoty czarnej prowadzi do ich zaniku i w efekcie do deficytu dopaminergicznego w prążkowie. Do osiowych objawów ruchowych choroby należą bradykinezja, sztywność i drżenie spoczynkowe³. Ciała Lewy'ego obecne są także w innych regionach mózgu, w efekcie czego zaburzeniu ulega również przekazywanie cholinergiczne, serotoninericzne i noradrenergiczne.¹ Prowadzi to do rozwoju szeregu objawów pozaruchowych, takich jak pogorszenie funkcji poznawczych, zaburzenia snu i nastroju, dolegliwości ze strony układu sercowo-naczyniowego, pokarmowego czy moczowo-płciowego⁴.

Dysautonomia sercowo-naczyniowa oraz zaburzenia funkcji poznawczych są częste i mogą występować już na wczesnym etapie choroby^{4,5}. Otępienie dotyczy około 30% chorych z PD⁶. Jego częstość wzrasta wraz z wiekiem i czasem trwania choroby: po 10 latach dotyczy około 50% chorych, a po 20 latach nawet 80%¹. Pozostałymi czynnikami ryzyka są m.in.: starszy wiek w momencie zachorowania, stopień zaawansowania choroby, obecność zaburzeń osiowych, niski poziom edukacji, depresja i płeć męska⁷. Istotnie obniża ono jakość życia chorych i ich opiekunów. Etiologia otępienia nie jest do końca poznana. Jego rozwój koreluje z występowaniem ciał Lewy'ego w korze nowej i układzie limbicznym.⁸ Kolejną często stwierdzaną patologią w badaniach pośmiertnych u PDD są zmiany o typie zwyrodnienia alzheimerowskiego, tj. zewnątrzkomórkowe

złogi β amyloidu oraz wewnątrzkomórkowe odkładanie białka tau.⁸ Dodatkowo obecność złogów β amyloidu w korze wiąże się ze zwiększeniem ilości α -synukleiny w układzie limbicznym i korze nowej. Nasilenie patologii tau koreluje z kolei z ciężkością zaburzeń językowych.⁸

Zanik neuronów miejsca sinawego, obecny od wczesnych etapów choroby, wiąże się z niedoborem noradrenaliny m.in. w korze czołowej i hipokampie, co prowadzi do pogorszenia uwagi, kontroli zachowań oraz zaburzeń pamięci roboczej i długotrwałej^{1, 9}. Obniżeniu ulega również stężenie noradrenaliny w obwodowym układzie nerwowym, m.in. w pozazwojowych włóknach unerwiających serce czy naczynia krwionośne¹⁰. W efekcie odruch z baroreceptorów w odpowiedzi na pionizację jest zaburzony i nie dochodzi do fizjologicznego skurczu naczyń w celu utrzymania prawidłowych wartości ciśnienia tętniczego¹¹. Spadek ciśnienia skurczowego (SBP) o 20 mmHg lub ciśnienia rozkurczowego (DBP) o 10 mmHg w trzeciej minucie po pionizacji nazywany jest hipotonią ortostatyczną (OH)⁵. Występuje ona u około 30% pacjentów z PD i choć jej częstość wzrasta wraz z wiekiem, czasem trwania choroby, jej nasileniem oraz ilością przyjmowanych leków dopaminergicznych, może być obecna już na wczesnym jej etapie. Najczęstszym objawem OH są nieukładowe zawroty głowy, uczucie zmęczenia oraz bóle głowy i karku, zasłabnięcia, a czasami omdlenia^{12,13}. Nawet jeśli OH pozostaje bezobjawowa, zwiększa ryzyko upadków i obniża jakość życia. Epizody OH wiążą się z nawracającą hipoperfuzją ośrodkowego układu nerwowego (OUN), co może być przyczyną pogorszenia funkcji poznawczych, w szczególności uwagi i funkcji wykonawczych¹⁴.

U około 50% chorych z OH współwystępuje nadciśnienie w pozycji leżącej (SH), czyli wzrost SBP ≥ 140 mmHg lub DBP ≥ 90 mmHg po 5 minutach odpoczynku w pozycji leżącej¹⁵. Prowadzi ono do przerostu lewej komory serca, pogarsza filtrację kłębuszkową i wiąże się z rozwojem zmian hiperintensywnych istoty białej mózgu (WMH). Pacjenci z SH często mają również nieprawidłowy dobowy profil ciśnienia tętniczego, z brakiem jego fizjologicznego spadku w godzinach nocnych a u części ze wzrostem powyżej wartości obserwowanych w ciągu dnia¹⁶. Nieprawidłowy dobowy profil ciśnienia tętniczego zwiększa ryzyko chorób sercowo-naczyniowych oraz również może prowadzić do rozwoju WMH¹⁷. W badaniu Tanaki obejmującym 137 pacjentów z PD wzrost ciśnienia w godzinach nocnych wiązał się ze zwiększonym ryzykiem rozwoju otępienia¹⁸. W innym

badaniu, do którego włączono 87 chorych, nieleczonych dotychczas dopaminergicznie, taką zależność zaobserwowano dla OH, SH i WMH, ale nie dla braku spadku ciśnienia w godzinach nocnych¹⁶.

Zmienność ciśnienia tętniczego (BPV), mierzona za pomocą takich wskaźników jak odchylenie standardowe (SD), współczynniki zmienności (CV) czy średnia rzeczywista zmienność (ARV) dla SBP i DBP, opisuje wahania wartości ciśnienia tętniczego w danym przedziale czasowym¹⁹. Długookresowa BPV, oceniana np. na podstawie pomiarów wykonywanych na kolejnych wizytach ambulatoryjnych w ciągu miesięcy lub lat, w populacji ogólnej, ma związek z pogorszeniem funkcji poznawczych²⁰. Sztywność tętnic związana ze starzeniem się, podwyższone wartości BP oraz zmniejszona objętość hipokampa może stanowić mechanizm leżący u podłoża związku między zmiennością SBP a zaburzeniami funkcji poznawczych.²¹ Natomiast wyższa zmienność DBP koreluje z większą objętością WMH, dysfunkcją śródbłonna oraz zwiększoną aktywnością układu współczulnego.^{21,22} Dodatkowo niestabilność hemodynamiczna wywołana zwiększoną BPV może prowadzić do hipoperfuzji OUN²³. W grupie chorych z PD zmienność ciśnienia tętniczego jest wyższa niż w populacji ogólnej^{24,25}. Alves i wsp. (2023) wykazali również tendencję do bezobjawowego uszkodzenia narządowego (zwiększona grubość kompleksu intima-media tętnic szyjnych, obecność blaszek miażdżycowych w odcinkach zewnątrzczaszkowych oraz podwyższone ciśnienie tętna) u pacjentów z PD z wyższą zmiennością SBP, co pozostaje w zgodzie z wyżej opisanymi badaniami opartymi na populacji ogólnej²⁴. W przypadku krótkookresowej oceny BPV analizowany jest okres 24h, a dane pochodzą z automatycznego, całodobowego monitorowania ciśnienia tętniczego (ABPM). Niewiele badań oceniało wpływ krótkookresowej BPV na funkcje poznawcze u pacjentów z PD, a ich wyniki są niespójne i trudne do porównania, ponieważ w analizach stosowano różne wskaźniki oceny. Dodatkowo współistnienie chorób sercowo naczyniowych nie stanowiło wykluczającego kryterium uczestnictwa w opublikowanych dotychczas badaniach. W większości badań wykorzystujących klasyczne wskaźniki wykazano istotne zwiększenie jedynie dziennej BPV w porównaniu z osobami zdrowymi^{23–25}. Odchylenie standardowe oraz CV obliczane dla okresu nocnego i 24-godzinnego mogą nie odzwierciedlać właściwie zmienności ciśnienia tętniczego w tej grupie pacjentów z powodu braku nocnego spadku ciśnienia tętniczego.

Obwodowy układ renina–angiotensyna-aldosteron (RAA) uczestniczy w regulacji ciśnienia tętniczego, utrzymaniu równowagi wodno-elektrolitowej oraz kontroli ogólnoustrojowego oporu naczyniowego, przez co pośrednio może wpływać na OUN. Jego składowe nie przenikają bariery krew-mózg. Angiotensynogen (AGT), prekursor angiotensyny II (Ang II), syntetyzowany jest głównie w wątrobie. W krwiobiegu, pod wpływem reniny uwalnianej przez nerki, przekształcany jest do nieaktywnej angiotensyny I (Ang I). Angiotensyna II, stanowiąca główny efektor klasycznego ramienia RAA, powstaje z Ang I przy udziale enzymu konwertującego angiotensynę (ACE). Aktywuje ona receptory typu 1 (AT1R), co prowadzi do skurczu naczyń oraz retencji sodu i wody, skutkując wzrostem ciśnienia tętniczego²⁶. Angiotensyna II, w tzw. alternatywnym szlaku, może również oddziaływać na receptory typu 2 (AT2R) oraz ulegać przekształceniu przez enzym konwertujący angiotensynę 2 (ACE2) do angiotensyny-(1–7), która wiąże się z receptorem Mas, bądź – pod wpływem aminopeptydaz A i N – do angiotensyny IV (Ang IV), oddziałującej z receptorami typu 4 (AT4R). Angiotensyna-(1–7) może także powstawać bezpośrednio z Ang I. Alternatywne ramie RAA wywiera efekty przeciwstawne wobec szlaku Ang II/AT1R, obejmujące rozszerzenie naczyń, poprawę funkcji odruchu z baroreceptorów oraz redukcję stanu zapalnego i stresu oksydacyjnego²⁶.

Ośrodkowy układ nerwowy posiada własny tkankowy układ RAA. Astrocyty są zdolne do syntezy AGT. Wysoką ekspresję ACE stwierdza się m.in. w szlaku nigrostriatalnym i jądrach podstawy. Enzym konwertujący angiotensynę inaktywuje substancję P oraz metabolizuje bradykininę, a oba te procesy mogą mieć znaczenie w patogenezie PD. W neuronach dopaminergicznych istoty czarnej obecne są receptory AT1R i AT2R, dodatkowo ekspresja AT1R jest zwiększona w modelach zwierzęcych PD. Pobudzenie receptorów AT1R aktywuje kompleks oksydazy NADPH, co skutkuje zwiększoną produkcją reaktywnych form tlenu i nasileniem stresu oksydacyjnego, co prowadzi do apoptozy, obejmującej również neurony dopaminergiczne^{27,28}.

Niedawno opublikowana metaanaliza sugeruje związek pomiędzy stosowaniem inhibitorów RAA a zmniejszonym ryzykiem rozwoju PD²⁹. Ponadto stosowanie leków z tej grupy, zdolnych do przenikania przez barierę krew-mózg, może wiązać się z wolniejszą progresją zaburzeń pamięci w populacji ogólnej³⁰. Efekt ten może wynikać ze zmniejszenia stresu oksydacyjnego oraz ograniczenia

utraty neuronów dopaminergicznych poprzez modulację funkcji mitochondriów. Sugeruje to, że tkankowy (mózgowy) układ RAA może uczestniczyć w procesie neurodegeneracji dopaminergicznej oraz progresji PD.

Dane literaturowe wskazują, że określone polimorfizmy genu AGT (AGT: rs699 A>G, rs4762 G>T), genów receptorów AT1R i AT2R (ATR1: rs5186, ATR2: rs5194, rs1403543) oraz genu ACE (genotyp DD, delecyjny) są związane ze zwiększoną aktywnością RAA^{31,32}. Zależność między zmiennością genetyczną w układzie RAA a funkcjami poznawczymi w PD oceniono dotychczas w jednym badaniu.³³ Pomimo braku bezpośredniej korelacji między badanymi polimorfizmami a rozwojem otępienia w PD, autorzy sugerują pośredni wpływ tych genotypów na funkcje poznawcze, np. poprzez związek z rozwojem zmian WMH albo modyfikacją odpowiedzi na inhibitory enzymu konwertującego angiotensynę.

Zmiany hiperintensywne istoty białej widoczne w sekwencjach T2- zależnych w badaniu rezonansu magnetycznego mózgowia są radiologicznym markerem jej uszkodzenia. Mogą powstawać w wyniku choroby małych naczyń w przebiegu schorzeń sercowo-naczyniowych (takich jak np. cukrzyca czy nadciśnienie tętnicze), wtórnie do opisanych wyżej zaburzeń regulacji ciśnienia tętniczego wynikających z dysautonomii czy w przebiegu procesów neurozwyrodnieniowych (np. angiopatii amyloidowej).³⁴ Ich nasilenie może mieć związek z pogorszeniem funkcji poznawczych w PD ³⁵, zwłaszcza z zaburzeniami funkcji wykonawczych, językowych i pamięcią. ³⁶ Zależność ta jest jednak niejednoznaczna i wymaga dalszych analiz, gdyż nie we wszystkich badaniach ją potwierdzono.³⁷

Również stosowane leczenie dopaminergiczne, niezależnie od występowania zaburzeń autonomicznych, może obniżać wartości ciśnienia tętniczego w PD. ³⁸ Mechanizm w jakim do tego dochodzi nie jest do końca poznany. Spekuluje się, że lewodopa może wywierać taki wpływ m.in. poprzez efekt kardiodepresyjny, ośrodkowe hamowanie układu współczulnego, zmniejszone uwalnianie noradrenaliny z zazwojowych włókien współczulnych oraz zwiększoną natriurezę.^{39,40}

W populacji pacjentów z PD zaburzenia regulacji ciśnienia tętniczego mają zatem charakter wieloczynnikowy. Istotną rolę mogą odgrywać m.in. leczenie dopaminergiczne, aktywność układu RAA, predyspozycje genetyczne oraz współistniejąca dysautonomia. Radiologicznym markerem tych zaburzeń mogą

być zmiany istoty białej typu WMH, które potencjalnie wiążą się ze zwiększonym ryzykiem rozwoju zaburzeń funkcji poznawczych. Poznanie zależności między tymi zmiennymi może pozwolić na wyodrębnienie, już na wczesnym etapie choroby, grupy pacjentów szczególnie narażonych na ryzyko rozwoju otępienia.

VI. CELE PRACY

Celem pracy było określenie roli wybranych czynników naczyniowych, warunkujących przepływ krwi w ośrodkowym układzie nerwowym przez wpływ na regulację ciśnienia tętniczego, w patogenezie otępienia w chorobie Parkinsona.

Cele szczegółowe pracy obejmowały:

- ocenę wpływu krótkookresowej zmienności ciśnienia tętniczego (BPV) na ryzyko wystąpienia otępienia
- ocenę wpływu krótkookresowej BPV na ryzyko wystąpienia zmian hiperintensywnych istoty białej mózgu (WMH) oraz ich korelacja z otępieniem
- ocenę związku hipotonii ortostatycznej (OH), nadciśnienia tętniczego w pozycji leżącej (SH) oraz zaburzeń profilu dobowego ciśnienia tętniczego (BP) z ryzykiem wystąpienia otępienia oraz WMH
- ocenę wpływu leków dopaminergicznych, ze szczególny uwzględnieniem lewodopy i agonistów receptorów dopaminergicznych, na krótkookresową BPV, OH i SH, profil dobowy BP oraz na ryzyko wystąpienia otępienia i WMH
- ocenę wpływu wybranych czynników naczyniowych (renina, aktywność reninowa osocza, angiotensyna II, aldosteron), metabolicznych (homocysteina, kwas foliowy, witamina B12) oraz genetycznych (polimorfizm genu angiotensynogenu, genu enzymu konwertującego angiotensynę I, receptorów dla angiotensyny II typu 1 i typu 2) na ryzyko rozwoju otępienia oraz ich związek z krótkookresową BPV i rozwojem WMH

VII. MATERIAŁ I METODY

A) Grupa badana

W przekrojowym badaniu wzięto udział 65 pacjentów z rozpoznaną na podstawie kryteriów Movement Disorders Society (MDS)⁴¹ idiopatyczną chorobą Parkinsona z Poradni Neurologicznej Szpitala św. Wojciecha w Gdańsku. Badanie zostało pozytywnie zaopiniowane przez Niezależną Komisję Bioetyczną ds. Badań Naukowych przy Gdańskim Uniwersytecie Medycznym (NKBBN/415/2018).

Kryteria wykluczenia obejmowały:

- parkinsonizm wtórny lub atypowy
- leczenie terapiami infuzyjnymi lub głęboką stymulacją mózgu
- choroby układu sercowo-naczyniowego (nadciśnienie tętnicze, choroba niedokrwienna serca, niewydolność krążenia, migotanie przedsionków), cukrzycę, niewydolność nerek lub wątroby
- przyjmowanie leków wpływających na układ renina-angiotensyna-aldosteron
- przeciwwskazania do wykonania badania rezonansu magnetycznego (MRI)

Nasilenie objawów PD oraz stadium jej zaawansowania zostały ocenione u wszystkich pacjentów przez tego samego neurologa (autora) następującymi skalami:

- Unified Parkinsons Disease Rating Scale (UPDRS) część III w stanie ON (zaburzenia ruchowe)
- Hoehn-Yahr (stopień zaawansowania klinicznego choroby)
- Schwab-England (poziom samodzielności w codziennych czynnościach)
- Non-Motor Symptoms Questionnaire (NMSQ) (występowanie objawów pozaruchowych)

Wszyscy pacjenci otrzymywali leczenie dopaminergiczne. Dawki przyjmowanych preparatów lewodopy, agonistów dopaminergicznych,

inhibitorów monoaminooksydazy typu B, inhibitorów katecholo-O-metylotransferazy oraz amantadyny przeliczono na dawki równoważne lewodopie (LEDD). Ponieważ wszyscy chorzy, z wyjątkiem dwóch, przyjmowali preparaty lewodopy, a większość stosowała również agonistów receptorów dopaminowych, wpływ tych dwóch grup leków na badane zmienne dodatkowo przeanalizowano osobno. Dawki agonistów receptorów dopaminowych zostały przeliczone na dawki równoważne ropinirolu.⁴²

Dwóch uczestników wykluczono z badania z powodu zdiagnozowania cukrzycy typu 2, już po otrzymaniu wyników wykonanych badań.

B) Badanie psychologiczne

Ocenę funkcji poznawczych przeprowadziła grupa trzech neuropsychologów według tej samej metodyki badania. Oceny przesiewowej dokonano z wykorzystaniem Montrealskiej Skali Oceny Funkcji Poznawczych (MoCA). Do oceny każdej z domen poznawczych zastosowano dwie skale:

- funkcje wzrokowo-przestrzenne: Visual Object and Space Perception Battery (VOSP, część przesiewowa oraz podtesty: Niekompletne litery, Liczenie kropek, Analiza sześciątów), Benton Judgment of Line Orientation (JOLO)
- pamięć epizodyczna i uczenie się: Kalifornijski Test Uczenia się Językowego (CVLT), Continuous Visual Memory Test (CVMT)
- uwaga, pamięć bezpośrednia i operacyjna: podskala powtarzania cyfr ze Skali Inteligencji Wechslera dla Dorosłych (WAIS), Corsi Block Tapping Test
- funkcje językowe: Bostoński Test Nazywania (BNT), rozumienie poleceń przestrzennych oraz konstrukcji fleksyjnych z baterii testów Łuckiego i Maruszewskiego
- funkcje wykonawcze: test wieży z Delis-Kaplan Executive Function System (D-KEFS), Test fluencji słownej (fonemiczna – K, semantyczna – zwierzęta i przedmioty ostre, COWAT), prakcja dynamiczna (Alternating Motor Pattern)
- ocena nastroju: Geriatryczna Skala Oceny Depresji

Łagodne zaburzenia poznawcze (MCI) zdefiniowano jako deficyty w zakresie jednej domeny poznawczej, a otępienie jako zaburzenia w zakresie więcej niż jednej domeny poznawczej z negatywnym wpływem na codzienne funkcjonowanie chorego, zgodnie z kryteriami Litvan i in. (2011)⁴³ oraz Emre i in. (2007)⁴⁴. Na podstawie badania neuropsychologicznego kohortę podzielono na trzy grupy: PD z prawidłowymi funkcjami poznawczymi (PD-NC), PD z łagodnymi zaburzeniami poznawczymi (PD-MCI) oraz PD z otępieniem (PDD).

C) Pomiary i ocena zmienności ciśnienia tętniczego

Do pomiarów ciśnienia tętniczego użyto naramiennego elektronicznego ciśnieniomierza. Pomiary wykonano po co najmniej 5 minutach odpoczynku w pozycji leżącej. Nadciśnienie w pozycji leżącej definiowano jako skurczowe ciśnienie krwi (SBP) ≥ 140 mmHg lub rozkurczowe (DBP) ≥ 90 mmHg. Aby rozpoznać hipotonię ortostatyczną (OH) wykonano test pionizacyjny. Hipotonię ortostatyczną definiowano jako spadek SBP ≥ 20 mmHg lub spadek DBP ≥ 10 mmHg po 3 minutach pionizacji. Gdy wynik pomiaru był prawidłowy po 3 minutach, badanie przedłużano do 10 minut i ciśnienie mierzono dodatkowo po 5 i 10 minutach.

U chorych przeprowadzono 24 godzinne ambulatoryjne monitorowanie ciśnienia krwi (ABPM) urządzeniem Watch BP03 na niedominującym ramieniu. Pomiary wykonywano co 20 minut między godziną 6:00 a 22:00 i co 30 minut między 22:00 a 6:00. Na podstawie uzyskanych wyników oceniono dobowe profile ciśnienia tętniczego – obliczane jako procentowa zmiana między średnim ciśnieniem tętniczym w ciągu dnia i w nocy. Klasyfikacja profili w zależności od wartości spadku nocnych wartości była następująca: reverse dipper $<0\%$, non-dipper $0-10\%$, dipper $10-20\%$, extreme-dipper $>20\%$.

Ocena wskaźników krótko-okresowej zmienności ciśnienia tętniczego (BPV) w oparciu o ABPM obejmowała:

- odchylenie standardowe (SD) liczone osobno dla SBP i DBP dla wartości z dnia, nocy i z 24 godzin
- współczynnik zmienności (CV, SD podzielone przez odpowiednią średnią) liczone osobno dla SBP i DBP dla wartości z dnia, nocy i z 24 godzin

- średnią rzeczywistą zmienność (ARV, obliczaną jako średnia bezwzględnych różnic między kolejnymi pomiarami ciśnienia) dla SBP i DBP w ciągu 24 godzin

D) Badania laboratoryjne

Próbki krwi żyłnej pobierane były na czczo około godziny 7 rano, po minimum 8 godzinnej przerwie w przyjmowaniu leków dopaminergicznych. Oceniono morfologię krwi obwodowej, lipidogram, wskaźnik filtracji kłębuszkowej, poziom kreatyniny, glukozy, aminotransferazy alaninowej, aminotransferazy asparaginianowej, hormonu tyreotropowego, homocysteiny, witaminy B12, kwasu foliowego. Ze składowych układu renina-angiotensyna-aldosteron (RAA) oznaczono poziom reniny, aktywności reninowej osocza (ARO), angiotensyny II (AngII), aldosteronu. Próbkę krwi do oznaczenia ARO pobierano bez użycia stazy, następnie niezwłocznie wirowano, a osocze szybko zamrażano. Rutynowe badania biochemiczne wykonywano przy użyciu analizatorów Cobas 6000/c501 lub Cobas 8000 (Roche Diagnostics Ltd.). Aktywność reninową osocza oznaczano metodą radioimmunologiczną za pomocą zestawu AngI RIA KIT (Beckman Coulter, Immunotech, Praga, Czechy). Stężenia aldosteronu i Ang II oznaczano metodą immunoenzymatyczną (ELISA) przy użyciu odpowiednio zestawu DRG (DRG Instruments GmbH, Marburg, Niemcy) oraz zestawu QAYEE-BIO (Shanghai Qayee Biotechnology Co., Ltd., Chiny).

E) Badania genetyczne

Genomowe DNA wyizolowano z 1 ml próbki krwi obwodowej pobranej od każdego pacjenta do probówek z EDTA, stosując zestaw Genomic Mini AX Blood 1000 Spin (A&A Biotechnology, Gdynia, Polska). Wyizolowane DNA następnie rozcieńczano do stężenia 20 ng/μL na podstawie pomiaru absorbancji spektrofotometrycznej (260/280 nm) przy użyciu spektrofotometru/fluorymetru DeNovix DS-11 FX+ (Wilmington, DE, USA).

Genotypowanie następujących polimorfizmów pojedynczego nukleotydu (SNP) w genach angiotensynogenu (AGT: rs699 A>G, rs4762 G>T) oraz receptorów Ang II (ATR1: rs5186 A>C, ATR2: rs5194 A>G; rs1403543 A>G) przeprowadzono z wykorzystaniem dyskryminacji allelicznej z zastosowaniem znakowanych sond TaqMan, metodą PCR w czasie rzeczywistym (Life Technologies, Waltham, MA,

USA; identyfikatory testów TaqMan: C___1985481_20, C___1985480_20, C___3187716_10, C___1841567_20, C___7481825_10, odpowiednio) oraz TaqMan GTXpress Master Mix (Life Technologies, Waltham, MA, USA).

Wszystkie reakcje prowadzono w duplikatach w końcowej objętości 12 μ L (profil temperaturowy reakcji: 95°C, 20 s; 40 $\times$ 95°C 1 s / 60°C 20 s; 40 cykli reakcji).

Genotypowanie przeprowadzono przy użyciu systemu ViiA7 Real-Time PCR (Applied Biosystems, Waltham, MA, USA). Genotypy przypisywano poszczególnym próbkom na podstawie analizy z wykorzystaniem oprogramowania TaqMan Genotyper (Thermo Fisher Scientific, Waltham, MA, USA).

Polimorfizm (insercja/delecja, I/D) w genie konwertazy angiotensyny (ACE) analizowano metodą PCR z zastosowaniem drugiej rundy amplifikacji u homozygotycznych nosicieli allelu D (ze względu na preferencyjną amplifikację allelu D). Genotypy ACE I/D określano poprzez rozdział produktów PCR w 3% żelu agarozowym z bromkiem etydy (1 μ g/mL) w świetle UV. Jako bufor zastosowano 1X Tris–boran–EDTA (TBE) (Thermo Scientific, USA).

F) Badanie rezonansu magnetycznego głowy

Badanie rezonansu magnetycznego głowy aparatem 3 T - Philips Achieva, Holandia, wykonano w II Zakładzie Radiologii GUMed. Do oceny nasilenia WMH w skali Fazekas wykorzystano sekwencje FLAIR (fluid-attenuated inversion recovery) w projekcji osiowej o parametrach: TR = 4800 ms, TE = 284,1 ms, FOV = 250 $\times$ 250 mm, kąt odchylenia 40°, wielkość wokseli 1,12 $\times$ 1,12 $\times$ 1,12 mm oraz grubość warstwy 1 mm. Do analiz statystycznych uwzględniono wynik odnoszący się do zmian w głębokiej istocie białej.

G) Analiza statystyczna

Test Shapiro–Wilka zastosowano do oceny normalności rozkładu danych demograficznych i klinicznych. Następnie przeprowadzono jednoczynnikową analizę wariancji (ANOVA) dla danych parametrycznych oraz jednoczynnikowy nieparametryczny test Kruskala–Wallisa. W analizach post hoc dla danych parametrycznych i nieparametrycznych użyto odpowiednio testu Tukeya oraz testu Dunna. Do oceny zależności między dwiema zmiennymi ilościowymi

zastosowano współczynnik korelacji ρ Spearmana. Porównania dla zmiennych kategoryalnych przeprowadzono za pomocą testów χ^2 . W przypadku trudności z wyznaczeniem wartości p na podstawie asymptotycznego rozkładu χ^2 statystyki testowej, wartość tę określano za pomocą symulacji Monte Carlo z 2000 powtórzeń. Do oceny korelacji między dwiema zmiennymi nominalnymi zastosowano współczynnik V Cramera.

Zbudowano także modele regresji porządkowej, w których zmiennymi zależnymi były kategorie opisujące funkcje poznawcze pacjentów, a zmiennymi niezależnymi — wartości charakteryzujące badanych chorych. Następnie przeprowadzono wielowymiarowe analizy regresji z wykorzystaniem metody progresywnej selekcji krokowej (porównywanymi parametrami były: kryterium informacyjne Akaikego — AIC, bayesowskie kryterium informacyjne — BIC oraz wartość p).

Krzywe ROC (Receiver Operating Characteristic) wyznaczono na podstawie modeli regresji logistycznej stworzonych dla pacjentów z prawidłowymi funkcjami poznawczymi oraz otępieniem, tak aby spełnić dwukategoryjne wymagania tej metody.

Przeprowadzono analizę mediacji, aby zbadać, czy krótkookresowa BPV pośredniczy w wpływie RAA na funkcje poznawcze.

Obliczenia wykonywano z użyciem funkcji i procedur środowiska R (R Core Team 2024). Poziom istotności statystycznej ustalono na $\alpha = 0.05$.

VIII. OMÓWIENIE PUBLIKACJI WCHODZĄCYCH W SKŁAD ROZPRAWY DOKTORSKIEJ

W skład rozprawy doktorskiej wchodzić dwie prace poglądowe i dwie prace oryginalne opublikowane w międzynarodowych, recenzowanych czasopismach naukowych.

Publikacja 1.

Cardiovascular dysautonomia and cognition in Parkinson's Disease -a possible relationship. (IF 2,223)

W omawianym artykule poglądowym scharakteryzowano wybrane aspekty zaburzeń sercowo-naczyniowych o podłożu autonomicznym u pacjentów z PD. Jej celem była analiza ich możliwego związku z zaburzeniami funkcji poznawczych oraz opisanie możliwości terapeutycznych. Zarówno zaburzenia autonomiczne jak i pogorszenie funkcji poznawczych należą do częstych objawów pozaruchowych mogących występować już na wczesnym etapie PD i istotnie obniżać jakość życia nie tylko pacjentów, ale także ich opiekunów.

We wstępie krótko podsumowano znane czynniki rozwoju otępienia u chorych z PD i podkreślono jego wieloczynnikową etiologię. Zawiera on również schemat mogący tłumaczyć wpływ zaburzeń autonomicznych na rozwój zaburzeń poznawczych. W dalszej jego części wymienione zostały zajęte przez proces chorobowy w PD struktury ośrodkowego i obwodowego układu nerwowego związane z rozwojem zaburzeń autonomicznych.

W głównej części artykułu scharakteryzowano kolejno najczęściej występujące zaburzenia sercowo-naczyniowe, tj. OH, SH oraz brak fizjologicznego spadku ciśnienia tętniczego w godzinach nocnych. Dla każdego z objawów podano kryteria rozpoznania, czynniki mające wpływ na ich nasilenie, wymieniono objawy kliniczne oraz możliwy mechanizm łączy je z rozwojem otępienia. Podkreślono rolę diagnostyczną 24 godzinnego ambulatoryjnego monitorowania ciśnienia tętniczego krwi i dołączono przykładowy, nieprawidłowy wynik badania pacjenta z PD w formie wykresu. Przytoczono również wyniki

dostępnych badań naukowych oceniających te zależności wśród pacjentów z PD.

W kolejnej części pracy przedstawione zostały opcje terapeutyczne dostępne w leczeniu zaburzeń autonomicznych, ze szczególnym uwzględnieniem preparatów stosowanych w leczeniu OH.

W zakończeniu podkreślono złożoność procesów mających wpływ na rozwój otępienia oraz niejednoznaczne wyniki dostępnych badań oceniających jego związek z dysautonomią sercowo-naczyniową i wynikającą z tego potrzebę kontynuowania badań w tym zakresie.

Publikacja 2.

Arterial Blood Pressure Variability and Other Vascular Factors Contribution to the Cognitive Decline in Parkinson's Disease. (IF 4,927)

Praca poglądowa w szerokim zakresie omawia wpływ czynników naczyniowych i metabolicznych na funkcje poznawcze w PD. Występująca w PD dysautonomia zaburza regulację BP, co może objawiać się jako OH, SH czy brak fizjologicznego spadku BP w godzinach nocnych. Zaburzenia te mogą prowadzić do przewlekłego niedokrwienia i uszkodzenia istoty białej OUN, widocznego jako WMH w badaniach obrazowych. W artykule przedstawiono wyniki dotychczasowych badań opublikowanych w bazie PubMed opisujących te zagadnienia. Pomimo iż badania charakteryzowały się różną metodologią, wydaje się, że zaburzenia te mogą wiązać się z pogorszeniem funkcji wykonawczych, uwagi i pamięci.

W publikacji zwrócono także uwagę na możliwe działania niepożądane stosowanego leczenia dopaminergicznego. Lewodopa oraz leki z grupy agonistów receptorów dopaminowych mogą nasilać OH i tym samym zwiększać dobowe wahania ciśnienia tętniczego. W niektórych badaniach przyjmowanie wyższych dawek lewodopy korelowało z nasileniem zaburzeń funkcji poznawczych. Częściowo może to wynikać ze zwiększonego stężenia homocysteiny w tej grupie chorych, co prowadzi do uszkodzenia śródbłonna naczyń i nasilenia stresu oksydacyjnego. Przewlekłe stosowanie lewodopy wiąże

się również ze zwiększoną ekspresją czynnika wzrostu śródbłonna naczyniowego (VEGF). Jego nadmierna aktywność sprzyja uszkodzeniu naczyń i zwiększa przepuszczalność bariery krew-mózg, prowadząc do uszkodzenia istoty białej.

W pracy zwrócono również uwagę na potencjalną rolę układu RAA w rozwoju zaburzeń poznawczych, który reguluje ciśnienie tętnicze a na poziomie tkankowym procesy zapalne i związane ze stresem oksydacyjnym.

W publikacji analizowano również znaczenie wybranych polimorfizmów genów kodujących katecholo-O-metylotransferazę (COMT), apolipoproteinę E, VEGF oraz elementy układu RAA w powstawaniu otępienia w PD.

W pracy podkreślono potencjalną zależność między czynnikami naczyniowymi a neurodegeneracyjnymi w rozwoju zaburzeń funkcji poznawczych. Wczesna identyfikacja oraz leczenie modyfikowalnych czynników naczyniowych i metabolicznych, takich jak np. SH lub podwyższony poziom homocysteiny, może mieć korzystny wpływ na funkcje poznawcze w PD.

Publikacja 3.

The impact of short-term blood pressure variability on cognitive decline in Parkinson's disease patients without co-morbidities. (IF 4,0)

Celem pracy była ocena wpływu krótkookresowej BPV oraz wybranych zaburzeń regulacji ciśnienia tętniczego krwi (OH, SH, braku fizjologicznego spadku ciśnienia tętniczego w godzinach nocnych) na rozwój zaburzeń poznawczych u pacjentów z PD bez chorób współistniejących oraz nieprzyjmujących leków wpływających na układ sercowo-naczyniowy.

Według wiedzy autorów jest to pierwsze badanie oceniające wpływ krótkookresowej BPV na funkcje poznawcze u pacjentów z chorobą Parkinsona bez obciążeń internistycznych mogących wpływać na układ sercowo-naczyniowy.

Do badania włączono 63 chorych (25 kobiet) z idiopatyczną chorobą Parkinsona. Przy użyciu wymienionych w rozdziale „Materiał i metody” skal dokonano oceny stopnia zaawansowania choroby. Zebrano wywiad dotyczący wykształcenia, czasu trwania choroby, stosowanej farmakoterapii. Wszystkich pacjentów zbadał ten sam neurolog. Na podstawie wyników badania psychologicznego pacjenci zostali przydzieleni do grupy: w normie poznawczej (20 chorych), z łagodnymi zaburzeniami poznawczymi (23 chorych) lub z otępieniem (20 chorych). Pacjenci w normie poznawczej byli istotnie młodszy, lepiej wykształceni oraz mieli łagodniejszy przebieg choroby niż chorzy z otępieniem. Grupy nie różniły się pod względem czasu trwania choroby lub stosowanego leczenia dopaminergicznego.

W oparciu o wyniki przeprowadzonej próby ortostatycznej u 33% pacjentów rozpoznano OH, u 31% SH a u 14% współwystępowały oba zaburzenia. Pomimo iż częstość występowania OH nie różniła istotnie między grupami, jej obecność korelowała z większym nasileniem zaburzeń pamięci werbalnej oraz funkcji wzrokowo-przestrzennych, językowych i wykonawczych. Spadek DBP korelował LEDD ($p = 0,46$, $p = 0,0001$) oraz niezależnie z dawką przyjmowanej lewodopy ($p = 0,44$, $p = 0,0003$).

Nadciśnienie w pozycji leżącej było związane z występowaniem otępienia (Cramer V = 0,2562, $p = 0,0473$).

Zaobserwowano korelację na poziomie trendu między mniejszym nocnym spadkiem ciśnienia tętniczego ($\% \Delta$ MAP), odwróconym profilem dobowym ciśnienia tętniczego („reverse dipping”) a pogorszeniem funkcji poznawczych (odpowiednio: Cramer V = 0,2971; $p = 0,09$ oraz Cramer V = 0,2971; $p = 0,08$).

Odchylenie standardowe dla DBP z dnia i ARV SBP były istotnie wyższe u chorych z otępieniem. Różnica na poziomie trendu dotyczyła również CV DBP z dnia i ARV DBP. Funkcje wzrokowo-przestrzenne, językowe i wykonawcze negatywnie korelowały z CV DBP dla wartości z dnia. Niższe wartości w skali MoCA i deficyty pamięci wzrokowo-przestrzennej oraz funkcji wykonawczych korelowały z wyższymi wartościami SBP ARV. Stosowana farmakoterapia nie wpływała na badane wskaźniki.

Wyniki badań laboratoryjnych nie różniły się między grupami, poza wyższym poziomem homocysteiny na poziomie trendu u chorych z otępieniem, co korelowało z wyższą dawką przyjmowanej lewodopy.

Jednoczynnikowa analiza regresji wykazała, że zmiennymi istotnie wpływającymi na rozwój otępienia były: wiek, bardziej zaawansowane stadium choroby oceniane w skali Hoehna–Yahra, wyższa punktacja w skali NMSQ, SH, odwrócony dobowy profil ciśnienia tętniczego (reverse dipping) oraz w sposób odwrotnie proporcjonalny: nocny spadek ciśnienia tętniczego, liczba lat edukacji i wynik w skali Schwab–England. Zwiększona zmienność SBP, wyrażona jako ARV, była związana z zaburzeniami funkcji poznawczych na poziomie trendu.

Wieloczynnikowe modele regresji identyfikujące istotne predyktory rozwoju otępienia były porównywalne i nie zawierały wystarczającej liczby parametrów umożliwiających wybór najlepszego modelu.

W analizie krzywych ROC, najwyższą wartość pola pod krzywą (AUC), tym samym najlepszą zdolność predykcyjną otępienia uzyskano dla SBP ARV, DBP ARV oraz dla wartości z dnia dla DBP SD i DBP CV.

Wyniki przeprowadzonego badania sugerują, że krótkookresowa BPV, SH oraz odwrócony dobowy profil ciśnienia tętniczego może mieć związek z rozwojem otępienia u pacjentów z PD.

Publikacja 4.

Peripheral renin-angiotensin system and cognitive decline in Parkinson's disease patients without co-morbidities. (IF 3,4)

Obwodowy układ RAA reguluje wysokość ciśnienia tętniczego oraz bierze udział w procesach zapalnych i związanych ze stresem oksydacyjnym. Celem badania była ocena zależności między obwodowym układem RAA a funkcjami poznawczymi u pacjentów z chorobą Parkinsona, bez obciążeń internistycznych i leków wpływających na ten układ. Dodatkowo oceniono wpływ układu RAA na krótkookresową BPV oraz na wybrane zaburzenia regulacji ciśnienia tętniczego

krwi (OH, SH, braku fizjologicznego spadku ciśnienia tętniczego w godzinach nocnych).

Do badania włączono łącznie 63 pacjentów z chorobą Parkinsona z Poradni Neurologicznej przy szpitalu św. Wojciecha w Gdańsku. Metody oceny i charakterystykę badanej grupy omówiono w publikacji nr 3. U wszystkich pacjentów zgodnie z opisem metody powyżej oznaczono na czczo stężenia reniny, Ang II i aldosteronu w osoczu oraz ARO.

Nie wykazano istotnych statystycznie różnic między ocenianymi składowymi układu RAA a PD-NC, PD-MCI czy PDD. Niemniej w grupie wszystkich chorych ocenianych łącznie wyższe stężenie reniny i wyższa ARO wiązała się z lepszymi wynikami w skalach oceniających funkcje wzrokowo-przestrzenne, fluencję słowną i bezpośrednią pamięć wzrokowo-przestrzenną. Dodatkowo wyższe stężenie reniny korelowało z wyższą punktacją w skalach oceniających funkcje językowe oraz bezpośrednią i odroczoną pamięć słowną. Przeciwnie, wyższe stężenia Ang II wpływały negatywnie na bezpośrednią i odroczoną pamięć słowną oraz na planowanie.

Osoczowe stężenia wybranych zmiennych układu RAA nie wpływały na oceniane zaburzenia regulacji ciśnienia tętniczego ani na krótkookresową BPV, poza ujemną korelacją między stężeniem reniny i ARO a SBP ARV (odpowiednio: Cramer's $V = -0,2549$, $p = 0,05$; Cramer's $V = -0,2555$, $p = 0,04$) oraz między stężeniem reniny a ortostatycznym spadkiem DBP (Cramer's $V = -0,2667$, $p = 0,04$).

Stosowane leczenie dopaminergiczne nie wpływało na układ RAA.

Analiza mediacji wykazała, że SBP ARV pośredniczyła w wpływie reniny i ARO na globalne funkcje poznawcze (ocenione za pomocą skali MoCA), planowanie oraz niektóre aspekty pamięci słownej (krzywa uczenia się). Ortostatyczny spadek DBP nie wykazywał istotnego efektu mediacyjnego między reniną a funkcjami poznawczymi.

Obwodowy układ RAA może wpływać na wybrane funkcje poznawcze w PD. Obniżone stężenia reniny oraz zmniejszona RAA u pacjentów z dysautonomią sercowo-naczyniową mogą sprzyjać zwiększonej krótkookresowej

BPV, ocenianej za pomocą SBP ARV. Dalsze długookresowe badania są niezbędne do pełniejszego wyjaśnienia zależności pomiędzy obwodową RAA, krótkookresową BPV oraz funkcjami poznawczymi w przebiegu choroby Parkinsona.

NIEPUBLIKOWANE WYNIKI

Częstości genotypów badanych polimorfizmów nie odbiegały od przewidywanych na podstawie równowagi Hardy'ego-Weinberga, z wyjątkiem AGT rs699 A>G, ATR1 rs5186 A>C oraz ACE I/D. Nie stwierdzono istotnych różnic w częstościach alleli ani genotypów pomiędzy trzema grupami chorych (Tab.1).

Różnice w nasileniu WMH w skali Fazekas między grupami pacjentów nie były istotne statystycznie ($p= 0,9971$). Oceniane w badaniu zaburzenia regulacji ciśnienia tętniczego, krótkookresowa BPV, stosowane leczenie dopaminergiczne czy czynniki metaboliczne nie wpływały na nasilenie WMH. Najwyższy poziom reniny i ARO był w grupie chorych z najbardziej nasilonymi WMH w badanej grupie (Fazekas 2) (Tab.2).

Polimorfizm	Genotyp/allele	PD-NC (n =20)	PD-MCI (n =23)	PD-D (n =20)	p
AGT rs699 A>G					0.3
	AG	9 (45.0)	9 (39.1)	13 (65.0)	
	GG	8 (40.0)	8 (34.8)	4 (20.0)	
	AA	3 (15.0)	6 (26.1)	3 (15.0)	
	MAF AG+GG	17 (85.0)	17 (73.9)	17 (85.0)	
AGT rs4762 G>T					0.64
	AA	0 (0)	2 (8.7)	2 (10.0)	
	AG	5 (25.0)	6 (26.1)	3 (15.0)	
	GG	15 (75.0)	15 (65.2)	15 (75.0)	
	MAF AG +GG	20 (100)	21 (91.3)	18 (90)	
ATR1 rs5186 A>C					0.82
	AA	10 (50.0)	11 (47.8)	11 (55.0)	
	AC	9 (45.0)	9 (39.1)	6 (30.0)	
	CC	1 (5.0)	3 (13.0)	3 (15.0)	
	MAF AC+CC	10 (50.0)	12 (52.2))	9 (45.0)	
ATR2 rs5194 A>G Mężczyźni+kobiety					0.77
	G	19 (65.5)	22 (68.75)	12 (44.44)	
	A	10 (34.5)	10 (31.25)	15 (55.56)	
	MAF G	19 (65.5)	22 (68.75)	12 (44.44)	
ATR2 rs5194 A>G kobiety					0.67
	GG	4 (44.44)	4 (44.44)	4 (57.14)	
	AG	3 (33.33)	4 (44.44)	2 (28.57)	
	AA	2 (22.23)	1 (11.12)	1 (14.29)	
	MAF AG + GG	7 (77.77)	8 (88.88)	6 (85.71)	
ATR2 rs5194 A>G mężczyźni					0.33
	G	8 (72.72)	10 (71.42)	6 (46.15)	
	A	3 (27.28)	4 (28.57)	7 (53.85)	
	MAF A	8 (72.72)	10 (71.42)	6 (46.15)	

ATR2 rs1403543 A>G				0.72
Mężczyźni + kobiety	A	18 (62.06)	21 (67.74)	11 (40.74)
	G	11 (37.94)	11 (32.26)	16 (59.26)
	MAF G	11 (37.94)	11 (32.26)	16 (59.26)
ATR2 rs 1403543 A>G				0.66
kobiety	AA	4 (44.44)	2 (22.22)	1 (14.3)
	AG	3 (33.33)	5 (55.56)	3 (42.85)
	GG	2 (22.23)	2 (22.22)	3 (42.85)
	MAF AG+GG	5 (55.56)	7 (77.78)	6 (85.7)
ATR2 rs1403543 A>G				0.42
mężczyźni	A	7 (63.63)	10 (71.42)	7 (53.85)
	G	4 (36.36)	4 (28.57)	6 (46.15)
	MAF G	4 (36.36)	4 (28.57)	6 (46.15)
ACE				0.17
	D/D	6 (30.0)	3 (13.0)	2 (10.0)
	I/D	7 (35.0)	16 (69.6)	12 (60.0)
	I/I	7 (35.0)	4 (17.4)	6 (30.0)
	MAF ID+II	14 (70)	20 (87)	18 (90)

Tab.1. Częstości występowania badanych polimorfizmów u pacjentów z chorobą Parkinsona bez zaburzeń poznawczych (PD-NC), z łagodnymi zaburzeniami poznawczymi (PD-MCI) oraz u pacjentów z otępieniem w przebiegu choroby Parkinsona (PDD).

AGT – angiotensynogen, ATR1 – receptor angiotensyny II typu 1, ATR2 – receptor angiotensyny II typu 2, ACE – enzym konwertujący angiotensynę, I – insercja, D – delecja, MAF – częstość występowania rzadszego allelu

	Zmiany hiperintensywne istoty białej				
	Fazekas 0 (n = 8)	Fazekas 1 (n = 35)	Fazekas 2 (n = 15)	p	Post-hoc
SBP SD dzień	14 (4 - 18)	11 (6 - 57)	12 (6 - 24)	0.55 ^a	-
SBP SD noc	10 (4 - 15)	9 (3 - 19)	10 (3 - 22)	0.67 ^a	-
SBP SD dobowe	14.5 (7 - 15)	12 (6 - 41)	12 (7 - 21)	0.71 ^a	-
SBP CV dzień	0.114 (0.0348 - 0.151)	0.0887 (0.0488 - 0.413)	0.099 (0.0588 - 0.178)	0.53 ^a	-
SBP CV noc	0.0908 (0.0323 - 0.13)	0.0707 (0.0261- 0.142)	0.0789 (0.027- 0.204)	0.44 ^a	-
SBP CV dobowe	0.123 (0.0625 - 0.128)	0.099 (0.0492 - 0.355)	0.0973 (0.068 - 0.168)	0.67 ^a	-
SBP ARV	10.1 (7.39 - 11.5)	9.87 (5.78 -18)	9.21 (6.65 -13.4)	0.52 ^a	-
DBP SD dzień	8 (4 - 10)	7 (4 - 54)	7 (4 - 27)	0.76 ^a	-
DBP SD noc	7 (5 - 15)	6 (3 - 15)	7.5 (3 - 16)	0.32 ^a	-
DBP SD dobowe	8 (6 - 11)	8 (4 - 39)	8 (5 - 22)	0.91 ^a	-
DBP CV dzień	0.105 (0.0571 - 0.125)	0.103 (0.0563 - 0.581)	0.094 (0.0597 - 0.307)	0.63 ^a	-
DBP CV noc	0.104 (0.0794 - 0.185)	0.083 (0.0405 - 0.224)	0.101 (0.0357 - 0.25)	0.15 ^a	-
DBP CV dobowe	0.123 (0.0882 - 0.135)	0.119 (0.0548 - 0.523)	0.1 (0.0694 - 0.282)	0.86 ^a	-
DBP ARV	7.15 (5.42 - 8.82)	6.47 (3.61 - 16)	6.23 (4.52 - 9.4)	0.58 ^a	-
ARO	0.52 (0.29 - 4.7)	0.43 (0.1 - 2.74)	0.83 (0.07 - 5.67)	0.04 ^a	Fazekas 1 < Fazekas 2
Renina	10.4 (3.3 - 47)	5.8 (1.1 - 22.1)	10.6 (0.7 - 65)	0.007 ^a	Fazekas 1 < Fazekas 2
Aldosteron	109 (75.7 - 332)	86.1 (37.3 -148)	99.9 (55.4 - 192)	0.15 ^a	-

Angiotensyna II	15 (2.10 - 120)	7.58 (3.25 - 71.7)	11.6 (3.56 - 116)	0.48 ^a	-
Homocysteina	16.1 (6.8 - 19.7)	13.8 (6.8 - 47)	17.2 (9.9 - 26.6)	0.15 ^a	-
B12	319 (191 - 647)	340 (163 - 798)	309 (151 - 766)	0.64 ^a	-
Kwas foliowy	8.78 (4.33 - 17.8)	6.68 (2.49 - 20)	8.02 (2.12 - 15.4)	0.24 ^a	-
ΔMAP %	8.27 (±3.55)	6.17 (±12.3)	7.72 (±8.79)	0.828 ^b	-
Profil dobowy BP	dipper - 25% extreme dipper - 0% inverse dipper - 0% non-dipper - 75%	dipper - 37% extreme dipper - 9% inverse dipper - 34% non-dipper - 20%	dipper - 33.3% extreme dipper - 6.7% inverse dipper - 20% non-dipper - 40%	0.08 ^c	-
SH	Nieobecne - 62.5% Obecne - 37.5%	Nieobecne - 71% Obecne - 29%	Nieobecne - 66.7% Obecne - 33.3%	0.91 ^c	-
Δ SBP (mmHg)	15 (3 - 31)	12 (-12 - 79)	12 (-17 - 63)	0.68 ^a	-
Δ DBP(mmHg)	1 (-6 - 10)	0 (-14 - 34)	-4(-13 - 24)	0.51 ^a	-
OH	Nieobecne - 75% Obecne - 25%	Nieobecne - 69% Obecne - 31%	Nieobecne - 60% Obecne - 40%	0.78 ^c	-
LEDD	1080 (680-1600)	1015 (260-2567)	1100 (550-2180)	0.66 ^a	-

Tab.2. Wartości ocenianych zmiennych a nasilenie WMH w skali Fazekas.

SBP – ciśnienie skurczowe, DBP – ciśnienie rozkurczowe, SD – odchylenie standardowe, CV – współczynnik zmienności, ARV – średnia rzeczywista zmienność, ARO – aktywność reninowa osocza, ΔMAP – spadek średniego ciśnienia tętniczego w godzinach nocnych w porównaniu do wartości z dnia wyrażony w %, BP – ciśnienie tętnicze, SH – nadciśnienie w pozycji leżącej, Δ SBP – ortostatyczny spadek SBP w próbie ortostatycznej, Δ DBP – ortostatyczny spadek DBP w próbie ortostatycznej, OH – hipotonia ortostatyczna, LEDD – dobową dawkę równoważną lewodopy, ^a test Kruskal-Wallis, ^b ANOVA, ^c test χ²

IX. PODSUMOWANIE CAŁOŚCI ROZPRAWY

1. Krótkookresowa zmienność ciśnienia tętniczego w badanej grupie była wyższa u chorych z otępieniem, bez względu na stosowane leczenie dopaminergiczne. Nowe wskaźniki oceniające BPV, takie jak SBP ARV i DBP ARV, które są niezależne od dobowych wahań ciśnienia tętniczego, mogą mieć szczególną wartość kliniczną u chorych z zaburzeniami autonomicznymi. Podwyższona krótkookresowa BPV, zwłaszcza wyższe wartości SBP ARV, u chorych z PD może stanowić czynnik ryzyka rozwoju otępienia.
2. Nadciśnienie w pozycji leżącej oraz zaburzenia dobowego profilu ciśnienia tętniczego (niewielki spadek lub wzrost w godzinach nocnych) korelowały z obecnością otępienia i w analizie jednoczynnikowej istotnie zwiększały ryzyko jego wystąpienia.
3. W grupie chorych z PD, bez towarzyszących chorób sercowo-naczyniowych, krótkookresowa BPV, OH, SH oraz nieprawidłowy dobowy profil ciśnienia tętniczego nie wpływał na nasilenie WMH w skali Fazekas. Stężenie reniny i ARO były wyższe u chorych z najbardziej nasilonymi WMH w badanej grupie. Nie zaobserwowano związku między WMH ocenianym w skali Fazekas a nasileniem zaburzeń poznawczych.
4. Układ RAA nie wpływał bezpośrednio na oceniane zaburzenia regulacji ciśnienia tętniczego ani na krótkookresową BPV, poza ujemną korelacją między stężeniem reniny i ARO a SBP ARV oraz między stężeniem reniny a ortostatycznym spadkiem DBP. Wpływ osocznego układu RAA na funkcje poznawcze w badanej grupie był złożony. Wyższe stężenia reniny i większa ARO wpływały korzystnie na wybrane funkcje poznawcze a w procesie tym częściowo pośredniczyła SBP ARV. Wysokie stężenia Ang II wiązały się z uzyskaniem gorszych wyników w zakresie wybranych domen poznawczych.
5. Oceniane czynniki metaboliczne (poziom witaminy B12, kwasu foliowego, TSH, glukozy) oraz genetyczne (polimorfizm genu AGT, ACE, AT1R, AT2R) nie miały wpływu na krótkookresową BPV, nasilenie WMH oraz ryzyko rozwoju otępienia. Poziom homocysteiny, na poziomie trendu, był wyższy w grupie chorych z otępieniem, co korelowało z przyjmowaną dawką lewodopy.

6. Ołępienie w PD wydaje się mieć podłoże wieloczynnikowe. Współwystępujące u chorych zaburzenia układu autonomicznego, poprzez wpływ na regulację BP, mogą prowadzić do nawracającej hipoperfuzji wybranych obszarów mózgu i przyczyniać się do pogorszenia funkcji poznawczych, nasilając deficyty związane z samym procesem neurodegeneracyjnym.
7. Powyższą hipotezę należy zweryfikować poprzez ocenę wpływu leczenia zaburzeń autonomicznych, w szczególności sercowo-naczyniowych, na rozwój deficytów poznawczych. Monitorowanie ciśnienia metodą ABPM, jako łatwa do wykonania, ogólnie dostępna i tania procedura, powinno być wykonywane w rutynowej opiece nad pacjentami z PD, przy zachowaniu standaryzacji pomiarów. Wczesne rozpoznawanie i leczenie zaburzeń dobowej regulacji ciśnienia może potencjalnie chronić przed dalszym pogorszeniem funkcji poznawczych, co wymaga potwierdzenia w kolejnych badaniach.

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XI. PUBLIKACJE WCHODZĄCE W SKŁAD ROZPRAWY DOKTORSKIEJ



Cardiovascular dysautonomia and cognition in Parkinson's Disease — a possible relationship

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ABSTRACT

Dementia in advanced Parkinson's Disease (PD) is a fatal milestone resulting in reduced life expectancy and nursing home placement. Cognitive impairment and cardiovascular dysautonomia are common and debilitating non-motor symptoms that frequently coexist in PD since the early stages and progress in subsequent years.

In particular, blood pressure (BP) abnormalities, including orthostatic hypotension (OH), supine hypertension (SH) and the loss of nocturnal BP fall (non-dipping) in PD have been associated with cognitive deterioration. They usually have multifactorial aetiology, including neuronal (central and peripheral) mechanisms and concomitant intake of medications. BP abnormalities can influence cognition in many ways, including repeated cerebral hypoperfusion leading to cerebral ischaemic lesions, higher burden of white matter hyperintensities, and possible impact on neurodegenerative process in PD. They are often asymptomatic and remain unrecognised, hence 24-hour ambulatory BP monitoring is recommended in patients with clinical symptoms of dysautonomia. Management is challenging and should address the multifactorial nature of BP disturbances. The aim of this review was to present the state of current knowledge regarding the possible relationship between cardiovascular dysautonomia and cognition in PD, its diagnosis and treatment.

Key words: cognitive impairment, dementia, orthostatic hypotension, Parkinson's Disease, supine hypertension

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Introduction

Parkinson's Disease (PD) is, after Alzheimer's Disease (AD), the most frequent neurodegenerative disorder. Bradykinesia, tremor, rigidity and postural instability are the most prominent motor features. PD pathophysiology includes the impairment of not only dopaminergic but also cholinergic, serotonergic and noradrenergic systems. Therefore, cognitive decline, sleep and mood disorders, gastrointestinal, genitourinary or cardiovascular disturbances are common since early stages and deteriorate with disease progression [1]. Among cardiovascular abnormalities there have been noted

orthostatic hypotension (OH), supine hypertension (SH) and the absence of a decrease of blood pressure (BP) during the night [2]. The aetiology of BP abnormalities in PD patients is multifactorial. It is neurogenic, regarding the pathophysiology of PD and both peripheral and central denervation, but also influenced by treatment, as almost all dopaminergic medications (levodopa, dopamine agonists) can decrease BP [3]. Dysautonomia and Parkinson's Disease-related dementia (PDD) are the most disabling non-motor symptoms resulting in short life expectancy and nursing home placement [4].

The pathogenesis of cognitive impairment in PD remains unclear [5]. Combination of Lewy- and Alzheimer-pathology

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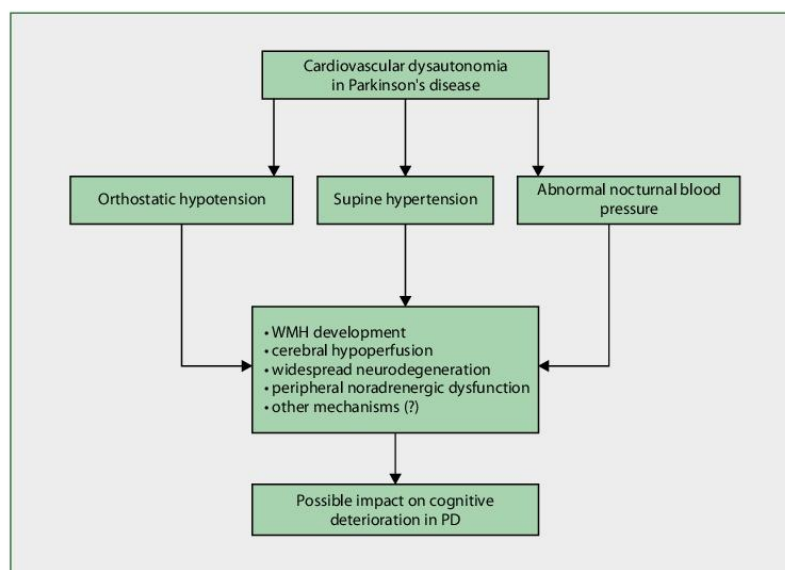


Figure 1. Cardiovascular dysautonomia in Parkinson's Disease: possible mechanisms linking it with cognitive impairment

have presumably an additive effect on cognition impairment [6]. Apolipoprotein E polymorphism ($\epsilon 4$ allele) was also considered as a risk factor for PDD, although results are inconsistent, with negative impacts [7, 8], not confirmed in other studies [9, 10]. Also genetic forms of PD (mutations in: a synuclein gene – SNCA, leucine-rich repeat serine/threonine protein kinase gene – LRRK2) or specific genes variants (glucocerebrosidase – GBA, microtubule-associated protein tau – MAPT, and catechol-*o*-methyl transferase – COMT) can influence cognition in PD [11, 12].

The relationship between cardiovascular risk factors and cognition in PD studies remains inconclusive [13–17].

White matter hyperintensities (WMH) — T2 hyperintense lesions seen on magnetic resonance imaging (MRI) scans, may result from cerebrovascular disease. Several studies have indicated a negative impact of WMH on cognition in PD [2, 14, 18, 19]. Increasing WMH volume leads to deteriorations in executive function, memory and language [20]. Correlation between WMH and progression from mild cognitive impairment (MCI) to PDD has been also described [21]. Higher scores of WMH rating scales have been observed in a group of PD patients with MCI and PDD than in a group with normal cognition [14, 20, 22], but these results were not confirmed in other studies [23, 24].

Autonomic dysfunction, especially BP fluctuations, are an early manifestation of the disease, more pronounced in advanced stages and may result (as part of the neurodegenerative process) in cognitive decline. Its aetiology might be multifactorial and likewise in AD, vascular risk factor potentially might be an important co-factor or even trigger the neurodegeneration.

The aim of this review was to present the current state of knowledge regarding the relationship between cardiovascular dysautonomia (with the particular role of OH, SH and non-dipping effect) and cognition in PD (Fig. 1).

Pathophysiology of dysautonomia in Parkinson's Disease

Structural — central and peripheral nervous system involvement

Autonomic dysfunction in PD has a complex aetiology, involving both central and peripheral mechanisms (Tab. 1) [25]. Neuronal loss and Lewy bodies (with neuronal cytoplasmic inclusions of α -synuclein) are observed not only in the zona compacta of the substantia nigra, but also in regions responsible for the control of autonomic functions such as the hypothalamus, nucleus vagus dorsalis, intermediolateral column of spinal cord and sympathetic ganglia, myenteric and submucosal plexus of intestines [26].

In healthy subjects, baroreceptors response caused by standing results in noradrenaline release from sympathetic post-ganglionic nerves causing vasoconstriction. This mechanism maintains BP in a standing position [27]. Post-ganglionic sympathetic neuron degeneration is the main cause of cardiovascular dysautonomia in PD [27, 28]. Sympathetic denervation of the heart in PD has been shown in ^{123}I -meta-iodobenzylguanidine (MIBG, radioactive molecular analogue of noradrenaline) scintigraphy (low myocardial uptake) and in neuropathological studies (fibres loss) [29, 30]. The neuropathological hallmark of PD – Lewy bodies

Table 1. Central and peripheral autonomic structures affected in Parkinson's Disease (modified according to [25])

Autonomic structures affected in PD			
Central		Peripheral	
Hypothalamus	+	Enteric nervous system	++
Periaqueductal grey	+	Postganglionic sympathetic neurons	++
Ventrolateral medulla	+	Cholinergic sudomotor	+
Medullary raphe	+	Noradrenergic cardiac	+++
Dorsal motor nucleus of vagus	+++	Noradrenergic vasomotor	+
Nucleus ambiguus	+	Adrenal gland	+
Pontine micturition centre	–	Postganglionic parasympathetic neurons	++
Sacral preganglionic neurons	+	Submandibular gland	++
		Gonadal tissue	+
Onuf nucleus	+	Pelvic ganglia	+

PD — Parkinson's Disease

(LB) were found in cardiac plexus of patients with PD [31]. The function of extracardiac peripheral sympathetic nervous system is also impaired, affecting sympathetic innervation of blood vessels interfering with noradrenaline release and vasoconstriction in a standing position [28]. Mean resting noradrenaline plasma levels in PD-OH patients is lower compared to patients without OH [32, 33]. Furthermore, during tilt test this level decreases in PD-OH group [33], whereas normally it should double after five minutes of standing [34]. Additionally, in this group of patients systolic BP increased after administration of low doses of adrenoreceptor agonists. This implies vascular adrenoreceptor supersensitivity resulting from noradrenaline deficiency [35]. It also proves extracardiac sympathetic denervation. Patients with neurogenic OH in phase II of Valsalva manoeuvre present a progressive BP decrease and lack of BP overshoot during phase IV, which suggests baroreflex sympathetic failure [28]. This may also lead to SH. Neurogenic OH may result in heart rate blunted response while changing from a supine/sitting position to standing [36]. Orthostatic hypotension with increase in heart rate ≤ 15 bpm [36] or baroreflex gain < 0.5 bpm/mmHg (change in heart rate/falling systolic blood pressure [SBP]) [37] can help to distinguish neurogenic from non-neurogenic OH. Furthermore, cardiac responses to orthostatic stress deteriorate in PD patients who begin to fall [38]. Moreover, Tipton et al. [39] observed among PD-OH group a decreased renal sympathetic innervation, presumably leading to natriuresis and diuresis, thus increasing susceptibility to blood volume depletion.

Levodopa intake (the main medication used in PD treatment), even when combined with carbidopa or benserazide, increases plasma levels of dopamine and its metabolites. This results in vasodilatation (via dopamine receptors on smooth muscle cells) and increased natriuresis and diuresis, which leads to a reduction of blood volume and extracellular fluid [28]. In PD patients, both baroreflex and cardiovascular sympathetic innervations are impaired, and together these

mechanisms may result in BP decrease [27, 28]. However, Noack et al. [40] suggested that hypotension response to levodopa may be caused by negative cardiac inotropism rather than vasodilatation.

The relationship between central autonomic structures involvement and dysautonomia manifestations in PD is poorly understood [25]. Affected structures are presented in Table 1. The suprachiasmatic nucleus (SCN) of the hypothalamus, as the central biological clock, regulates circadian rhythm of BP and heart rate [41]. The SCN stimulates autonomic nervous system not only through GABA-ergic neurons, but also by regulation of melatonin release [41]. De Pablo-Fernandez et al. in a neuropathological case control study found α -synuclein depositions in the SCN of PD patients [26], and another group observed blunted circadian rhythm of melatonin serum levels in PD compared to controls [42]. Nucleus coeruleus, a main source of noradrenaline in the brain, is affected in the early stage of the disease [43] and noradrenaline transporter density is decreased [44]. The number of catecholaminergic neurons of nucleus of the solitary tract is reduced, which could be connected with the baroreflex impairment [45].

In PD-OH patients, the increased density of Lewy Bodies in the insular cortex has been observed [46] along with a reduced functional connectivity between hypothalamus, thalamus and striatum [47].

Orthostatic hypotension

Orthostatic hypotension (OH) is a common nonmotor PD manifestation (30% of patients) [48] and increases with age, disease duration, its severity and LD equivalent dose (LEDD) [49]. It is defined as a reduction in SBP ≥ 20 mmHg or ≥ 10 mmHg in diastolic blood pressure (DBP) after 3 minutes of standing from a supine position. In some patients, testing should be prolonged, as they may suffer from a delayed OH [50]. Standards for such testing have not been provided yet. Delayed OH can evolve to classic OH after 10 years in up to 50% of cases [50]. Although age is one OH risk factor, it can also be observed in

early stages of the disease and is one of the diagnostic markers of prodromal PD in the Movement Disorder Society's research criteria [51, 52], predicting motor decline in this group [53].

Blood pressure drop during an orthostatic test depends on the duration of rest before supine BP measurement, the way of obtaining upright position (active stand or passive tilt), and the duration of standing [54]. Orthostatic hypotension in PD occurs more frequently after tilting than on standing and is often delayed [54]. Symptomatic OH presents as lightheadedness, dizziness, presyncope, syncope, visual disturbances, fatigue, and generalised weakness [36]. Both symptomatic and asymptomatic OH are associated with an increased prevalence of falls, hospital admissions and lower quality of life [55].

Mild cognitive impairment may be present at the early stage of PD in 25% of patients and may develop into dementia in up to 78% after 12 years of follow up [56].

Several pathological mechanisms are considered to be responsible for the relationship between OH and cognition, such as cerebral hypoperfusion as a result of recurrent episodic hypotension, widespread neurodegeneration, or central and peripheral noradrenergic dysfunction [27, 57, 58].

In several cross-sectional studies, a positive correlation between OH and cognitive deterioration has been observed (Tab. 2). Attentional/executive and visuospatial functions were more impaired among patients with OH [58]. Age, male sex, baseline REM-sleep Behaviour Disorder (RBD), OH and MCI have been identified as predictors of PDD [59, 60]. In studies that included only a Mini Mental State Examination (MMSE) in the neuropsychological assessment, OH did not influence cognition [61–63]. The MMSE is a screening tool dedicated to AD that may be not sensitive enough, and is not indicated as the only tool to diagnose cognitive decline in PD.

Cicero et al. [4] examined the correlation between cardiovascular autonomic function and MCI among 185 PD patients from two Movement Disorders centres. Orthostatic hypotension was recorded in 52 of them, significantly more frequently in patients with long disease duration, and was associated with amnesic MCI.

The relationship between OH and posture-related cognitive impairment in PD has been investigated, comparing cognition among PD patients with and without OH to controls. Groups were matched for age, sex, premorbid verbal IQ and PD groups also for disease stage/duration and LEDD. In supine position, both PD groups demonstrated fronto-striatal and visuospatial cognitive deficits, but a transient exacerbation of cognition in an upright-tilted position was observed only in PD-OH group [65]. Sforza et al. replicated these findings in a small cohort of 28 PD patients [66]. Additionally, asystolic drop was greater and attention more deteriorated among PDD than PD patients while standing [67].

Differences in cognitive impairment between symptomatic and asymptomatic PD-OH patients were compared in the Longardner et al. study. The first part was performed as a cross-sectional, retrospective study and included 226 PD

patients of whom 62 had longitudinal follow-up (second part). Lower Montreal Cognitive Assessment (MoCA) scores and worse decline during follow-up period were observed among PD-OH group. Presence of OH symptoms did not influence cognitive deterioration [68].

It is still unclear whether the relationship between OH and cognitive dysfunction is causative or associative, because the results of some studies were not adjusted for important variables e.g. comorbidities, medications, or age [57].

Supine hypertension

In approximately 50% of PD-OH patients, orthostatic hypotension often coexists with supine hypertension (SH) [69, 70]. Patients with SH often have an abnormal nocturnal BP profile as well [2]. SH is defined as a SBP ≥ 140 mmHg or a DBP ≥ 90 mmHg after at least 5 min of rest in supine position [71]. This is often overlooked, because BP is usually measured in a seated position and it remains asymptomatic. The underlying mechanisms may result from baroreflex failure or vascular hypersensitivity, or both mechanisms combined [71]. Supine hypertension is probably associated with milder peripheral sympathetic denervation than OH alone [72]. Older age, akinetic-rigid motor subtype (predisposing to cognitive decline), and pre-existing hypertension are independent risk factors [72]. Supine hypertension alone can cause cognitive impairment and white matter hyperintensities (WMH), also in early PD [2]. The impairment is more severe when SH is combined with OH [2]. However, a few studies did not confirm this observation [68, 69, 73].

Palma et al. [74], in a prospective study of patients with α -synucleinopathies (35 with multiple system atrophy, 14 with PD, and eight with pure autonomic failure) and coexisting OH, observed that SH is associated with an increased risk of left ventricular hypertrophy, higher blood urea nitrogen levels, glomerular filtration rate decrease and WMH volume, and, in longitudinal observation, with cardiovascular adverse events and premature death. Both chronic SH and OH are associated with the development of WMH [75].

Abnormal nocturnal blood pressure

Physiologically, BP follows a circadian rhythm characterised by a decrease of $>10\%$ BP at night (dipping) [76]. An abnormal nocturnal BP profile is another frequent manifestation of autonomic dysfunction in PD. Most PD patients present as either non-dippers or reverse dippers (also called risers) i.e. with loss of nocturnal BP fall or even an increase of BP values during the night, respectively [76, 77] (Fig. 2). These disturbances of circadian BP pattern have been associated with coronary heart disease, stroke and increased mortality [77]. Furthermore, they have been linked with target organ damage, impairment of cognition in the elderly, and increased burden of WMH [77, 78].

The literature on the disturbances of the circadian BP rhythm in PD is scarce and only a few studies have explored this topic. Tanaka et al. [77] assessed 137 PD patients with

Table 2. Studies on association between orthostatic hypotension and cognitive decline (modified according to [58], with supplement of later studies)

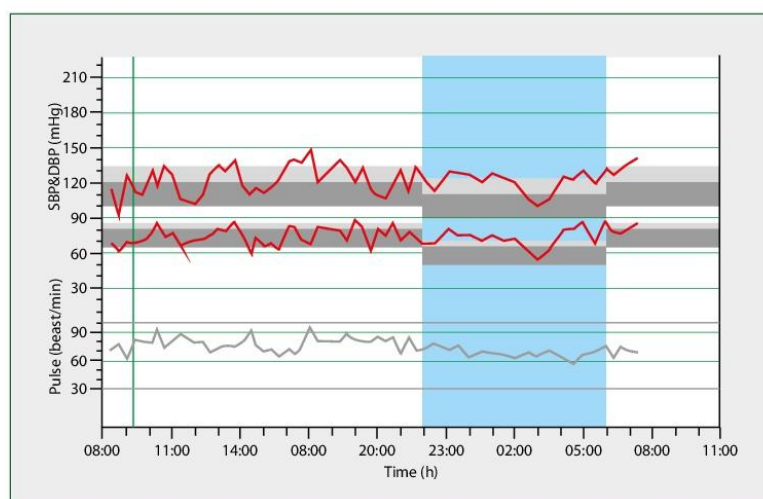
Study	Design	Subjects	Cognitive outcome
Allcock et al. (2004) [62]	Cross-sectional	PD-OH, n = 42, mean age 72.6 PD without OH, n = 45, mean age 68.2	No difference in MMSE score between two groups
Allcock et al. (2006) [63]	Cross-sectional	PD-OH, n = 80, mean age 72.1, median UPDRS 19, median PD duration 3 years PD without OH, N = 79, mean age 69.1, median UPDRS 17, median PD duration 5 years	No difference in MMSE score between two groups
Allcock et al. (2006) [96]	Cross-sectional	PD-OH, n = 87, mean age 72.4, median UPDRS 18.5, median PD duration 3.5 years PD without OH, n = 88, mean age 69.2, median UPDRS 17, median PD duration 5 years	PD-OH group performed worse on digit vigilance and picture recognition tasks. No difference in MMSE score between two groups
Peralta et al. (2007) [67]	Cross-sectional	PD, n = 10, mean age 74.1, mean disease duration 6.4 years, mean H&Y 2.1 PDD, n = 8, mean age 77.3, mean disease duration 7.8, mean H&Y 2.9	OH in 5 PDD, 2 PD. Decrease in attention scores in PDD in tilt position. Significant correlation between orthostatic changes and attention scores in PDD and no influence on word fluency tasks observed. Results not adjusted for dopaminergic medication
Idiaquez et al. (2007) [61]	Cross-sectional	PD, n = 29, mean age 66.2, mean PD duration 9.9 years, mean H&Y 2.6 PDD, n = 11, mean age 76.4, mean PD duration 10.5 years, mean H&Y 3.4	No correlation between PD, OH, cognitive impairment (MMSE, FAB). In PDD, cardiovascular symptoms more prominent
Hohler et al. (2012) [97]	Cross-sectional	PD-OH, n = 17 PD without OH, n = 27	PD-OH patients had lower cognitive FIM score and lower MMSE, worse motor, walking and balance compared to PD without OH. Results not adjusted for dopaminergic medication or age
Kim et al. (2012) [2]	Cross-sectional	PD with normal cognition, n = 25, mean age 63.4, mean PD duration 1.8 years, mean H&Y 1.4 PD-MCI, n = 48, mean age 70, mean PD duration 1.9, mean H&Y 1.7 PDD, n = 14, mean age 66.2, mean PD duration 1.6 years, H&Y 2.1	Drug-naïve patients, early stage disease. OH was correlated with verbal immediate and delayed memory and CHIPS scale. Patients with coexisting OH and SH had more severe cognitive impairment and higher CHIPS scores. Mean CHIPS score was higher in PDD than in others
Pillari et al. (2013) [73]	Cross-sectional	PD-OH, n = 23, mean age 64.96, mean PD duration 11.48 years, mean H&Y 2.76 PD without OH, n = 25, mean age 65.6, mean PD duration 11.6 years, mean H&Y 2.76	Among PD-OH patients, impairment of attention, visuospatial working memory, verbal delayed recall compared to PD without OH were observed. No differences in WMH between groups. LEDD were similar
Bae et al. (2014) [98]	Cross-sectional	PD-OH, n = 18, mean age 61.3, mean PD duration 13.8 months, mean H&Y 2 PD without OH, n = 27, mean age 65.5, mean PD duration 16.1 months, mean H&Y 2	Drug-naïve patients. Verbal memory recognition performance worse in PD-OH patients
Anang et al. (2014) [99]	Prospective – followed up mean 4.4 years	PDD, n = 27, mean age 70.5, mean PD duration 6.02 years, mean H&Y 2.8 PD without dementia, n = 53, mean age 63.5, mean PD duration 5.4 years, mean H&Y 2.3	Strong association between OH and risk of dementia. SBP drop of >10 mmHg increased odds of developing dementia by 84%. Risk factors for developing dementia: baseline MCI, RBD, higher baseline BP, abnormal colour vision, proportion of gait involvement, falls and freezing. Not adjusted for dopaminergic medication or age
Centi et al. (2016) [65]	Cross-sectional	PD-OH, n = 18, mean age 64.3, mean PD duration 6.7 years, mean H&Y 2 PD without OH, n = 19, mean age 65.6, mean PD duration 5.7 years, mean H&Y 2 Controls, n = 18, mean age 62.9	In both PD groups, in supine position deficits in sustained attention, response inhibition, semantic fluency, verbal memory observed. In upright posture, they exacerbated and broadened (phonemic fluency, psychomotor speed, auditory working memory) only in PD-OH group
Sforza et al. (2018) [66]	Cross-sectional	PD-OH, n = 14, mean age 73.5, mean PD duration 9 years, mean H&Y 2.54 PD without OH, n = 14, mean age 72.5, mean PD duration 8 years, mean H&Y 2.39	In supine position, no differences in cognition between two groups observed. In upright position, PD-OH patients were worse at Stroop's test word reading time, interference time, number of errors at interference section than patients without OH

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Table 2 cont. Studies on association between orthostatic hypotension and cognitive decline (modified according to [58], with supplement of later studies)

Study	Design	Subjects	Cognitive outcome
Cicero et al. (2019) [4]	Cross-sectional	PD with normal cognition, n = 106, mean age 63.6, mean PD duration 4.9 years, mean H&Y 2.2 PD-MCI, n = 79, mean age 66, mean PD duration 6.5 years, mean H&Y 2.3	OH significantly more frequent in patients with long disease duration and associated only with amnesic MCI subgroup
Longardner et al. (2020) [68]	First part cross-sectional, second part longitudinal observation (mean follow-up 5.3 years)	First part: PD-OH, n = 69, mean age 71.0, mean PD duration 6.9 years, mean H&Y 2.4 PD without OH, n = 157, mean age 64.8, mean PD duration 4.5 years, mean H&Y 2.1 Second part: PD-OH, n = 28, baseline mean age 62.7, baseline PD duration 3.2 years, follow-up interval 5.5 years, baseline mean H&Y 1.8, follow-up mean H&Y 2.3 PD without OH, n = 14, baseline mean age 58.3, baseline PD duration 2.4 years, follow-up interval 5.0 years, baseline mean H&Y 1.6, follow-up mean H&Y 2.4	PD-OH patients had lower MoCA scores than patients without OH. After adjusting for age and disease duration, this difference was observed at trend level. Furthermore, MoCA score declined more for PD-OH group during follow-up period. Cognitive deterioration did not differ between symptomatic and asymptomatic PD-OH patients, either in cross-sectional or in longitudinal analyses

CHIPS scale — cholinergic pathways hyperintensities scale, a measure of WMH; FAB — frontal assessment battery; FIM — functional independence measure; MoCA — Montreal Cognitive Assessment

**Figure 2.** Non-dipping pattern at 24h ambulatory blood pressure monitoring in patient with Parkinson's Disease

24-hour ambulatory BP monitoring, MMSE, the Hasegawa dementia scale-revised (HDS-R), Hoehn and Yahr scale (H&Y) and MRI. Twenty-seven patients met the diagnostic criteria of the Movement Disorder Society Task Force for Parkinson's Disease with dementia (PDD). The authors found statistically significant correlations between non-dipping pattern (negative) and riser pattern (positive) and dementia [77]. The correlation between abnormal nocturnal BP and dementia was independent of age, gender, H&Y score, diabetes, history of stroke and WMH [77]. Moreover, non-dipping pattern was

significantly associated with an increased burden of periventricular hyperintensities [77]. Kim et al. [2] assessed 87 patients with early, not treated (medication-naïve) PD at average H&Y score of 1.7 ± 0.7 with 24-hour BP recording, 3.0-Tesla MRI of the brain and neuropsychological tests. They found MCI and PDD in 48 and 14 patients, respectively. The non-dipping pattern was present in the majority of patients (79.3%) and was associated with higher burden of WMH and lower scores in the neuropsychological tests, although the differences were not statistically significant [2].

Table 3. Medications used to treat orthostatic hypotension in Parkinson's Disease (modified according to [27])

Medication	Recommended dosing	Mechanism of action	Adverse event
Midodrine	2.5–5 mg three times a day (last dose 3–4 hours before bedtime)	Direct α_1 — adrenergic receptor agonist	SH, piloerection, scalp tingling, urinary retention; use carefully in congestive heart failure and chronic renal failure
Droxidopa*	100–600 mg three times a day (last dose 3–4 hours before bedtime) or according to patient's needs	Synthetic noradrenaline precursor	SH, headache, dizziness, nausea; use carefully in congestive heart failure and chronic renal failure
Fludrocortisone	0.05–0.2 mg daily	Synthetic mineralocorticoid — increase of sodium and water reabsorption	SH, low potassium level, renal failure, myocardial fibrosis, oedema; use carefully in congestive heart failure
Pyridostygmine	30–60 mg twice or three times a day	Acetyl-cholinesterase inhibitor. Marginal efficacy in nOH	Abdominal pain, diarrhoea, sialorrhea, excessive sweating, muscle twitches; does not cause SH
Atomoxetine	10–18 mg twice a day	Noradrenaline transporter (NET) blocker	SH, insomnia, irritability, decreased appetite

nOH — neurogenic orthostatic hypotension; SH — supine hypertension; *The only one licensed for this indication

As in other neurodegenerative diseases, cognitive deterioration in PD most probably develops as a result of multiple underlying processes [79]. In addition to alpha-synuclein aggregations spread into limbic and neocortical regions, there are also accompanying Alzheimer's type and vascular pathologies [79]. In previous studies, patients with cognitive decline due to AD exhibited a non-dipping or a reverse dipping pattern significantly more often than healthy controls [80]. Additionally, abnormal nocturnal BP was linked with greater β -amyloid deposition in the brain [81]. Abnormal nocturnal BP was found to be also associated with cognitive deterioration related to cerebrovascular lesions [77, 82]. An absence of dipping significantly correlated with vascular cognitive impairment and dementia (VCI) and WMH burden [82]. Moreover, there was a statistically relevant association between periventricular WMH and VCI [82]. The relationship between the extent of WMH and abnormal nocturnal BP was also demonstrated in PD and it was most pronounced in the reverse dipping pattern [78]. Furthermore, the burden of WMH significantly correlated with risk of dementia in PD [21].

Thus, disturbances of circadian BP rhythm may contribute to cognitive decline in PD through many different and independent mechanisms.

Treatment options

Before starting the treatment, 24h ambulatory BP monitoring should be performed. This can provide information about the frequency of OH episodes as well as the severity and duration of SH or abnormal nocturnal BP.

The first step in OH treatment should be a revision of concomitant medications and non-pharmacological interventions. Many PD patients previously treated with antihypertensive medications (also those for benign prostate hyperplasia as α -1 receptor antagonists) present OH when dopaminergic therapy (levodopa, dopamine agonists as ropinirole, pramipexole or rotigotine) is started, due to a cumulative effect.

Therefore, doses should be adjusted, or even some medications withdrawn, if possible [83]. When it is safe for the PD patient, there should be avoided substances causing intravascular volume reduction, vasodilatation and affecting noradrenaline release or its activity — mainly antihypertensive and tricyclic antidepressants [27]. Antiparkinsonian medications such as monoamine oxidase B inhibitors (MAO-B, like selegiline), and N-Methyl-D-aspartate receptor antagonist (amantadine) may also exacerbate OH [84].

Fluid and salt intake are recommended, to 2–2.5 L/day and by adding 1–2 teaspoons of salt daily respectively [27, 36]. Fast but short-lasting increase of BP can be achieved by quickly drinking 500 mL of water [85]. Consumption of caffeine and alcohol needs to be restricted, due to their diuretic effect [27]. Postprandial hypotension can be improved by eating more, but smaller, meals, with a limited amount of carbohydrates [86]. Other recommended methods are: physical counterpressure manoeuvres, abdominal binders, and high waist compression stockings [87]. Physical exercises in a lying or sitting position may also be helpful [27]. Some patients, despite properly performed non-pharmacological methods, require pharmacological treatment to relieve OH symptoms. If OH is symptomatic and results in syncope with falls, the use of specific medications is recommended: acting via increasing intravascular volume (fludrocortisone) or increasing peripheral vascular resistance (midodrine, droxidopa, noradrenaline transporter inhibitors). Droxidopa is the only licensed medication for OH treatment; others are included in experts' recommendations (Tab. 3). Most of them (particularly fludrocortisone and midodrine) cause SH as a side effect. Therefore, 24h BP monitoring is crucial to avoid long-acting medication effects and in cases of nocturnal non-dipping. After midodrine, supine position is not recommended [88]. Short-acting drugs taken before bedtime, such as captopril, clonidine, hydralazine, losartan or a nitroglycerin patch are recommended in non-dippers [36, 88]. α -blockers, β -blockers and short-acting calcium channel blockers should be used with caution.

Moreover, patients should be aware of drugs used for different indications which can raise BP (e.g. ibuprofen, indomethacin, atomoxetine) [88]. Sleeping with a head-up tilt can be helpful for both OH and SH. This reduces night time natriuresis and thus improves morning orthostatic tolerance [89]. Patients suffering from SH should also avoid lying down during the day and limit water intake near bedtime [88].

Conclusions

Our literature review suggests a possible association between cardiovascular dysautonomia, OH in particular, and cognitive impairment not only among PD patients, but also in the general population [90–94]. The observed differences between the studies may result from small groups of patients, short follow-ups, no controls, or different methods used to assess OH. Cognitive screening tests such as MMSE or MoCA are inappropriate for a full assessment of cognition in α -synucleinopathies [95]. Active screening for OH, SH and abnormal nocturnal BP profile should be provided among PD patients, since these treatable abnormalities are commonly unrecognized and undertreated [49].

A few questions still need to be answered, such as the safe level of SH among patients treated for OH, or the way of treating OH with pre-existing hypertension [70]. The relationship between dysautonomia and the possible prevention of cognitive decline needs more thorough studies.

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Review

Arterial Blood Pressure Variability and Other Vascular Factors Contribution to the Cognitive Decline in Parkinson's Disease

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Abstract: Dementia is one of the most disabling non-motor symptoms in Parkinson's disease (PD). Unlike in Alzheimer's disease, the vascular pathology in PD is less documented. Due to the uncertain role of commonly investigated metabolic or vascular factors, e.g., hypertension or diabetes, other factors corresponding to PD dementia have been proposed. Associated dysautonomia and dopaminergic treatment seem to have an impact on diurnal blood pressure (BP) variability, which may presumably contribute to white matter hyperintensities (WMH) development and cognitive decline. We aim to review possible vascular and metabolic factors: Renin-angiotensin-aldosterone system, vascular endothelial growth factor (VEGF), hyperhomocysteinemia (HHcy), as well as the dopaminergic treatment, in the etiopathogenesis of PD dementia. Additionally, we focus on the role of polymorphisms within the genes for catechol-O-methyltransferase (COMT), apolipoprotein E (APOE), vascular endothelial growth factor (VEGF), and for renin-angiotensin-aldosterone system components, and their contribution to cognitive decline in PD. Determining vascular risk factors and their contribution to the cognitive impairment in PD may result in screening, as well as preventive measures.

Keywords: white matter hyperintensities; dysautonomia; genetic polymorphisms; dementia; levodopa; renin-angiotensin system; orthostatic hypotension

1. Introduction

Parkinson's disease (PD) is a neurodegenerative disorder with a wide spectrum of motor (bradykinesia, tremor, rigidity, loss of postural stability) and non-motor (cognitive decline, depression, dysautonomia, psychosis) symptoms. Parkinson's disease dementia mostly affects the executive and visuospatial functions, as well as attention. However, the impairment in memory and language functions are less pronounced than in Alzheimer's disease (AD) [1]. Dementia in PD is six times more common than in age-matched general population [2]. As a result of an 8-year prospective study, the cumulative prevalence of dementia was assessed to be 78% [3]. According to a 5-year prospective study in more than 400 patients with PD, the risk factors for dementia included older age, longer disease duration, later age-at-onset and higher daily levodopa (L-dopa) dosage [4]. In contrast to Alzheimer's disease, vascular contribution to PD dementia is not so obvious. The available data demonstrate the multifactorial origin of PD dementia: The combination of pathological findings of Alzheimer-like and cortical Lewy-bodies, but also a possible role of vascular burden due to hyperhomocysteinemia and dysautonomia with abnormal blood pressure (BP) variability [5,6]. In this review paper, the authors present the current state

of information about the role of BP variability and other vascular risk factors, as well as selected genetic polymorphisms, in the pathogenesis of PD dementia.

2. Blood Pressure Variability

In healthy individuals a compensatory mechanism, involving the sympathetic and parasympathetic systems, provides an adequate response of BP and cerebral perfusion to environmental (e.g., seasons, altitude), physical (e.g., posture), and emotional factors. The size and patterns of these BP variations constitute BP variability, which occurs within seconds and minutes (very short-term), along 24 h (short-term), between days (mid-term), months or even years (long-term; visit-to-visit BP variability) [7].

Numerous studies have shown a dysfunctional response of autonomic nervous system controlling blood pressure in PD [8,9]. Dysautonomia in PD is manifested, among others, in orthostatic hypotension (OH), supine hypertension or loss of circadian rhythm of BP, which may be the results of both autonomic nervous system dysfunction and pharmacological management, including dopaminergic medications.

Orthostatic hypotension is defined as a systolic pressure fall of at least 20 mmHg and/or diastolic pressure fall of 10 mmHg upon standing or passive tilting. Supine hypertension in PD is often associated with OH and causes an increase in BP when lying down—to at least 150 mmHg in systolic and/or 90 mmHg in diastolic BP. This phenomenon often remains unrecognized, thus an ambulatory 24-h BP monitoring provides a valuable insight into the BP alterations and enables non-pharmacological and pharmacological management. Supine hypertension can be additionally worsened by the drugs prescribed against OH. On the other hand, the treatment of hypertension may worsen OH, thus it should include non-pharmacological measures as a priority [8]. Four clinical trials have addressed OH in conditions with dysautonomia, including PD, and have posted results by the time of this review (clinicaltrials.gov: NCT00738062, NCT00782340, NCT01176240, NCT00633880). In all of them droxidopa—a precursor of norepinephrine—was compared with placebo. The results showed some discrepancies, as only two of the trials established significant clinical changes favoring droxidopa in terms of increasing upright systolic BP, ameliorating symptoms associated with OH and improving daily life activities (i.e., standing, walking) (NCT00782340, NCT00633880) [10].

Evaluating the circadian blood pressure profile in healthy subjects demonstrated a physiological decrease of arterial BP at night, while sleeping (dipping) [11]. This phenomenon is influenced by several factors, and we briefly describe only some of them. First of all, photoreceptor cells in retina detect the environmental darkness, subsequently, the information is conveyed via the suprachiasmatic nucleus—the central oscillator—to the pineal gland, which reacts by producing melatonin. Melatonin decreases BP by its impact on vasodilation, nitric oxide, and norepinephrine levels. Accordingly, the pivotal role in the circadian BP pattern is exerted by the sympathetic nervous system with norepinephrine and epinephrine having the lowest levels in the evening and the highest in the morning. Sleep itself affects BP, decreasing its values especially during the deep sleep stages [12]. Similarly, physical activity may change the circadian rhythm—people who work at night, are likely to have blunted nocturnal drop in systolic BP. Dipping depends also on the BP liability upon dietary sodium intake and endothelial function [13]. The loss of night BP reduction (non-dipping) has been recognized as a risk factor of cardiovascular pathologies, e.g., left ventricle hypertrophy [14]. Nocturnal hypertension is usually diagnosed when BP is higher than 120/70 mmHg [8]; whereas the term “non-dipping” relates to a relative difference between daytime and nighttime BP (i.e., <10% of difference). It is often associated with other cardiovascular autonomic abnormalities, such as OH and supine hypertension [15]. The 24-h BP monitoring showed that over 70% of PD patients did not have a proper circadian BP profile compared to 48% in the control group [16]. The analysis performed by Berganzo et al. revealed that the most frequent phenotype among the PD patients was non-dipper, while the number of the risers (mean arterial BP higher in the night than during the day) was the same as subjects having the physiological diurnal

pattern [16]. Orthostatic hypotension was more prevalent in non-dippers and risers; those phenotypes administered a higher dose of dopaminergic treatment; however, none of the associations reached statistical significance.

Neurocirculatory abnormalities in PD have been linked to cognitive impairment. In patients with early stage of the disease, who were not receiving dopaminergic medication, dementia was significantly more often in the subjects with OH or supine hypertension [17]. Strikingly, none of the patients suffering from both OH and supine hypertension was cognitively intact. The disruption of the nocturnal BP fall was related to worse visuospatial memory registration; however, mild cognitive impairment (MCI) or dementia were similarly frequent in dipper and non-dipper groups. Anang et al. carried out a prospective research with a comprehensive assessment of 80 PD patients who were cognitively intact at baseline [18]. After 4.4 years' follow-up, higher BP at the entry and OH were predisposing factors for cognitive decline. Some of the cross-sectional studies reviewed by Udow et al. did not provide a correlation linking OH in PD with cognitive impairment assessed with Mini-Mental State Examination (MMSE) [19]. On the other hand, in analyses using more detailed neuropsychological tests OH was associated with worse performance. In one of the recent studies the riser pattern in PD was significantly correlated with dementia, whereas the dipper status was much less common in demented (3.7%) than non-demented (23.6%) subjects [20]. The authors found no association between dementia and non-dipper or extreme dipper (nocturnal BP lower >20% compared to daytime) phenotypes. Both OH and supine hypertension were significantly more prevalent in the dementia group. Thus, cardiovascular autonomic dysfunction can be considered as a plausible predictor of PD dementia.

3. The Role of Levodopa in Neurocirculatory Abnormalities and Cognitive Decline in Parkinson's Disease

The dopaminergic medications used in the treatment of PD produce positive effects on PD motor manifestations, but at the same time may promote the development of side effects, e.g., dyskinesia may enhance autonomic disturbances [21]. Positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) in experimental models and in PD patients have shown changes in dopaminergic synapses during long-term administration of L-dopa. The chronic use of L-dopa resulted in endothelial cell proliferation, promoted angiogenesis in the striatum and other structures of the basal ganglia in animals with L-dopa-induced dyskinesia [22]. Animal models have also evidenced that chronic L-dopa treatment induced expression of vascular endothelial growth factor (VEGF) in the basal ganglia in a dose-dependent manner [23]. VEGF exerts angiogenic activity and is essential for vasculogenesis. It can also enhance blood–brain barrier permeability, which in turn increases the bioavailability of L-dopa to the central nervous system (CNS). In the aforementioned model, VEGF was expressed predominantly in astrocytes and astrocytic processes around blood vessels. Administration of a VEGF signaling inhibitor blocked the appearance of markers of blood–brain barrier permeability (albumin extravasation) as well as of angiogenic response—nestin (a marker of immature endothelial cells) and VEGF expression. Furthermore, it was found that VEGF inhibition significantly attenuated the expression of dyskinesia in animal models with L-dopa-induced dyskinesia. Human tissue from the autopsies of chronically L-dopa-treated PD patients established increased nestin staining and VEGF mRNA expression in the striatum [23,24]. Pulsatile stimulation of dopamine receptors, which may be a result of abnormal L-dopa pharmacokinetics in the absence of efficient, endogenous regulatory mechanisms, is regarded as the main mechanism of peak-of-dose choreic dyskinesia (the result of D-receptor hypersensitivity or excessive dopamine release). Chronic L-dopa administration, apart from inducing angiogenesis and changes in blood–brain barrier permeability, stimulates vasodilation through D1 receptor agonist action, thus increasing regional blood flow [24].

According to a 5-year prospective study higher L-dopa dose was established as one of dementia risk factors in PD—the mean L-dopa dosage equivalent (LDE) was 514 mg per day, whereas non-demented patients received 316 mg of LDE per day [4]. Moreover, L-dopa-

induced dyskinesia were correlated with the progression of cognitive decline, especially executive functions [25]. Daily changes in BP, dipper or non-dipper phenotype, OH and supine hypertension may modulate CNS blood flow, and thus affect L-dopa distribution, which may result in cognitive performance deterioration, and other side effects. Up to now, no studies have addressed the role of BP variability, especially nocturnal BP reduction, in the development of L-dopa complications, e.g., peak-of-dose dyskinesia due to impaired drug distribution.

Dopaminergic treatment was suggested to exacerbate dysautonomia in PD; L-dopa may worsen or cause OH [26], however, Goldstein et al. indicated that OH occurs independently from L-dopa treatment [27]. Although L-dopa is well known for its BP decreasing function [9,28], the available literature does not give a clear answer to the question whether it decreases supine hypertension [28,29]. There are some discrepancies on the role of dopamine agonists as well. Non-ergot derivatives of dopamine agonists possibly influence cardiovascular functions less, compared to ergot-derivatives [30]. Nevertheless, the side effects of non-ergot derivatives depend on the affinity to dopaminergic and α -adrenergic receptors [31]. Although non-ergot dopamine agonists were generally correlated with OH occurrence, rotigotine was showed to improve the abnormal 24-h BP pattern in PD patients [32]. On the other hand, rotigotine may increase the risk of the atrioventricular block. Pramipexole in turn, due to its high affinity towards α 2-adrenergic receptors, may decrease the adrenergic tone and myocardial contractility, facilitating heart failure occurrence. Pramipexole may unmask a subclinical heart failure or exacerbate preexisting cardiovascular comorbidities [31]. Another non-ergot dopamine agonist—apomorphine—was suggested to prolong QT interval; however, no causality has been established [31,33]. Undoubtedly, the aforementioned cardiovascular side effects influence BP and may lead to the impairments within the cerebrovascular functions, such as episodes of hypo- and hyperperfusion.

The relationship between dopaminergic treatment and the BP variability needs to be further assessed. It seems important because disturbances in the diurnal BP pattern, especially nocturnal hypertension, are associated with an increased risk of cerebrovascular complications. Nevertheless, despite many side effects, levodopa is still the most often prescribed antiparkinsonian medication due to its effectiveness against motor symptoms. Non-ergot derivatives are in turn beneficial in treating non-motor symptoms, e.g., depression, sleep disorders, and nocturnal akinesia [31]. In most cases positive effects of dopaminergic medication (L-dopa and dopamine agonists) surpass potential side effects in the cardiovascular system, however, the risk must be always individually estimated.

4. White Matter Hyperintensities

Shimada et al. documented that an absent or insufficient nocturnal BP fall in elderly hypertensives was associated with a silent cerebrovascular damage seen in MRI as white matter hyperintensities (WMH) [34]. In recent years, WMH appearance has become the radiological marker of CNS ischemia. White matter hyperintensities are more frequently observed in subjects over 60 years of age with cardiovascular disease, diabetes, hyperhomocysteinemia, and other vascular risk factors [35,36]. Chronic ischemia being a consequence of BP variability was established as one of the possible factors leading to the development of WMH. In addition to a non-dipper phenotype, an excessive nocturnal BP fall of more than 20% compared to daytime BP values was found to be an important risk factor of WMH. The extreme dipper phenotype also was proven to be a risk factor for clinically silent brain ischemia episodes, particularly those associated with more extensive white matter damage, and can be related to nocturnal cerebral hypoperfusion [37,38]. Studies analyzing neurocirculatory abnormalities in PD demonstrated a correlation between WMH and OH [17,39]. Cerebral hypoxia along with hypoperfusion were proposed as mechanisms linking OH and WMH [40]. Indeed, hippocampal atrophy was correlated with WMH in the study performed by Sławek et al. [41]. Furthermore, WMH in PD was also associated with other cardiovascular dysautonomic features, as supine hypertension [17] or nocturnal

hypertension [42]. Up to date, the only study examining nighttime BP fall and WMH in PD showed no correlation between non-dipping status and WMH [42].

According to the meta-analysis performed by DeBette and Markus, WMH predicted faster decline in global cognitive performance and executive function [43]. In PD associated dysautonomia and dopaminergic medication-induced hypotension may be responsible for WMH formation and cognitive decline. In a prospective study in PD patients a significant relationship between increased WMH volume and cognitive burden was demonstrated. Moreover, the risk for the development of MCI in the course of PD was higher in the subjects with greater WMH [44]. Subsequent studies supported the finding, demonstrating a significant correlation between WMH and MCI or dementia in PD [45,46].

Cardiovascular dysautonomia in PD, along with dopaminergic therapy, leading to episodes of cerebral hypo- and hyperperfusion, may be one of the most important pathophysiological mechanisms leading to WMH and, presumably, dementia.

The studies on the impact of BP variability on cognition and WMH in PD are summarized in Table 1.

Table 1. Studies on the impact of blood pressure (BP) variability and white matter hyperintensities (WMH) on cognitive performance in Parkinson's disease (PD).

Blood Pressure Variability			
Authors (year), Type of the Study	Subjects	Factor	Outcome
Oka et al. (2020) [47], retrospective study	PD = 75 (de novo) DLB = 24	Circadian blood pressure variability. Supine hypertension.	Better performance assessed with MMSE positively associated with the percentage of nocturnal BP fall in PD. No correlation with SH. Nocturnal BP fall (%) positively associated with better performance in Frontal Assessment Battery. SH negatively correlated with Frontal Assessment Battery.
Sforza et al. (2018) [48], retrospective study	PD = 28	Orthostatic hypotension.	In upright position, PD-OH(+) performed worse at the Stroop's test word reading time and number of errors at the interference section compared to PD-OH(−).
Tanaka et al. (2018) [20], retrospective study	PD-NCI = 110 PDD = 27	Circadian blood pressure variability. Orthostatic hypotension.	The riser pattern associated with dementia. Coexistence of the riser pattern and OH more associated with dementia than the riser pattern alone.
Centi et al. (2017) [49], retrospective study	PD-OH(+) = 18 PD-OH(−) = 19 controls = 18	Orthostatic hypotension.	Upright posture correlated with the deficits in sustained attention and response inhibition, reduced semantic fluency and verbal memory in the PD-OH(+). OH correlated with the deficits in executive function, memory and visuospatial function.
Anang et al. (2014) [18], prospective study	PD = 80 (dementia free at baseline)	Orthostatic hypotension.	OH strongly associated with dementia risk.
Pilleri et al. (2013) [50], retrospective study	PD = 48	Orthostatic hypotension.	PD-OH(+) performed significantly worse in sustained attention, visuospatial and verbal memory, compared with PD-OH(−).
Kim et al. (2012) [17], retrospective study	PD-NCI = 25 PD-MCI = 48 PDD = 14	Circadian blood pressure variability, supine hypertension and orthostatic hypotension.	The OH group had more severe impairment in verbal immediate/delayed memory. Dementia significantly more prevalent in patients having OH, SH or OH + SH. Non-dipping not associated with cognitive impairment.
Allcock et al. (2006) [51], retrospective study	PD-OH(+) = 87 PD-OH(−) = 88	Orthostatic hypotension.	OH(+) subjects worse in sustained attention and visual episodic memory. OH not associated with the MMSE score, the prevalence of dementia, or the simple and choice reaction times, working memory or long term memory.
White Matter Hyperintensities			
Authors (Year), Type of the Study	Subjects	Factor	Outcome
Nicoletti et al. (2021) [52], prospective study	PD-NCI = 84 PD-MCI = 55	WMH	WMH was a predictor of PDD development.
Huang et al. (2020) [53], retrospective study	Early PD: PD-NCI = 81 PD-MCI = 94	WMH	PD-MCI associated with the periventricular WMH but not with total WMH. Periventricular WMH associated with worse executive function and visuospatial function.
Ramirez et al. (2020) [54], retrospective study	PD = 139	WMH	WMH negatively associated with global cognition.

Table 1. Cont.

Dadar et al. (2020) [55], prospective study	PD = 50 controls = 45	WMH	No correlation between WMH and total Dementia Rating Scale. Greater WMH burden in patients diagnosed with dementia at 36 months.
Linortner et al. (2020) [56], retrospective study	PD = 85 controls = 18	WMH	Dementia and executive impairment significantly more prevalent in PD patients with WMH than without WMH. WMH associated with worse performance in Symbol Digit Modalities and Stroop tests.
Lee et al. (2020) [57], retrospective study	PD = 136 (de novo)	WMH	Performance in language function, frontal/executive and visual memory associated with the severity of WMH.
Chahine et al. (2019) [58], prospective study	PD = 141 controls = 63	WMH	Annual rate of change in global cognition correlated with WMH. Higher temporal WMH associated with greater decline over time in verbal memory.
Hanning et al. (2019) [59], prospective study	Drug-naïve: PD-NCI = 79 PD-MCI = 29 controls = 107	WMH (volume and CHIPS score)	No association between global or localised WMH and cognitive decline, both cross-sectional and longitudinal.
Pozorski et al. (2019) [60], prospective study	PD = 29 controls = 42	WMH	Greater regional and global WMH at baseline more strongly associated with lower executive function in PD than in controls. Increased regional WMH more strongly associated with impaired memory performance in PD relative to controls. Longitudinally, no associations between WMH and cognitive change.
Stojkovic et al. (2018) [61], retrospective study	PD-NCI = 49 PD-MCI = 61 PDD = 23	WMH	PDD patients had significantly greater whole brain WMH than PD-NCI subjects.
Dadar et al. (2018) [62], prospective study	PD = 365 (de novo) controls = 174	WMH	PD subjects with greater WMH had significantly more severe cognitive decline than PD subjects with low WMH load or controls with high WMH load.
Ham et al. (2016) [63], retrospective study	PD = 171 (non-demented)	WMH	Total WMH and deep WMH associated with worse performance in semantic fluency.
Mak et al. (2015) [64], retrospective study	PD-NCI = 65 PD-MCI = 25	WMH	Greater total and periventricular WMH in PD-MCI than in PD-NCI. Spatial distribution of WMH associated with global cognition, performance on the Frontal Assessment Battery and Fruit Fluency.
Sunwoo et al. (2014) [45], prospective study	PD-NCI = 46 PD-MCI = 65	WMH (volume and CHIPS score)	The progression from PD-MCI to PDD correlated with WMH volume and CHIPS score. In PD-MCI patients WMH volume and CHIPS score associated with longitudinal decline in general cognition, semantic fluency and Stroop test scores.
Kandiah et al. (2013) [44], prospective study	PD-NCI = 67 PD-MCI = 24	WMH	PD-MCI patients had significantly greater volume of periventricular and deep subcortical WMH than PD-NCI. Regional WMH significantly greater among PD-MCI in the frontal, parietal and occipital regions.
Slawek et al. (2013) [41], retrospective study	PD-NCI = 135 PDD = 57 controls = 184	WMH	WMH significantly greater in PDD than PD-NCI group.
Kim et al. (2012) [17], retrospective study	PD-NCI = 25 PD-MCI = 48 PDD = 14	WMH (CHIPS score)	The severity of WMH in the periventricular and subcortical white matter higher in PDD than in PD-NCI or PD-MCI. No difference in WMH between PD-NCI and PD-MCI.
Shin et al. (2012) [65], retrospective study	PD-NCI = 44 PD-MCI = 87 PDD = 40	WMH (CHIPS score)	The CHIPS score significantly higher in PDD than in PD-NCI or PD-MCI. WMH negatively associated with performance in MMSE. The CHIPS score correlated with the performance in contrasting programme and forward digit span tests.
Lee et al. (2010) [66], retrospective study	PD-NCI = 11 PD-MCI = 25 PDD = 35	WMH	Greater total and periventricular WMH in the PDD group compared to PD-MCI and PD-NCI groups. No difference in WMH between PD-MCI and PD-NCI groups.
Dalaker et al. (2009) [67], retrospective study	Drug-naïve: PD-NCI = 133 PD-MCI = 30 controls = 102	WMH	No differences between the groups in total volume or spatial distribution of WMH. No correlation between WMH and cognitive functions.
Beyer et al. (2006) [68], retrospective study	PD-NCI = 19 PDD = 16 controls = 20	WMH	PDD group had significantly more WMH in deep white matter and periventricular areas than the PD-NCI group.

Table 1. Cont.

Interaction between WMH and BP Variability			
Authors (year), type of the study	Subjects	Factor	Outcome
Dadar et al. (2020) [69], prospective study	PD = 365 (de novo) controls = 174	WMH Orthostatic hypotension.	A correlation between WMH burden and worse Montreal Cognitive Assessment (MoCA) score in PD over time. WMH linked with diastolic OH. Direct effect of diastolic OH on the rate of cognitive decline via WMH burden.
Oh et al. (2013) [39], retrospective study	PD = 117	WMH Orthostatic hypotension, supine hypertension.	Orthostatic hypotension and supine hypertension correlated with WMH score.
Oh et al. (2013) [42], retrospective study	Drug-naïve: PD = 129	WMH Circadian blood pressure variability.	Nocturnal hypertension associated with WMH in the basal ganglia. No influence of the non-dipping pattern on WMH. Nighttime systolic BP closely correlated with WMH.
Kim et al. (2012) [17], retrospective study	PD-MCI = 25 PD-MCI = 48 PDD = 14	WMH (CHIPS score) Circadian blood pressure variability, supine hypertension and orthostatic hypotension.	WMH significantly more severe in patients having OH, SH or OH + SH. No difference in WMH between the dippers and non-dippers.

BP—blood pressure; DLB—dementia with Lewy Bodies; CHIPS—Cholinergic Pathways Hyperintensities Scale, measures the extent of WMH in the periventricular and subcortical white matter; MCI—mild cognitive impairment; MMSE—Mini-Mental State Examination; NCI—no cognitive impairment; OH(+)—with orthostatic hypotension; OH(−)—without orthostatic hypotension; PDD—PD dementia; WMH—white matter hyperintensities.

5. Metabolic and Vascular Risk Factors

The etiology of cognitive impairment in PD presumably involves other than dopamine-dependent mechanisms, from which factors affecting the cerebrovascular status seem highly probable (Figure 1) [61]. Hypertension, diabetes mellitus and hypercholesterolemia lead to structural changes in the vessels [52], hypoperfusion, endothelial disorders, and altered blood–brain barrier permeability [70]. This results in cerebrovascular pathologies, seen as WMH—a marker of cognitive deterioration [52].

Vascular risk factors and their significance in PD and PD dementia have been investigated in several analyses, one of which was a cohort study on Finnish population assessing the impact of diabetes on PD occurrence. The hazard ratio of PD among patients with type 2 diabetes at baseline was estimated as 1.83 (95% CI 1.21–2.76) [71]. However, in the Nurses' Health Study and the Health Professionals Follow-up Study the relationship between PD and self-reported diabetes was not confirmed [72]. In the same analysis self-reported history of hypertension or high cholesterol levels were not established as PD risk factors either. In the meta-analysis performed by Cereda et al. diabetes was correlated with PD, although the diagnosis of idiopathic PD without imaging techniques in some studies seemed to be uncertain, since diabetes might lead to microvascular complications with parkinsonism as clinical outcome [73]. The impact of diabetes on PD dementia in a meta-analysis by Xu et al. was not confirmed, in contrast to hypertension (OR 1.57, 95% CI 1.11–2.22) [74]. The relationship between hypertension and cognitive performance was additionally found in Doiron et al. research [70]. In this prospective study, the history of hypertension was followed by lower Z-scores on immediate and delayed free recall, recognition, and verbal fluency tests. However, the numbers of years with hyperlipidemia did not correlate with a change in any of the Z-scores at the 24-month follow-up. In a prospective research, hypertension was correlated with an increased risk of the MCI development in PD patients, whereas MCI and WMH predicted the conversion to PDD [52]. No impact of hypertension on the progression from MCI to PDD was established. Thus, it is likely that hypertension contributes to increasing WMH, which in turn modulates the risk of dementia. On the other hand, vascular factors (e.g., smoking status, body mass index, hypertension, and diabetes)—calculated together into Framingham General Cardiovascular Disease Risk Score—increased the risk of both MCI and dementia in PD [61]. Homocysteine (Hcy) is an established risk factor for vascular damage. Additionally, it has been correlated with neurodegeneration related to oxidative stress, calcium accumulation and apoptosis [75]. An elevated concentration of homocysteine (hyperhomocysteinemia: HHcy;

value over 15 $\mu\text{mol/L}$ of blood) was more frequently observed in PD dementia than in PD patients without dementia [41]. Hcy elevated levels might result from L-dopa methylation by catechol-O-methyltransferase (COMT), but the authors assessed the correlation between Hcy levels and L-dopa dose as weak (coefficient of determination $R^2 = 0.12$). However, an increase in Hcy level was established for the treatment with duodenal levodopa gel (duodopa), due to its formulation which negatively affects the absorption of B6 vitamin and folate, necessary for reducing Hcy levels [76,77]. The correlation between Hcy and cognitive status in PD was demonstrated in a meta-analysis performed by Xie et al., with suggestion that the detrimental effect of HHcy could be mitigated with folate and/or B12 vitamin supplementation [78].

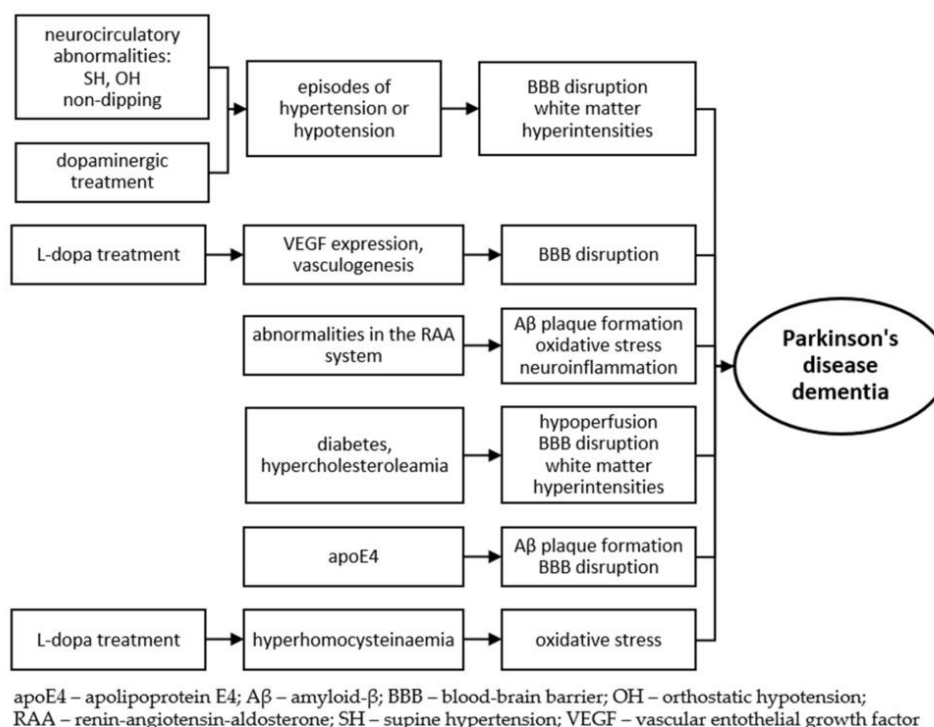


Figure 1. Possible vascular-related mechanisms leading to dementia in Parkinson's disease.

The plasma and tissue renin–angiotensin–aldosterone (RAA) system has recently emerged as another risk factor for PD and PD dementia. It plays a key role in controlling BP as well as water and electrolytes homeostasis. The conversion of angiotensinogen to angiotensin II (AngII) is catalyzed by renin, and then angiotensin converting enzyme (ACE). The resultant AngII binds to type 1 or 2 angiotensin receptors (AT1R, AT2R), expressed among others in peripheral vessels, heart, kidneys and CNS. Initially, the effects of the RAA system in CNS were considered to be mediated only through circumventricular organs, since active products of this system do not cross the blood–brain barrier [79]. However, at this moment it is known that the brain has an independent local RAA system, and the existence of the intracellular RAA system has been confirmed. As demonstrated in the experimental model, angiotensinogen in CNS is produced by astrocytes with a limited contribution from neurons, and central AngII levels may be even higher than the peripheral concentration [80]. The role of the RAA system in the nigro-striatal pathway seems to be of

particular interest. Dopamine deficiency leads to compensatory RAA system hyperreactivity and an increased expression of AT1R and AT2R [81]. In neurons, interaction of AngII with its receptor AT1 leads to activation of neuronal NADPH oxidase and production of reactive oxygen species (ROS). This triggers oxidative stress and inflammatory processes that are additionally enhanced by ROS from other sources i.e., mitochondria or activated microglia. Free radicals from the latter are released extracellularly, and consequently, may lead to progressive damage to dopaminergic neurons [79].

Experimental and clinical evidence demonstrates beneficial effects of AT1 receptor blocking or converting enzyme inhibition on RAA system function, and dopamine concentration in striatum, as well as a reduction in inflammatory processes [79,82]. The RAA system is closely linked to VEGF synthesis, and like AngII, VEGF stimulates angiogenesis, affects permeability of blood vessels and blood brain barrier function. Janelidze et al. established the correlation between cerebrospinal fluid (CSF) biomarkers of angiogenesis and PD with and without dementia [40]. Levels of VEGF, placental growth factor (PlGF), and one of VEGF receptors (VEGFR-2) were significantly higher in both demented and non-demented PD patients comparing to the control group. However, no difference was observed between PD and PD dementia groups. In another study, the CSF level of VEGF was considerably higher in PD dementia (grouped together with patients with Lewy bodies dementia) than in the control subjects [83]. VEGF was suggested as a potent trigger of vascular leakage and blood–brain barrier dysfunction, which is in line with elevated endothelial cell nuclei and vessels in the substantia nigra pars compacta of PD patients found in post-mortem studies [23,84]. Moreover, it was noted that patients with diastolic OH had increased levels of VEGF and PlGF in comparison with subjects without OH. Insufficient autoregulation of cerebral blood flow in PD patients results in hypoxia-induced VEGF signaling and, consequently, in an angiogenic response [40].

Some proteins from the VEGF family demonstrate neuroprotective activity (VEGF-B), as revealed in diencephalon cell cultures exposed to rotenone (widely used as an experimental model of PD). The neuroprotective effect of VEGF on 6-hydroxydopamine (6-OHDA) treated dopaminergic neurons was reported to be mediated by both direct and indirect vascular and neuronal mechanisms. The neuroprotective effect of VEGF in PD models was dose-dependent, i.e., the low dose protected dopaminergic neurons, whereas the high dose induced severe brain edema [85]. Excessive activation of the tissue and/or plasma RAA system resulting from dopamine deficiency may lead to the fostering of processes damaging dopamine neurons. This in turn may increase the risk of L-dopa-induced side effects (e.g., dyskinesia) due to both increased neurodegeneration and changes in L-dopa distribution within CNS (pulsatile dopamine receptor stimulation).

Muñoz et al. demonstrated that administration of candesartan, AT1 receptor blocker, significantly reduced dyskinesia in the 6-OHDA induced, experimental model of PD [86]. In animals with dyskinesia, higher concentrations of VEGF and IL-1 β within striatum and substantia nigra were found. Furthermore, animals treated with candesartan along with L-dopa were characterized by lower levels of VEGF, IL-1 β , and less severe dyskinesia compared to animals receiving only L-dopa. L-dopa monotherapy reduces the activity of the RAA system. It is likely that the effects of L-dopa on angiogenesis in the course of chronic treatment cannot be eliminated, but can be mitigated by AT1R blockade. Moreover, the reduction of L-dopa-induced dyskinesia did not diminish L-dopa effectiveness against motor symptoms. Taking into consideration the aforesaid facts that long-term L-dopa treatment is a risk factor for developing PD dementia and that L-dopa-induced dyskinesia correlate with cognitive decline, it is possible that blocking AT1R may decrease the risk of cognitive decline.

A recent prospective study assessed the impact of several angiotensin II-stimulating (thiazides, dihydropyridine calcium channel blockers, AT1R blockers) and angiotensin II-inhibiting (ACE inhibitors, β -blockers, nondihydropyridine calcium channel blockers) antihypertensive drugs on the risk of dementia in older people (70–78 years at baseline) [87]. Subjects administrating AngII-stimulating antihypertensives had significantly lower risk

of developing dementia compared to AngII-inhibiting drugs, independently of systolic BP or the baseline history of stroke, diabetes or CV diseases. As for the individual types of antihypertensives, the only significant decrease of dementia risk was associated with dihydropyridine calcium channel blockers. The beneficial role of upregulating AngII may result from the neuroprotection connected with AT2R. On the other hand, as ACE was showed to degrade amyloid- β (A β) in experimental models, the use of ACE inhibitors may promote A β plaque formation [87,88]. Regardless of the pivotal role of A β in AD, its deposition in PD was associated with cognitive decline [89]. However, in the aforementioned prospective study, the incidence rate of dementia in the group using ACE inhibitors did not differ from other types of antihypertensive drugs [87]. Moreover, Zhuang et al. showed in their meta-analysis that ACE inhibitors, as well as AT1R blockade, lowered the risk of AD, and AT1R blockade additionally decreased the risk of cognitive impairment associated with age [90]. Thus, the possible involvement of ACE in cognitive impairment and the effects exerted by ACE inhibitors seem to be far from being elucidated.

6. Genetic Factors

Although several causative genes for PD have been found, they scarcely account for some of the familial cases, whereas for the idiopathic form of PD and PD dementia, only susceptibility genes have been established, though not without inconsistency. Among the analyzed susceptibility genes are these coding for catechol-O-methyltransferase (*COMT*), apolipoprotein E (*APOE*), vascular endothelial growth factor (*VEGF*) and for renin-angiotensin-aldosterone system.

6.1. *COMT*

Catechol-O-methyltransferase (*COMT*) catalyzes the transfer of a methyl group from S-adenosyl-methionine to a hydroxyl group on a catecholamine (e.g., dopamine, norepinephrine, or catechol estrogen), thus regulating dopamine level in the prefrontal cortex, and is also a crucial enzyme involved in L-dopa metabolism [91,92]. Furthermore, the methylation of L-dopa is followed by the production of S-adenosylhomocysteine, hydrolyzed to homocysteine, which in turn may be responsible for HHcy in L-dopa medicated PD patients. However, homocysteine levels can be reduced by concurrent administration of *COMT* inhibitors in PD patients [93]. A common polymorphism in *COMT* gene—a G→A substitution (rs4680) results in an amino acid codon alteration (Val158Met in the membrane-bound form of *COMT*), and according to Chen et al., significantly lower enzymatic activity in homozygous *COMT*-Met in comparison with homozygous *COMT*-Val in post-mortem human prefrontal cortex tissues [91]. The dopaminergic imaging study demonstrated that Met homozygotes were characterized by an increased level of caudate striatal dopamine transporter (DAT), and a slightly protective effect on dementia was found for homozygous *COMT*-Met carriers [94]. Additionally, in a prospective analysis, Val homozygotes were at greater risk of developing PD-MCI than the other *COMT* genotypes, although the correlation with PD dementia was not observed [95]. Interestingly, Williams-Gray et al. [96] demonstrated in their longitudinal CamPaIGN study a varying impact of *COMT* alleles in relation to the disease duration. In “early” disease (<1.6 years), there was a significant decrease in the Tower of London (TOL; test of planning) scores with an increasing number of Met alleles, whereas no effect was observed in the “later” disease group (>1.6 years). Moreover, after 5.2-year follow-up, Met homozygotes were more likely to improve the TOL test score, in contrast to Val homozygotes or heterozygotes. The observed difference is possibly a consequence of an inverted U-shaped relationship between dopamine levels and prefrontal function, assessed mainly by working memory [96].

The *COMT* polymorphism seems to affect Hcy total level as well. Tunbridge et al. established that Val carriers had 1 $\mu\text{mol/L}$ higher Hcy plasma values compared with Met homozygotes [92]. Additionally, the effect correlated with a polymorphism in methylenetetrahydrofolate reductase (*MTHFR* 677C > T; rs1801133) gene, which is commonly analysed with regard to Hcy/folate metabolism, resulting in the highest Hcy level among PD pa-

tients with both *MTHFR* 677TT and *COMT*-Val genotypes [92,97]. This indicates a necessity of *COMT* inhibitors administration, especially in patients at the greatest genetic risk for developing HHcy. However, in another study, significantly higher Hcy plasma levels were observed only in PD patients with *MTHFR* 677TT and low activity-determining *COMT* genotypes (based on the genotyping of four *COMT* single nucleotide polymorphisms—SNPs: rs4680, rs6269, rs4633 and rs4818) at the same time. The authors showed a correlation between Hcy levels and PD dementia, although none of the analyzed polymorphisms had an impact on cognitive impairment [97].

6.2. APOE

Apolipoprotein E (apoE) is associated with cerebrovascular and neurodegenerative diseases, such as late onset AD and PD [98,99]. The *APOE* gene polymorphism is identified in the form of three major alleles *APOE2*, *APOE3*, and *APOE4*, which determine three protein isoforms (E2, E3, and E4, resp.) and six possible genotypes (*e2/e2*, *e2/e3*, *e2/e4*, *e3/e3*, *e3/e4*, and *e4/e4*). Several studies showed that the *e2* allele is associated with a higher risk of PD [100,101], whereas in others, the *e4* allele was a risk factor. However, the data is inconsistent [102,103]. It was suggested that *APOE4* expression exerts detrimental effects on the cerebrovascular system, including blood–brain barrier impairments [104]. Indeed, Bell et al. showed that mice expressing human *APOE4* had altered blood–brain barrier permeability and reduced cerebral blood flow compared with animals expressing *APOE2* or *APOE3* [105]. In addition, apoE mediates the clearance of A β across blood–brain barrier, through binding to its liver receptor (low-density lipoprotein receptor-related protein-1—LRP1), and that *APOE4* allele contributes to cerebral accumulation of A β [105].

In a study performed by Janelidze et al., blood–brain barrier permeability characterized by the use of the cerebrospinal fluid/plasma albumin ratio (Qalb) differed significantly in groups with dementia (AD, dementia with Lewy bodies or PD dementia, vascular dementia or frontotemporal dementia) compared to healthy controls, although no impact of *APOE4* allele on Qalb was found [83]. Nevertheless, Qalb seemed to correlate with CSF biomarkers of angiogenesis or endothelial damage, i.e., intracellular adhesion molecule 1 (ICAM-1), vascular cell adhesion molecule 1 (VCAM-1) and VEGF, in all diagnostic groups. Those results support the role of the blood–brain barrier leakage in dementia, including PD dementia.

Despite some discrepancy in the studies assessing the role of *APOE4* in cognitive status of PD patients, possibly due to different diagnostic criteria for dementia [106], two meta-analyses [101,107] showed an over-representation of *APOE4* carriers in PD dementia groups compared to cognitively normal PD patients. Additionally, the most recent meta-analysis revealed that *APOE4* was a risk factor for PD dementia development regardless of the population origin [107].

6.3. VEGF

Variability in *VEGF* expression, induced by specific *VEGFA* variants, is involved in angiogenesis-related disorders. At least 30 SNPs in this gene have been described, and some SNPs can alter VEGF serum levels. Three common SNPs, namely −2578C/A in the promoter region (rs699947), −634C/G in the 5-untranslated region (rs2010963) and +936C/T in the 3-untranslated region (rs3025039) are related to VEGF protein production [108,109], although no association between VEGF serum level and PD has been established so far [110]. Some *VEGF* SNPs have been examined as susceptibility factors to AD. Del Bo et al. found a correlation between AD and −2578A/A and −1198C/T genotypes [111]. Although the VEGF serum level did not differ between AD patients and controls, increased values were correlated with *VEGF* polymorphisms, which had previously been described as associated with AD. Furthermore, a link between the severity of cognitive impairment and VEGF level was determined in Alvarez et al. study—the protein values were higher in AD than in MCI patients and in the controls [112]. The number of wild-type *VEGF* −2578C alleles was positively associated with total grey matter volume, total white matter volume and

total arterial blood volume in young adults [113]. Considering that brain atrophy, thus smaller brain volume, correlates with cognitive decline in PD [114], this can suggest a protective role of the C allele.

In the studies on *VEGF* genetic polymorphisms in PD patients, rs3025039 was the only *VEGF* polymorphism determined to correlate with PD development [110,111,115]. *VEGF* gene expression interacted with the genetic susceptibility factor for PD dementia, i.e., *APOE4*, on global cognition in AD, but not on AD neuropathology suggesting independence of the interaction from AD neuropathology [116]. However, no research has analyzed the impact of *VEGF* polymorphisms on cognitive performance or dementia in PD.

6.4. RAA System Genes

The neuroprotective effects of ACE inhibitors or AT1R antagonists observed in animal PD models suggest that abnormalities in the RAA system may promote the PD development [117]. Over the past several years, numerous polymorphic loci in genes encoding various components of the RAA system were defined, e.g., an insertion/deletion polymorphism in angiotensin converting enzyme gene (*ACE*) [118] or SNPs in angiotensin II receptor type 1 (*AGTR1*) [119], angiotensin II receptor type 2 (*AGTR2*) [120] or in angiotensinogen (*AGT*) [121] genes.

The insertion/deletion polymorphism in the angiotensin-converting enzyme gene (*ACE* I/D) was the first in the RAA system to be examined as a potential susceptibility factor in PD [122]. Though no association was found by Mellick et al. in an Australian population [122], or Pascale et al. in an Italian one [123], a study in a Chinese population showed an increased frequency of *DD* genotype in PD compared to the control group [124]. This discrepancy may result from differences in *ACE* I/D polymorphism frequency among the respective populations, since the prevalence of the *D* allele is estimated to be 50–58% in Caucasians and 35–39% in a Chinese population [124].

On the other hand, in a Swedish study the *II* homozygotes had a two-fold higher risk of dementia (including AD and vascular dementia) than the other *ACE* I/D carriers [125]. However, the polymorphism was not associated with dementia in the follow-up. Similarly, the *CC* genotype of *AGTR1* rs5186 was associated with dementia only at baseline [126]. Three other SNPs in *AGTR1* (rs2638363, rs1492103, rs2675511) were signs of worse episodic memory performance in a 4 years' follow-up and additionally correlated with a hippocampal atrophy in older adults [127].

Purandure et al. reported a link between *ACE* I/D polymorphism and WMH in patients of Caucasian origin with AD or vascular dementia [128]. White matter hyperintensities were more severe in patients carrying the *DD* than *ID* ($p = 0.01$) or *II* genotype ($p = 0.009$) and the correlation remained significant after a correction for cardiovascular risk factors, thus suggesting other mechanisms contributing to WMH development. It is worth mentioning that carriers of both *APOE4* genotype and *ACE* *I* allele were at higher risk of developing late-onset AD [129].

Other *ACE* polymorphisms (rs4362), along with the SNP in the angiotensinogen gene (*AGT* rs699) and the SNP in angiotensin II receptor type 1 gene (*AGTR1* rs5182) were evaluated in older Australians [130]. A male-only relationship between *AGT* rs699 and *ACE* rs4362 polymorphisms and WMH was found, independently of hypertension. Moreover, the authors reported a synergistic effect of *AGT* rs699 and *AGTR1* rs5182 on WMH. Although it was established that *ACE* I/D polymorphism accounts for 47% of the variation in *ACE* serum level [131], other genetic polymorphisms, including synonymous ones, can affect gene expression and protein synthesis. Therefore, they may exert an impact on WMH and cognitive functions.

The available literature does not provide a comprehensive assessment of variability in genes encoding the RAA system components and their associations with BP variability in the course of PD or cognitive decline in PD (Table 2).

Table 2. Genetic factors influencing vascular functions and cognitive decline in PD.

Gene	Name of the Protein	Function of the Protein	Role in Cognitive Decline	References
COMT	catechol-O-methyltransferase	metabolism of catecholamines and L-dopa, involved in Hcy synthesis	polymorphism associated with Hcy overproduction	[92]
APOE	apolipoprotein E	component of several lipoproteins	APOE4 variant linked to A β accumulation and BBB disruption	[105]
VEGF	vascular endothelial growth factor	angiogenic activity, essential in vasculogenesis.	microvascular pathologies, BBB disruption	[23]
MTHFR	methylenetetrahydrofolate reductase	Hcy and folate metabolism	polymorphism correlated with HHcy	[132]
ACE	angiotensin converting enzyme	catalyzes AII synthesis; its inhibitors lower BP	A β degradation; polymorphism associated with WMH	[87,130]
AGT	angiotensinogen	precursor of all components within the RAA system	polymorphism associated with WMH	[130]
AGTR1	angiotensin receptor type 1	AII receptor	oxidative stress and neuroinflammation; polymorphisms associated with hippocampal atrophy	[79,127]
AGTR2	angiotensin receptor type 2	AII receptor	possible neuroprotection	[87]
HMGCR	HMG-CoA reductase	rate-controlling enzyme in the cholesterol synthesis pathway	polymorphism decreases cholesterol production	[133]

AII—angiotensin II; A β —amyloid- β ; BBB—blood–brain barrier; Hcy—homocysteine; HHcy—hyperhomocysteinemia; HMG-CoA—3-hydroxy-3-methylglutaryl-CoA; RAA—renin-angiotensin-aldosterone; WMH—white matter hyperintensities.

7. Conclusions

There is a growing demand to determine factors predisposing to the development of PD dementia. The impact of abnormal circadian BP variability observed in PD patients seems to contribute to WMH, which in turn may be a radiological marker for cognitive decline. Many of the presented factors, correlating with WMH hyperintensities and/or cognitive decline in PD, may and should be treated as far as possible (Figure 2). Hypertension, OH, supine hypertension and the absence of nocturnal BP fall can be diagnosed by an ambulatory 24-h BP monitoring and then managed by both nonpharmacological and pharmacological measures. Similarly, the impact of hyperhomocysteinemia—a metabolic risk factor for dementia in PD—may be possibly alleviated by more frequent blood concentration assessments and folate and/or B12 vitamin supplementation. As for the genetic risk factors, they may serve as markers of cognitive decline in PD or indicate a future direction for specific treatment, e.g., AGT1 receptor blockers and inhibitors of the RAA system. In summary, knowledge on vascular risk factors and their contribution to the cognitive impairment in PD may result in prophylaxis and better screening methods. However, this matter needs to be addressed in future studies, including clinical trials.

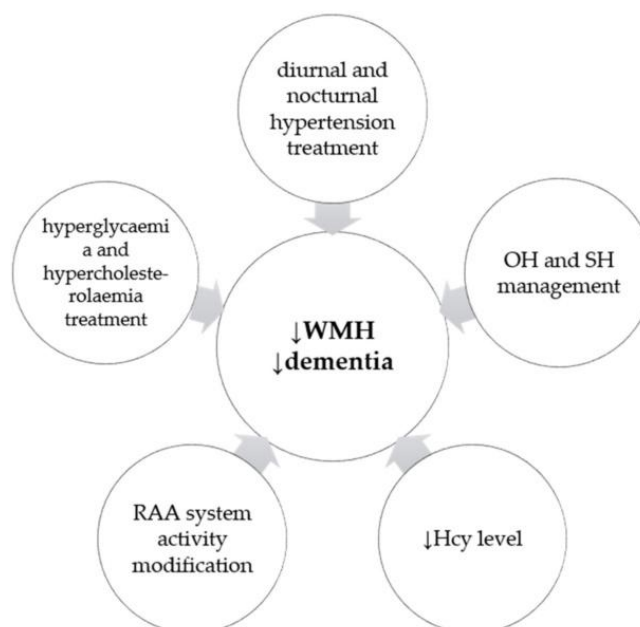


Figure 2. Possible measures decreasing the risk of developing WMH, and/or dementia, in Parkinson’s disease.

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The impact of short-term blood pressure variability on cognitive decline in Parkinson's disease patients without co-morbidities

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Abstract

Cardiovascular dysautonomia, cognitive decline and dementia are common non-motor features of Parkinson's disease. Short-term blood pressure variability may play a role in the pathogenesis of dementia. Sixty five patients with Parkinson's disease, without cardiovascular comorbidities, with no concomitant medications affecting cardiovascular system were enrolled in this cross-sectional study. They were divided according to their cognitive status and underwent clinical examination, 24 h ambulatory blood pressure monitoring, orthostatic test, brain magnetic resonance imaging and laboratory tests. Twenty patients were cognitively intact, 23 presented mild cognitive impairment and 20 had dementia. There were no differences in duration of the disease or dopaminergic therapy between the groups. Patients with dementia when compared to those cognitively intact, had higher short-term blood pressure variability, assessed as standard deviation of daytime diastolic blood pressure and average real variability of systolic blood pressure. They also had a higher frequency of supine hypertension and lower nocturnal blood pressure fall (reverse dipping). Average real variability of systolic blood pressure, supine hypertension and reverse dipping correlated with cognitive impairment, especially with visuospatial, language and executive functions. Short-term blood pressure variability, supine hypertension and reverse dipping may contribute to the pathogenesis of dementia in PD.

Keywords Parkinson's disease · Dementia · Dysautonomia · Short-term blood pressure variability

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Introduction

Parkinson's disease (PD) is one of the most common neurodegenerative disorders with motor (bradykinesia, rigidity and tremor) and non-motor symptoms (Alster and Madetko-Alster 2024). Among non-motor symptoms cognitive impairment and cardiovascular dysautonomia are frequent and can be present from early stages of the disease (Chaudhuri et al. 2006a, b; Fanciulli et al. 2025). Moreover, cardiovascular dysautonomia, particularly orthostatic hypotension (OH), at prodromal phase may predict phenocconversion and may be associated with more severe disease progression (Goldstein and Sharabi 2023).

Dementia is noticed in up to 17% of PD patients within 5 years from the disease onset, 46% at 10 and even 80% at 20 years and probably has a complex aetiology (Aarsland et al. 2021). Cardiovascular dysautonomia may contribute to this process (Longardner et al. 2022). Orthostatic hypotension is a frequent manifestation of PD with 30% prevalence, increasing with age, disease duration or levodopa equivalent dose (LEDD) (Espay et al. 2016; Malkiewicz

and Siuda 2024). It coexists often with supine hypertension (SH) (Espay et al. 2016). Loss of nocturnal blood pressure fall (non-dipping) has been also observed in this group of patients (Tanaka et al. 2018). Furthermore, they tend to have higher blood pressure variability (BPV) compared with healthy subjects (Alves et al. 2023; Kanegusuku et al. 2017).

This study aims to determine whether a short-term BPV (measured within 24 h) and other blood pressure abnormalities may contribute to cognitive impairment in a highly selected group of PD patients without co-morbidities and concomitant medications affecting cardiovascular system.

Subjects and methods

Sixty five patients of Caucasian origin, recruited from Out-patient Movement Disorder Clinic, with clinical diagnosis of idiopathic PD based on Movement Disorders Society Clinical Diagnostic Criteria (Postuma et al. 2015) were enrolled in the cross-sectional study (Table 1). Recruitment lasted 3 years and during that time approximately 500 patients were screened. The exclusion criteria were: secondary or atypical Parkinsonism, advanced therapies for PD (deep brain stimulation or infusion therapies), renal or liver impairment. To assess the real impact of dysautonomia on cognitive impairment in PD we excluded patients with cardiovascular diseases (e.g. hypertension, ischemic heart disease, heart failure, atrial fibrillation) or known as major risk factors (diabetes mellitus) and any medications (except for PD treatment) with known mechanism of action influencing blood pressure (renin-angiotensin system, RAS). Two participants were subsequently excluded due to diabetes mellitus diagnosed after initial evaluation.

The severity of the disease was assessed with the use of the Unified Parkinson's Disease Rating Scale (UPDRS; part III) in "on" state, Hoehn–Yahr staging, and the Schwab-England activities of daily living scale (Poewe 2009). Non motor symptoms were assessed with the non-motor symptoms questionnaire (NMSQ) (Chaudhuri et al. 2006a, b). All assessments were performed by the same physician. All patients received dopaminergic treatment. Dopaminergic therapies (levodopa, dopamine receptors agonists, MAO-B inhibitors, COMT inhibitors and amantadine) were converted to levodopa equivalent dosage (LEDD). All patients, except two, were taking levodopa and the majority were taking dopamine receptors agonists, therefore these two drug groups are listed separately in Table 1. Dopamine agonists were converted to ropinirole dose equivalence (Thobois 2006). Nevertheless, the influence of dopamine agonists and levodopa was analysed separately.

The detailed neuropsychological testing methods are presented in Table 3. Mild cognitive impairment (MCI) was defined as deficits in single cognitive domain and dementia

as impairment in more than one cognitive domain with negative impact on daily life, according to Litvan et al. (2011) and by Emre et al. (2007) criteria respectively. Based on the neuropsychological examination, the cohort was divided into three groups: PD with normal cognition (PD-NC), with mild cognitive impairment (PD-MCI) and with dementia (PD-D) (Table 1).

The examination with 3 T MRI (Philips Achieva, Netherlands) was performed in all subjects to exclude brain structural lesions. The groups did not differ in terms of white matter hyperintensities assessed in Fazekas scale, but specific imaging data were not analysed in this paper.

To measure BP an electronic inflatable brachial sphygmomanometer was used. Blood pressure was measured after at least five minutes of rest in a supine position. Supine hypertension was defined as systolic blood pressure (SBP) ≥ 140 mmHg or diastolic blood pressure (DBP) ≥ 90 mmHg (Fanciulli et al. 2018). Orthostatic hypotension was defined as a reduction in SBP ≥ 20 mmHg or ≥ 10 mmHg in DBP after 3 min of standing from a supine position. When the result was negative after 3 min, testing was prolonged to 10 min and BP was additionally measured after 5 and 10 min (Fanciulli et al. 2025).

Patients underwent 24-h ambulatory blood pressure monitoring (ABPM) using a Watch BP03 device on the non-dominant arm. Recordings were made every 20 min between 6:00 am and 10:00 pm and every 30 min between 10:00 pm and 6:00 am. The classification of nocturnal BP profiles, computed as percent change between daytime and night-time values, was as following: reverse dipper $< 0\%$, non-dipper 0–10%, dipper 10–20%, extreme-dipper $> 20\%$. Measured indices of BPV, based on ABPM, were: standard deviation (SD), coefficient of variation (CV, SD divided by a corresponding mean) both calculated for daytime, night-time and 24 h SBP and DBP as well as average real variability (ARV, calculated as the average of absolute changes between following BP readings) of 24 h SBP and DBP (Schutte et al. 2022).

Blood samples were collected early in the morning, after overnight fasting, at least 8 h after the last dose of dopaminergic medications. Vascular and dementia risk factors (vitamin B12, folic acid, thyrotropic hormone, glucose) together with renal and hepatic functions were assessed.

Informed written consent was obtained from all patients. Study protocol was approved by the Bioethics Committee for Scientific Research of Medical University of Gdansk (NKBBN/415/2018).

Statistical analysis

The Shapiro–Wilk test was used for the assessment of normal distribution for demographic and clinical data. The one-way parametric ANOVA and one-way non-parametric

Table 1 Demographic and clinical data of the study group

Variable	PD-NC (n = 20)	PD-MCI (n = 23)	PD-D (n = 20)	p-values
Sex (female/male)	9/11	9/14	7/13	0.81 ^a
Age (years)	62.6 (± 4.62)	64.6 (± 6.92)	67.7 (± 5.11)	0.02 ^b
Years of education	15.5 (11–23)	14 (10–24)	13 (10–17)	0.02 ^c
Duration of the disease (years)	7 (2–20)	6 (4–20)	9.5 (3–20)	0.25 ^c
LEDD (mg)	1017 (± 418)	1110 (± 492)	1314 (± 511)	0.139 ^b
Levodopa (mg)	693 (± 408)	812 (± 445)	1011 (± 442)	0.075 ^b
Ropinirole dose equivalence (mg)	9.42 (0–20)	7.38 (0–24)	8 (0–20)	0.246 ^c
Hoehn-Yahr scale	2 (1–3)	2 (1–3)	2 (1–3)	0.01 ^c
NMSQ	9.15 (± 3.69)	11.4 (± 3.96)	13.6 (± 3.70)	0.003 ^b
UPDRS (part III)	10 (3–35)	15 (2–40)	19.5 (4–31)	0.06 ^c
Schwab&England scale	90 (70–100)	85 (60–100)	77.5 (40–90)	0.004 ^c
SBP SD daytime	11 (4–57)	11 (6–29)	13.5 (6–43)	0.29 ^c
SBP SD night-time	8.5 (3–15)	9 (3–22)	10 (3–19)	0.25 ^c
SBP SD 24 h	12 (7–41)	10 (6–28)	14 (6–34)	0.27 ^c
SBP CV daytime	0.09 (0.03–0.41)	0.089 (0.05–0.21)	0.11 (0.06–0.35)	0.51 ^c
SBP CV night-time	0.08 (0.03–0.14)	0.07 (0.03–0.2)	0.08 (0.03–0.14)	0.28 ^c
SBP CV 24 h	0.09 (0.05–0.35)	0.08 (0.05–0.18)	0.11 (0.04–0.3)	0.38 ^c
SBP ARV	8.75 (5.78–18.0)	9.46 (7.68–17.6)	10.5 (7.39–17.7)	0.059 ^c
DBP SD daytime	6 (4–54)	7 (3–27)	8 (6–45)	0.028 ^c
DBP SD night-time	7 (3–11)	5 (3–16)	6.5 (3–15)	0.74 ^c
DBP SD 24 h	8 (4–39)	8 (5–22)	8.5 (6–34)	0.47 ^c
DBP CV daytime	0.08 (0.05–0.58)	0.09 (0.04–0.31)	0.1 (0.07–0.55)	0.10 ^c
DBP CV night-time	0.1 (0.04–0.2)	0.08 (0.04–0.25)	0.08 (0.03–0.19)	0.67 ^c
DBP CV 24 h	0.11 (0.05–0.52)	0.11 (0.06–0.28)	0.12 (0.07–0.46)	0.80 ^c
DBP ARV	5.52 (3.61–16)	6.67 (3.95–9.64)	6.58 (4.65–15.5)	0.059 ^c
Homocysteine (μmol/l)	14 (7.9–26.6)	14 (6.8–47)	18.4 (6.8–31.2)	0.09 ^c
%Δ MAP (%)	11.1 (± 9.92)	6.95 (± 9.91)	2.76 (± 10.4)	0.04 ^b
Nocturnal blood pressure profile	Dipper—40%	Dipper—43.5%	Dipper—25%	0.28 ^a
	Extreme dipper—10%	Extreme dipper—4%	Extreme dipper—5%	
	Reverse dipper—10%	Reverse dipper—30%	Reverse dipper—45%	
	Non-dipper—40%	Non-dipper—22.5%	Non-dipper—25%	
Supine hypertension	Present—15%	Present—26%	Present—50%	0.05 ^a
ΔSBP (mmHg)	5.5 (– 12 to 35)	12 (– 6 to 67)	16 (– 17 to 79)	0.20 ^c
ΔDBP (mmHg)	– 3 (– 12 to 9)	0 (– 12 to 32)	2 (– 14 to 34)	0.27 ^c
Orthostatic hypotension	Present—20%	Present—43%	Present—35%	0.52 ^a

Data are presented as a mean (± standard deviation) or a median (minimum–maximum)

LEDD levodopa equivalent dose (mg), UPDRS Unified Parkinson's Disease Rating Scale, NMSQ non-motor symptoms questionnaire, SBP systolic blood pressure, DBP diastolic blood pressure, SD standard deviation, CV coefficient of variation, ARV average real variability, %Δ MAP nocturnal blood pressure fall in %, ΔSBP orthostatic systolic blood pressure drop, ΔDBP orthostatic diastolic blood pressure drop, PD-NC patients with normal cognition, PD-MCI patients with mild cognitive impairment, PD-D patients with dementia

^aχ²

^bANOVA

^cKruskal–Wallis test

Kruskal–Wallis testing were further performed. For post hoc analyses of parametric and non-parametric data were used Tukey's test and Dunn's test, respectively. Spearman's ρ coefficient was used to determine the correlation between the two quantitative variables. Comparisons for categorical variables were performed using χ² tests. In case of problems

with determining the p-value from the asymptotic χ² distribution of the test statistic, Monte-Carlo simulations with 2000 repetitions were used to determine this value. Cramer's V was used to test the strength of the relation between the two nominal variables.

Ordinal regression models were also constructed. In these models, the dependent variables were categories related to the patients' cognitive functions, and the independent variables were values characterizing the studied individuals. Then multivariate regression analyses, using the forward stepwise selection method, were conducted (compared parameters were: Akaike information criterion—AIC, Bayesian information criterion—BIC, p).

Receiver Operating Characteristic (ROC) curves were determined from the logistic regression models created for patients with normal cognition and dementia, to meet the dichotomous requirements for this method. The sensitivity and specificity values shown in the graph determine the classification correctness of variables describing BP abnormalities and short-term BPV indices as predictors of dementia (Fig. 1).

The calculations used functions and procedures from the R environment (R Core Team 2024). The significance level was set at $\alpha = 0.05$.

Results

Demographic data

The detailed demographics are presented in Table 1. Among 63 patients, 25 were women (39.7%). Twenty patients had normal cognition, 23 and 20 were diagnosed MCI and dementia respectively. Patients with normal cognition were significantly younger, better educated and had a more benign disease course than PD-D (Table 2). There were no differences in duration of the disease or dopaminergic therapies between the groups.

Blood pressure abnormalities

Thirty three percent of patients had OH (12% delayed to 5–10 min), 31% SH and in 14% both coexisted. Although differences in a prevalence of OH in all three groups were not statistically significant, it was correlated with more

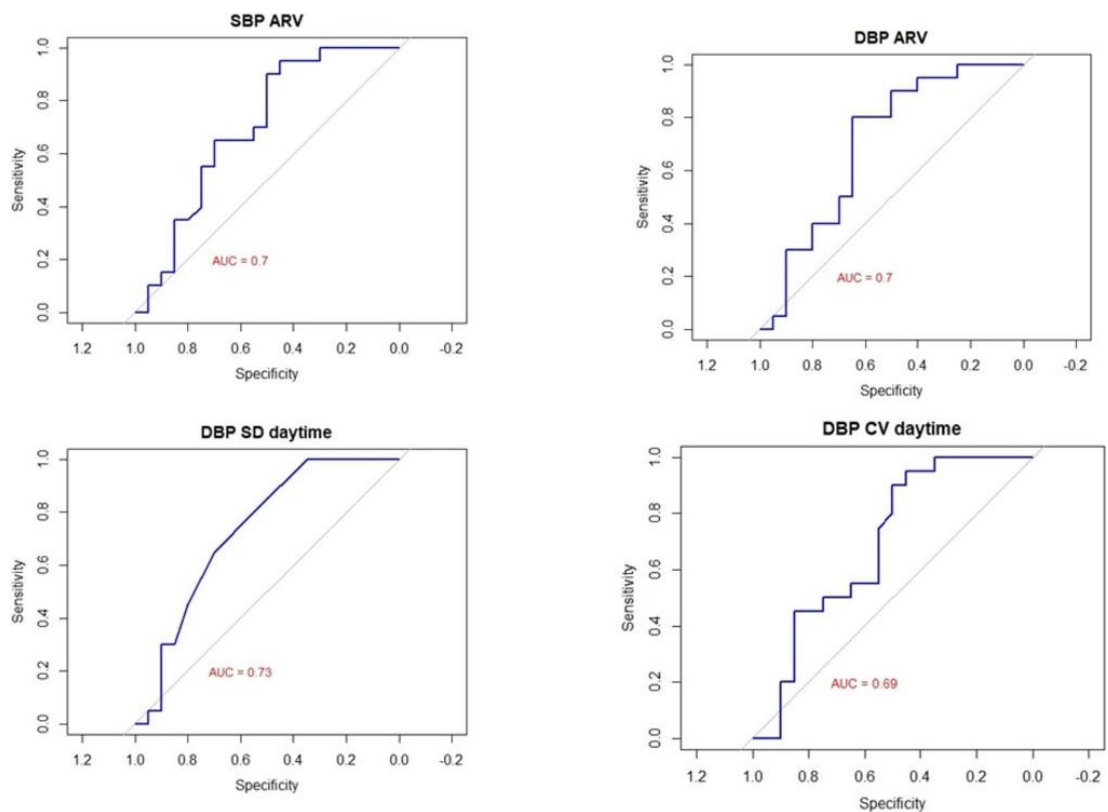


Fig. 1 ROC curves. Accuracy of short-term BPV indices as predictors for dementia. *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *ARV* average real variability, *CV* coefficient of variation, *SD* standard deviation

Table 2 Post hoc test results (p-values) presenting specific differences between the study groups

Variable	PD-NC vs PD-MCI	PD-NC vs PD-D	PD-MCI vs PD-D
Age ^d	0.26	0.03	0.24
Years of education ^c	0.26	0.01	0.26
NMSQ ^d	0.17	0.003	0.17
Schwab&England scale ^c	0.31	0.003	0.04
UPDRS ^c	0.39	0.05	0.40
SBP ARV ^e	0.42	0.05	0.42
DBP ARV ^e	0.09	0.09	0.83
DBP SD daytime ^c	0.28	0.02	0.28
DBP CV daytime ^c	0.53	0.09	0.53
Homocysteine (μmol/l) ^e	0.64	0.10	0.19
%Δ MAP (%) ^d	0.38	0.07	0.28
Supine hypertension ^f	0.43	0.05	0.18

UPDRS Unified Parkinson's Disease Rating Scale, NMSQ non-motor symptoms questionnaire, SBP systolic blood pressure, DBP diastolic blood pressure, SD standard deviation, CV coefficient of variation, ARV average real variability, %Δ MAP nocturnal blood pressure fall in %, PD-NC patients with normal cognition, PD-MCI patients with mild cognitive impairment, PD-D patients with dementia

^dTukey's test

^cDunn's test

^fMcNemar corrected with Bonferroni method

severe impairment in a verbal memory and visuospatial, language and executive functions (Table 3). Drop in DBP correlated with LEDD ($p = 0.46$, $p\text{-value} = 0.0001$) and separately with levodopa dose ($p = 0.44$, $p\text{-value} = 0.0003$).

Supine hypertension was associated with dementia (Cramer's $V = 0.2562$, $p\text{-value} = 0.0473$).

There was a trend towards association between lower nocturnal blood pressure fall (%ΔMAP), reverse dipping pattern and cognitive decline (Cramer's $V = 0.2971$, $p\text{-value} = 0.09$; Cramer's $V = 0.2971$, $p\text{-value} = 0.08$, respectively).

Short-term blood pressure variability

Standard deviation of daytime DBP was significantly higher in PD-D (Table 1). Also average real variability of SBP was significantly higher in the PD-D when compared to PD-NC (Table 2). Coefficient of variation of daytime DBP and DBP ARV were also higher in PD-D patients, but differences remained at the trend level. Visuospatial, language and executive functions were negatively related to CV of daytime DBP (Table 3). Average real variability of SBP correlated with decreased MoCA scores and deficits in visuospatial memory and executive functions (Table 3). Levodopa equivalent dosage and ropinirole dose equivalence did not show any correlation with assessed parameters.

Laboratory tests

Laboratory tests, including vascular or dementia risk factors (vitamin B12, folic acid, thyrotropic hormone, glucose) did not differ between groups. There was a trend towards higher homocysteine level in PD-D group and it correlated with higher levodopa dosage (Table 2).

Regression analyses

Univariate regression analyses in models for dementia identified age, Hoehn-Yahr's more advanced stage, NMSQ score, SH, reverse dipping pattern and inversely: nocturnal blood pressure fall, years of education and scores in Schwab-England scale as significant variables. Higher SBP ARV was associated with cognitive impairment at the trend level (Table 4). Multivariate regression analyses models identifying significant predictors for the development of dementia were comparable and did not have sufficient parameters to choose the best one.

The highest accuracy as predictors of dementia was achieved for SBP ARV, DBP ARV and DBP SD and DBP CV, both calculated for daytime period. (Fig. 1).

Discussion

This is to our knowledge the first study assessing the impact of short-term BPV on cognition in a highly selected group of PD patients without comorbidities and co-medications. We found that PD-D patients presented higher BPV, reverse dipping and SH when compared to PD-NC. Moreover, results of our study suggest, that those variabilities may be associated with cognitive decline in PD.

Blood pressure variability

Short-term BPV characterizes BP fluctuations through 24 h (ABPM) (Schutte et al. 2022). It can be assessed with several indices and the classic ones include: SD (correlated with average BP) and CV (independent on the average BP), both influenced by diurnal BP variation (Schutte et al. 2022). Average real variability is not affected by alterations in circadian rhythm, but depends on the number of BP measurements (Mena et al. 2005; Schutte et al. 2022). In the literature there are no clear recommendations which of the indices should be used and which has the strongest prognostic value. Results of a recent, large meta-analysis indicate an association of long-term systolic and diastolic BPV (visit to visit assessments during months or years) with cognitive decline in a general population, stronger than for mean BP (Heus et al. 2021). However, there are only few studies assessing such relationship between short-term BPV and

Table 3 Tests used for cognitive assessment and their correlations with blood pressure variables (performed by the Spearman's rank correlation coefficient)

Cognitive domain	ΔDBP	ΔSBP	SHSBP ≥ 140 mmHg	SH-DBP ≥ 90 mmHg	%ΔMAP	SD DBP day	ARV SBP	ARV DBP	CV DBP day
General cognitive functions									
MoCA	− 0.14	− 0.24 [^]	− 0.25 [^]	− 0.16	− 0.07	− 0.16	− 0.29*	− 0.21	− 0.21
Visuospatial functions									
Benton JoLO	− 0.27*	− 0.41**	− 0.22	− 0.03	− 0.06	− 0.05	− 0.19	− 0.08	− 0.09
VOSP									
Screening test	− 0.01	− 0.05	− 0.02	0.08	− 0.09	− 0.23	− 0.11	− 0.12	− 0.31*
Incomplete letters	− 0.20	− 0.27*	− 0.05	− 0.05	− 0.10	− 0.17	− 0.16	− 0.26 [^]	− 0.34*
Dots counting	0.11	− 0.09	− 0.11	− 0.17	− 0.08	0.00	− 0.25 [^]	0.10	0.03
Cube analysis	− 0.12	− 0.22	− 0.07	− 0.03	− 0.12	− 0.21	− 0.22	− 0.12	− 0.30*
Verbal memory									
WAIS									
Digit span forward	− 0.14	− 0.11	− 0.13	− 0.04	0.08	0.08	− 0.01	− 0.06	− 0.13
Digit span backwards	0.04	− 0.07	− 0.12	0.15	0.11	0.01	0.03	− 0.08	− 0.25 [^]
CVLT									
List A Tasks 1–5	− 0.19	− 0.30*	− 0.17	− 0.10	− 0.08	− 0.20	− 0.20	− 0.22	− 0.23
List A Task 1	− 0.20	− 0.24 [^]	− 0.17	− 0.12	− 0.07	− 0.24 [^]	− 0.14	− 0.12	− 0.11
List A Task 5	− 0.14	− 0.25 [^]	− 0.16	− 0.11	− 0.17	− 0.19	− 0.22	− 0.23	− 0.24 [^]
List A Free recall after distraction	− 0.04	− 0.01	− 0.08	− 0.10	0.03	− 0.07	0.00	− 0.17	− 0.22
List A Free recall after 20 min	− 0.15	− 0.24	− 0.16	− 0.19	− 0.18	− 0.14	− 0.16	− 0.12	− 0.18
Guided recall after distraction	− 0.13	− 0.22	− 0.07	− 0.21	− 0.15	− 0.06	− 0.24 [^]	− 0.18	− 0.10
Guided recall after 20 min	− 0.13	− 0.25	− 0.13 [^]	− 0.10	− 0.05	− 0.22	− 0.30*	− 0.25 [^]	− 0.23
Perseverations	− 0.19	− 0.20	− 0.11	− 0.09	− 0.22	− 0.17	− 0.15	− 0.13	− 0.27*
Confabulations in free recall	0.09	− 0.01	− 0.01	0.18	0.05	0	0.09	− 0.10	− 0.05
Confabulations in guided recall	− 0.08	0.14	− 0.12	− 0.15	0	0.15	0.22	0.18	0.16
Recognition—total hits	0.08	0.26*	0.16	0	0.02	0.08	0.12	0.11	0.07
Recognition mistakes	0.03	− 0.12	− 0.09	− 0.16	− 0.20	− 0.14	− 0.23	− 0.24 [^]	− 0.19
Visuospatial memory									
Corsi Block-Tapping test									
Span forward	− 0.01	0.02	0.03	0.04	0.06	0.02	0.04	− 0.07	− 0.16
Span backward	0.01	0.02	− 0.05	0.04	− 0.05	− 0.19	− 0.13	− 0.10	− 0.27 [^]
CVMT									
Hits	0.07	− 0.09	− 0.15	− 0.10	− 0.03	− 0.12	− 0.32*	− 0.20	− 0.17
False alarms	0.24	0.14	0.17	0.18	0.13	0.01	− 0.03	0.10	− 0.15
d'	− 0.19	− 0.17	− 0.18	− 0.21	− 0.18	− 0.05	− 0.11	− 0.17	0.09
Total score	− 0.16	− 0.27 [^]	− 0.25	− 0.09	− 0.08	− 0.06	− 0.12	− 0.05	0.12
Delayed recognition	0.02	− 0.13	− 0.10	0	− 0.02	− 0.06	− 0.31*	− 0.25	0.06
Language									
BNT-30	− 0.27*	− 0.41**	− 0.08	0.08	− 0.08	− 0.25	− 0.15 [^]	− 0.08	− 0.30*
Executive functions									
D-KEFS Tower test									
Mean time of first move	0.31*	0.28*	− 0.02	0	0.06	0.15	0.12	− 0.04	0.09
Sum 1–9 trial	− 0.22	− 0.26 [^]	− 0.16	− 0.12	− 0.05	− 0.07	− 0.34**	− 0.17	− 0.14
Total number of rule violations	0.15	0.15	0.01	− 0.10	− 0.03	0.06	0.19	0.14	0.30*
COWAT									
Phonemic (“K”)	− 0.27*	− 0.28*	− 0.17	− 0.10	− 0.03	− 0.15	− 0.04	− 0.16	− 0.34**
Animals	− 0.20	− 0.28*	− 0.18	− 0.07	− 0.04	− 0.17	− 0.19	− 0.21	− 0.38**

Table 3 (continued)

Cognitive domain	Δ DBP	Δ SBP	SHSBP ≥ 140 mmHg	SH-DBP ≥ 90 mmHg	% Δ MAP	SD DBP day	ARV SBP	ARV DBP	CV DBP day
Sharp items	-0.03	-0.17	-0.11	0.05	0.09	-0.11	-0.16	-0.15	-0.34**
Dynamic praxis (sum)	-0.12	-0.35**	-0.33*	-0.28*	-0.14	-0.08	-0.20	-0.21	0.01
Alternating motor pattern									
Total number	0	0.12	-0.06	-0.13	-0.06	0.01	-0.11	-0.12	-0.08
Number of errors	0.25	0.28^	0.16	0.22	0.27	0.11	0.04	0.04	-0.10
Correct rate	-0.28^	-0.31*	-0.23	-0.34*	-0.27^	-0.11	-0.11	-0.12	0.02

MoCA Montreal cognitive assessment, *JoLO* judgement of line orientation, *VOSP* visual objects and space perception battery, *WAIS* Wechsler Adult Intelligence Scale, *CVLT* California verbal learning test, *CVMT* continuous visual memory test, *BNT* Boston naming test, *D-KEFS* Delis-Kaplan executive function system, *COWAT* controlled oral word association test, Δ SBP orthostatic systolic blood pressure drop, Δ DBP orthostatic diastolic blood pressure drop, % Δ MAP nocturnal blood pressure fall in %, *SH* supine hypertension, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *SD* standard deviation, *CV*—coefficient of variation, *ARV* average real variability

Significance codes: **p-value < 0.01, *p-value < 0.05, ^p-value < 0.1

Table 4 Ordinal regression analysis for risk of dementia

Explanatory variables (predictors)	Ordinal regression				p-value
	B	OR	CI		
			Lower	Upper	
Age	0.1	1.11	1.03	1.21	0.01
Years of education	− 0.23	0.79	0.67	0.93	0.005
Hoehn-Yahr scale	1.1	2.99	1.348	7.092	0.01
Schwab-England scale	− 0.08	0.92	0.876	0.969	0.002
NMSQ	0.21	1.24	1.095	1.419	< 0.001
SBP ARV	0.19	1.21	1.002	1.494	0.059
Reverse dipping	1.39	4.02	1.199	14.470	0.03
SH	1.29	3.63	1.297	10.783	0.02
% ΔMAP	− 0.06	0.94	0.894	0.985	0.01

B—unstandardized regression coefficient, *SH* supine hypertension, % Δ MAP nocturnal blood pressure fall in %, *SBP ARV* average real variability of systolic blood pressure, *NMSQ* non-motor symptoms questionnaire

cognition (Sun 2023). Arterial stiffness related to ageing, high BP values and reduced hippocampal volume may be the underlying mechanisms linking systolic BPV with cognitive impairment, whereas higher diastolic BPV is correlated with greater white matter hyperintensities (WMH) volume, endothelial dysfunction and increased sympathetic activity (Gutteridge et al. 2022; Schillaci et al. 2012). Furthermore increased BPV may cause hemodynamic instability, what may lead to cerebral hypoperfusion (Sun 2023). An Alves et al. (2023) showed a tendency to asymptomatic organ damage (carotid intima-media thickness, extracranial plaques and increased pulse pressure) in PD patients with higher systolic BPV, what is in concordance with described above studies based on general population (Heus et al. 2021; Schillaci et al. 2012). Higher levels of BPV were also observed among advanced PD patients (Shen et al. 2022).

The results of studies assessing short-term BPV in PD patients are inconsistent and difficult to compare as different

indices were used for the assessments (Alves et al. 2023; Chen et al. 2024; Kanegusuku et al. 2017; Kim et al. 2012; Sebastian et al. 2022; Shen et al. 2022; Tsukamoto et al. 2013; Yoo et al. 2020). In the majority of studies using classical ones, only daytime BPV was significantly increased, when compared to healthy controls (Kanegusuku et al. 2017; Alves et al. 2023; Shen et al. 2022). Standard deviation and CV from night-time and 24 h period may not show the BPV adequately in this group of patients due to reduced nocturnal blood pressure fall.

The association between short-term BPV and cognition in PD was previously analysed in one study with drug naive patients (Kim et al. 2012). Participants with hypertension or diabetes mellitus were also enrolled and BPV of DBP was not studied. In our study we excluded such patients to make the results more clear and related to PD or PD medications itself. Although our group was treated for PD, LEDD was not statistically different between the groups. In Kim et al.

(2012) study SD and CV of SBP were significantly higher in PDD. Moreover, frontal executive functions were negatively related to the SD of SBP. It is partly consistent with our results, where higher levels of BPV also characterized the PD-D group (together with decrease in executive functions) for SBP ARV, SD of daytime DBP and on a trend level for daytime DBP CV and DBP ARV. Furthermore, our findings suggest, that increased SBP ARV may predict dementia and it was precisely associated with the worse global cognitive function and poor performance in visuospatial memory and executive function (Table 3, Fig. 1).

Orthostatic hypotension

Orthostatic hypotension along with SH are supposed to be a risk factors for cognitive decline (Espay et al. 2016). The prevalence of both increases with the disease duration (Kwaśniak-Butowska et al. 2021). The association of OH with dementia was not confirmed in our study, however orthostatic changes in SBP and DBP affected certain cognitive domains (verbal memory, visuospatial, language and executive functions) (Table 3). This may be due to limited number of recruited patients, early disease stage or the assessment method, as OH occurs more frequently after tilting than on standing (Jamnadas-Khoda et al. 2009). It seems to be consistent with the findings by Vallelonga et al. (2019, 2024), who observed that a number of ABPM hypotensive episodes (defined as systolic drop ≥ 15 mmHg compared with the average 24-h SBP during the waking period) have a stronger association with dementia than the simple bedside assessment. Executive performances in PD patients with OH are also temporarily worsen upon postural change, owing to impair cerebral autoregulation during orthostatic stress, with a negative influence on patients quality of life (Centi et al. 2017). Prevalence of SH in our study was similar to that observed by other authors and it was associated with dementia (Kim et al. 2012; Umehara et al. 2016). Longitudinal presence of SH was recently found to be associated with verbal memory decline, possibly resulting from hippocampal atrophy (Miller-Patterson et al. 2024).

Nocturnal blood pressure

Abnormal nocturnal BP profile in PD patients is common, independently from coexisting hypertension (Milazzo et al. 2018). Reverse pattern, according to Milazzo et al. (2018), can be a marker of cardiovascular dysautonomia and may lead to left ventricular hypertrophy, similar to essential hypertensive patients (Di Stefano et al. 2020) and development of WMH (Tanaka et al. 2018). In our study it was also identified as a predictor of dementia, what was confirmed in Tanaka et al. (2018) and Chen et al. (2024) studies as well.

Role of laboratory findings

We failed to demonstrate an association between Hcy, cognitive dysfunction and WMH described in previous study (Sławek et al. 2013). However Hcy levels correlated with higher levodopa doses and potentially may be harmful due to its vascular and neurotoxic properties (Sławek et al. 2013).

Role of medications

Levodopa dose in our study group correlated with orthostatic drop of DBP. However, like other authors, we did not observe such association for orthostatic drop of SBP (Earl et al. 2024; Jost et al. 2020). Levodopa may affect BP due to baroreflex impairment (Earl et al. 2024). Stimulation of central D1 receptors (Durrieu et al. 1990) and peripheral D2 receptors on postganglionic sympathetic nerves (Mannelli et al. 1999) can lead to lower norepinephrine plasma levels, as it was found in previous studies (Bouhaddi et al. 2004). It might be hypothesized that due to autonomic denervation in PD, dopaminergic therapy enhance a deficit in blood pressure regulation, what needs to be investigated in further studies.

Strengths and limitations

The major strength was the study design. Neuropsychological testing was detailed and based on both general and highly specific outcome measures. Each cognitive domain was assessed with two tests and the number of patients in each group according to cognitive status was equal. This was in concordance with the current dementia and PD related MCI definitions (Emre et al. 2007; Litvan et al. 2011). Groups also did not differ in terms of dopaminergic therapies. One of the most important strengths of the study was the exclusion of patients with cardiovascular diseases or taking medications affecting RAS, thus potential confounders leading to dysautonomia or having influence on BPV were excluded. However, this limited the total number of patients enrolled. A weakness of this study is a relatively small sample size, but it was related to the mentioned above restrictions in recruiting patients without co-morbidities and commonly used in this population medications. Nonetheless this had a negative impact on the statistical power of our analyses and strength of our conclusions. Furthermore, ABPM was performed only once and OH was assessed on standing, not on tilting, but it resembles the clinical practice (Fanciulli et al. 2025).

Conclusions

Increased SBP ARV, SH and reverse dipping correlated with dementia in PD. The ABPM should be considered in the monitoring of PD patients as it is an easy to perform and

inexpensive. The procedure should be standardized, as some of the BPV indices depend on the number of the measurements. Recognition and treatment of circadian BP abnormalities in PD patients potentially may protect them from further cognitive decline what requires further longitudinal studies.

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Author contributions All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Magdalena Kwaśniak-Butowska, Agnieszka Konkel, Agnieszka Skrzypkowska, Dariusz Wiczorek and Piotr Wąż. The first draft of the manuscript was written by Magdalena Kwaśniak-Butowska and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Data Availability The data that support the findings of this study are available from the corresponding author upon reasonable request.

Declarations

Conflict of interest The authors declare that they have no conflict of interest.

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Short communication

Peripheral renin-angiotensin system and cognitive decline in Parkinson's disease patients without co-morbidities

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ABSTRACT

Introduction: Peripheral renin angiotensin system (RAS) regulates blood pressure and is involved in inflammation and oxidative stress processes. We aimed to determine whether a peripheral RAS may contribute to cognitive impairment in a highly selected group of Parkinson's disease (PD) patients without co-morbidities and concomitant medications affecting RAS. Correlations between RAS, blood pressure abnormalities and short-term blood pressure variabilities (BPV) were additionally assessed.

Material and methods: A total of 63 PD patients were enrolled. Clinical evaluation included assessment of motor abilities with dedicated scales. According to neuropsychological examination patients were classified into a group: with normal cognition ($n = 20$), mild cognitive impairment (MCI) ($n = 23$) or dementia ($n = 20$). All groups did not differ in terms of disease duration and dopaminergic treatment. Patients underwent 24h ambulatory blood pressure monitoring and orthostatic test. Plasma levels of renin, angiotensin II, aldosterone and plasma renin activity (PRA) were measured in a fasting state.

Results: There were no differences in assessed parameters of RAS between all 3 groups. Better performance in visuospatial memory, visuospatial and executive functions was correlated to higher renin levels and PRA. Angiotensin II higher levels correlated with poor verbal memory and executive functions. Lower levels of renin and PRA resulted in increase of short-term BPV.

Conclusions: Peripheral RAS did not correlate with dementia or MCI, but may have an impact on selected cognitive domains and may contribute to an increase in BPV.

1. Introduction

Patients with Parkinson's disease (PD) tend to have higher blood pressure variability (BPV) [1]. Furthermore cardiovascular dysautonomia is a part of non-motor symptoms of PD [2] and may decrease cognitive functions in this group [3]. Peripheral renin-angiotensin system (RAS) is involved in blood pressure (BP) regulation, maintaining water and electrolyte balance and systemic vascular resistance [4]. The classic axis of RAS, with angiotensin II (AngII) as a main component,

synthesized by angiotensin converting enzyme (ACE-1), promotes also pro-inflammatory processes and oxidative stress [5]. Its effects are mediated mainly by type 1 receptors (AT1R). Elevated peripheral ACE-1 levels in cognitively intact study group of general population were associated with worse processing speed and working memory, whereas higher AngII concentrations with lower total grey matter and hippocampal volumes assessed in MRI [6,7]. Brain poses its own RAS [4]. Excessive activation of AngII/AT1R in the substantia nigra can lead to degradation of dopaminergic neurons, due to activation of microglia and

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the development of neuroinflammation [4]. Furthermore use of antihypertensive medications acting on RAS may reduce risk of PD [8] and AT1R blockers in particular were reported to improve motor impairment [9] and showed potentially protective effect on cognitive decline in PD [10].

However till now, the relationship between peripheral RAS and cognitive function in PD remains unclear and the impact on cognition was only suspected and based on indirect evidence.

This study aims to determine whether a RAS activity may contribute to cognitive impairment in a highly selected group of PD patients without co-morbidities and concomitant medications affecting cardiovascular functions. We assessed additionally correlations between RAS and blood pressure abnormalities and short-term blood pressure variabilities (BPV).

2. Material and methods

The study protocol and outcomes regarding blood pressure abnormalities and BPV have been published previously [11].

In this cross-sectional study were enrolled 63 patients of Caucasian origin with idiopathic PD according to Movement Disorders Society Clinical Diagnostic Criteria (Table 1). Patients with advanced therapies for PD (deep brain stimulation or infusion therapies), renal or liver impairment, electrolyte imbalance, cardiovascular diseases (including hypertension, ischemic heart disease or diabetes mellitus) and taking medications affecting RAS were excluded from the study. The Unified Parkinson's Disease Rating Scale (UPDRS; part III) in „on” state, Hoehn-Yahr staging, the Schwab-England activities of daily living scale and non-motor symptoms questionnaire (NMSQ) were used to assess the severity of the disease. All assessments were performed by the same physician. Dopaminergic therapies were converted to levodopa equivalent dosage (LEDD).

Each cognitive domain was assessed with two dedicated testing methods (Table 2). Litvan et al. [12] and Emre et al. [13] criteria were

used to define mild cognitive impairment (MCI) and dementia, respectively. Patients were classified into three groups: PD with normal cognition (PD-NC), with mild cognitive impairment (PD-MCI) and with dementia (PDD) (Table 1).

Blood pressure was measured with an electronic inflatable brachial sphygmomanometer. Measurement was conducted after at least 5 min of rest in a supine position. Supine hypertension was defined as systolic blood pressure (SBP) ≥ 140 mmHg or diastolic blood pressure (DBP) ≥ 90 mmHg. A fall in SBP ≥ 20 mmHg or ≥ 10 mmHg in DBP after 3 min of standing from a supine position was defined as orthostatic hypotension (OH). Testing was prolonged to 10 min, if the result was negative after 3 min, and BP was measured then also after 5 and 10 min.

Twenty-four-hour ambulatory blood pressure monitoring (ABPM) was recorded using a Watch BP03 device on the non-dominant arm. Measurements were made in 20 min intervals between 6:00 a.m. and 10:00 p.m. and in 30 min intervals between 10:00 p.m. and 6:00 a.m. Standard deviation (SD), coefficient of variation (CV) both calculated for daytime, night-time and 24h SBP and DBP as well as average real variability (ARV, calculated as the average of absolute changes between following BP readings) of 24h systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured indices of short-term BPV.

Blood samples were collected early in the morning, around 7 a.m. in all patients, after overnight fasting, at least 8 h after the last dose of dopaminergic medications. Renin, plasma renin activity (PRA, calculated as a synthesis rate of AngI by a plasma sample under controlled conditions), angiotensin II and aldosterone were assessed as the parameters of RAS. Blood sample for PRA measurement was collected without venous stasis, promptly centrifuged and quickly frozen. Renin concentration was determined by chemiluminescence immunoassay (CLIA) on LIAISON XL analyzer. Plasma renin activity was measured by radioimmunoassay using an Ang I RIA KIT (Beckman Coulter, ImmunoTech, Prague, Czech Republic). Aldosterone and angiotensin II concentrations were determined by enzyme-linked immunosorbent assay (ELISA) using a DRG kit (DRG Instruments GmbH, Marburg, Germany)

Table 1

Demographic and clinical data of the study group. LEDD-levodopa equivalent dose (mg), UPDRS - Unified Parkinson's Disease Rating Scale, NMSQ - non-motor symptoms questionnaire, SBP - systolic blood pressure, DBP - diastolic blood pressure, SD - standard deviation, CV - coefficient of variation, ARV - average real variability, Δ SBP - orthostatic systolic blood pressure drop, Δ DBP - orthostatic diastolic blood pressure drop, PD-NC- patients with normal cognition, PD-MCI - patients with mild cognitive impairment, PD-D - patients with dementia.

Variable	PD-NC (n = 20)	PD-MCI (n = 23)	PD-D (n = 20)	p-values	Post-hoc analysis
Sex (Female/Male)	9/11	9/14	7/13	0.81 ^a	–
Age (years)	62.6 (± 4.62)	64.6 (± 6.92)	67.7 (± 5.11)	0.02 ^b	PD-NC < PDD ^d
Years of education	15.5 (11–23)	14 (10–24)	13 (10–17)	0.02 ^c	PD-NC > PDD ^e
Duration of the disease (years)	7 (2–20)	6 (4–20)	9.5 (3–20)	0.25 ^c	–
LEDD (mg)	1017 (± 418)	1110 (± 492)	1314 (± 511)	0.139 ^b	–
Levodopa (mg)	693 (± 408)	812 (± 445)	1011 (± 442)	0.075 ^b	–
Ropinirole dose equivalence (mg)	9.42 (0–20)	7.38 (0–24)	8 (0–20)	0.246 ^c	–
Hoehn-Yahr scale	2 (1–3)	2 (1–3)	2 (1–3)	0.01 ^c	–
NMSQ	9.15 (± 3.69)	11.4 (± 3.96)	13.6 (± 3.70)	0.003 ^b	PD-NC > PDD ^c
UPDRS (part III)	10 (3–35)	15 (2–40)	19.5 (4–31)	0.06 ^c	PD-NC < PDD ^e
Schwab&England scale	90 (70–100)	85 (60–100)	77.5 (40–90)	0.004 ^c	PD-NC > PDD ^e , PD-MCI > PDD ^e
SBP ARV	8.75 (5.78–18.0)	9.46 (7.68–17.6)	10.5 (7.39–17.7)	0.059 ^c	PD-NC < PDD ^e
DBP SD daytime	6 (4–54)	7 (3–27)	8 (6–45)	0.028 ^c	PD-NC < PDD ^e
DBP CV daytime	0.08 (0.05–0.58)	0.09 (0.04–0.31)	0.1 (0.07–0.55)	0.10 ^c	PD-NC < PDD ^e
DBP ARV	5.52 (3.61–16)	6.67 (3.95–9.64)	6.58 (4.65–15.5)	0.059 ^c	PD-NC < PDD ^e , PD-MCI < PDD ^e
Δ SBP (mmHg)	5.5 (-12 - 35)	12 (-6 - 67)	16 (-17 - 79)	0.20 ^c	–
Δ DBP (mmHg)	-3 (-12 - 9)	0 (-12 - 32)	2 (-14 - 34)	0.27 ^c	–
Renin	7.8 (1.3–65)	7.3 (0.7–47)	5.4 (1.5–42.5)	0.3609 ^c	–
PRA (ng/ml/h)	0.49 (0.16–4.7)	0.49 (0.07–3.26)	0.535 (0.13–5.67)	0.73 ^c	–
Aldosterone (pg/ml)	96.3 (50–152)	95 (37.3–332)	90.1 (55.4–192)	0.88 ^c	–
Angiotensin II (pg/ml)	8.56 (3.74–71.7)	8.22 (3.25–116)	7.64 (2.10–120)	0.596 ^c	–

Data are presented as a mean ($\pm$ standard deviation) or a median (minimum-maximum).

^a χ^2 .

^b ANOVA.

^c Kruskal-Wallis test.

^d Tukey's test.

^e Dunn's test.

Table 2

Tests used for cognitive assessment and their correlations with renin-angiotensin system (performed by the Spearman's rank correlation coefficient). Significance codes: ** p-value <0.01, * p-value <0.05, ^ p-value <0.1

	PRA	Renin	Aldosterone	Angiotensin II
General cognitive function				
MoCA	0.07	0.21	0.10	−0.07
Visuospatial function				
Benton JoLO	0.387**	0.34**	0.23	−0.1
VOSP				
Screening test	0.24^	0.13	0.22	−0.03
Incomplete letters	0.26^	0.15	−0.03	0.19
Dots counting	0.33*	0.29*	−0.21	−0.04
Cube analysis	0.21	0.05	0.02	0.08
Verbal Memory				
WAIS-R				
Digit span forward	0.16	0.26^	0.34*	−0.26^
Digit span backwards	0.2	0.27*	0.29*	−0.29*
CVLT				
List A Tasks 1-5	0.10	0.07	−0.13	0.19
List A Task 1	0.2	0.13	−0.06	0.05
List A Task 5	0.12	0.07	−0.1	0.20
List A Free recall	0.27*	0.30*	0.001	0.13
after distraction				
List A Free recall	0.17	0.21	−0.08	0.08
after 20 min				
Guided recall after	0.14	0.13	−0.14	0.13
distraction				
Guided recall after	0.15	0.16	−0.10	0.08
20 min				
Perseverations	−0.2	−0.32*	−0.22	0.1
Confabulations in	−0.1	−0.21	−0.004	0.30*
free recall				
Confabulations in	0.01	−0.04	0.17	0.11
guided recall				
Recognition - total	0.1	0.01	−0.18	0.09
hits				
Recognition -	−0.01	−0.10	−0.02	−0.05
mistake				
Visuospatial memory				
Corsi				
Span forward	0.454**	0.22	0.16	0.07
Span backward	0.61**	0.45**	0.23	−0.06
CVMT				
Hits	0.2	0.23	0.23	0.04
False alarms	−0.04	0.02	−0.10	0.18
d'	0.16	0.14	0.18	−0.17
Total score	0.19	0.13	0.17	−0.14
Delayed recognition	0.14	0.19	0.04	0.04
Language				
BNT	0.21	0.35**	0.22	0.09
Executive functions				
DKEFS				
Mean time of first	0.14	0.03	0.23	−0.37**
move				
Sum 1-9 trial	−0.21	−0.14	−0.09	0.003
Total number of rule	0.17	0.06	0.16	0.15
violations				
COWAT				
Phonemic („K")	0.25^	0.31*	0.38**	0.003
Animals	0.22	0.17	0.09	0.15
Sharp items	0.42**	0.31*	0.30*	0.004
Dynamic praxis (sum)	0.19	0.28*	0.17	0.15
Alternating motor pattern				
Total number	0.2	0.08	0.08	0.29^
Number of errors	−0.01	0.06	0.16	−0.01
Correct rate	0.12	−0.02	−0.11	0.17

Abbreviations: MoCA – Montreal Cognitive Assessment, JoLO – Judgement of Line Orientation, VOSP – Visual Objects and Space Perception Battery, WAIS-R – Wechsler Adult Intelligence Scale Revised, CVLT – California Verbal Learning Test, CVMT – Continuous Visual Memory Test, BNT – Boston Naming test, DKEFS – Delis-Kaplan Executive Function System, COWAT – Controlled Oral Word Association.

and QAYEE-BIO kit (Shanghai Qayee Biotechnology Co., Ltd., China), respectively.

All patients signed informed consent. Study protocol was approved by the Bioethics Committee for Scientific Research of Medical University of Gdańsk (IHKBBH/415/2018).

2.1. Statistical analysis

After assessing normal distribution for collected data with the Shapiro-Wilk test, the one-way parametric ANOVA and one-way non-parametric Kruskal-Wallis testing were performed. Categorical variables were compared with χ^2 tests. Tukey's test and Dunn's test were used for post hoc analyses of parametric and non-parametric data, respectively. Correlation analyses were performed with Cramer's V or Spearman's ρ coefficients, depending on the type and distribution of the variables. Mediation analysis was conducted to assess the mediating role of short-term BPV in the effect of RAS on cognition. In case of problems with determining the p-value from the asymptotic χ^2 distribution of the test statistic, Monte-Carlo simulations with 2000 repetitions were used to determine this value. The results were generated with R and R Studio version 4.2.3 (www.r-project.org). At the level significance $\alpha < 0.05$ between-group differences were considered significant.

3. Results

The detailed characteristics of the groups are presented in Table 1. Patients with dementia were significantly older, less educated and had a more advanced disease than PD-HC. Disease duration and dopaminergic therapy were similar across the groups [11].

There were no differences in assessed parameters of RAS between all three groups (Table 1). Nevertheless, in all groups higher renin levels and increased PRA were associated with better performance in scales assessing visuospatial functions, visuospatial immediate memory and verbal fluency (Table 2). Additionally, higher renin levels were related to better verbal immediate/delayed memory and language functions. On the contrary patients with higher AngII levels had more severe impairment in verbal immediate/delayed memory and in planning (Table 2). Plasma concentrations of RAS were not related to assessed BP abnormalities nor to short-term BPV, except from reverse correlations of renin and PRA with SBP ARV (Cramer's V = −0.2549, p = 0.05; Cramer's V = −0.2555, p = 0.04, respectively). Additionally, renin levels negatively correlated with orthostatic drop of DBP (Cramer's V = −0.2667, p = 0.04). There was no correlation between dopaminergic therapy and RAS.

Mediation analysis showed that SBP ARV mediated the influence of PRA and renin only on general cognition (assessed with MoCA score), planning and some aspects of verbal memory (learning curve). Orthostatic drop of DBP did not mediate the association between renin and cognitive function. (Supplementary material).

4. Discussion

To our knowledge this is the first study assessing the impact of peripheral RAS components on cognitive function in PD patients without comorbidities and medications affecting RAS. Therefore, our data reflect RAS activity related to PD itself.

In our cohort, worse scores of neuropsychological tests assessing verbal memory and executive functions were related to increased AngII levels (Table 2). Study based on general population has shown elevated ACE-I levels to be correlated with worsening of processing speed and working memory during 1 year follow up [6]. In addition, a correlation between ACE-I and AngII levels was observed. In the same group of patients higher AngII concentration correlated with hippocampal, rostral middle frontal, supramarginal parietal and total grey matter atrophy [7], namely structures associated with memory and executive functions [14]. There were no associations of ACE-I and AngII with baseline SBP

or DBP. Results from another study have shown hippocampal atrophy volume to be predictive of cognitive decline, independently of β -amyloid (A β) or tau measures. This may suggest that other mechanisms are involved in these processes as well, like for example limbic age-related TDP43 encephalopathy, primary age-related tauopathy or vascular lesions [15]. In a study involving patients with chronic kidney disease, AT1R blockers inhibited the development of cognitive impairment by reducing oxidative stress in the hippocampus, suggesting a possible mechanism linking the RAS to cognitive decline [16]. The relationship between circulating RAS components and cognition in PD was previously analysed in just one study with 30 PD patients and 20 controls, where patients with cardiovascular diseases (including diabetes mellitus and hypertension) were also enrolled. Plasma levels of AngI, AngII, angiotensin $-(1-7)$ (Ang-(1-7)), ACE-1 and ACE-2 were measured in non-fasting state. Authors failed to demonstrate an association with cognition, what may result from the use of screening tests (Mini-Mental State Examination and the Frontal Assessment Battery) for cognitive assessment only (instead of full battery of tests for each domain) and co-morbidities. Lower circulating levels of Ang I, Ang II and Ang- (1-7) were associated with increased severity of depressive symptoms though [17].

Recently, Yang et al. in a study of 107 newly diagnosed PD patients with hypertension, treated with AT1R blockers, found a significantly slower cognitive decline progression and improvement of global cognitive function, visuospatial function, processing speed attention, executive function and working memory tests during five years of follow up, when compared to other hypertensive drugs [10]. These results seem to be consistent with the data on the impact of AT1R blockers on cognition. Angiotensin II receptor blockers provide greater neuroprotection than other classes of anti-hypertensive medication. The underlying mechanisms, beyond BP control, include inhibiting AngII/AT1R pathway and activating alternative, opposite arm of RAS: AngII/angiotensin type 2 receptors (AT2R), angiotensin IV(AngI-V)/angiotensin type 4 receptors (AT4R) and Ang-(1-7)/Mas receptors (MasR) may enhance vasodilatation, baroreflex function and reduce inflammation or oxidative stress, by inhibiting NADPH oxidase and the expression of pro-inflammatory cytokines. This may result in prevention of the accumulation of β -amyloid and reducing the hyperphosphorylation of tau [18]. Angiotensin converting enzyme inhibitors down regulate AngII production and thus block not only AngII/AT1R pathway, but also neuroprotective AngII/AT2R and AngIV/AT4R pathways, what can be a possible explanation. Moreover, antihypertensive medications increasing renin levels (an enzyme converting angiotensinogen to inactive AngI), such as thiazide diuretics or dihydropyridine calcium channels blockers, also stimulate AT2R and AT4R and therefore may reduce cognitive decline risk in a general population [19]. This is in line with our results, where higher renin and PRA levels correlated positively with visuospatial and executive functions.

Higher BPV, particularly SBP ARV, may contribute to the pathogenesis of cognitive decline in PD, as we have shown in our previous publication [11]. In the present study lower renin and PRA levels were related to increased SBP ARV. Renin secretion is stimulated by sympathetic renal activity (noradrenergic stimulation of β_2 receptors), intrarenal SBP in juxtaglomerular cells below 90 mmHg or a decrease in sodium and chloride delivery to the dense macula cells [4]. Also dopamine receptors placed in different parts of the nephron may regulate renin release. Renal dopaminergic receptors are classified into two subtypes: D1-like (D1 and D5) and D2-like (D2, D3, D4), their stimulation may reduce BP in different ways [19]. Stimulation of D1-like receptors causes vasodilatation, diuresis and natriuresis with modest increase in PRA. Stimulation of D2-like receptors induces a decrease in norepinephrine release, what results in bradycardia, without alerting renal function [20]. Stimulation of D3 receptor though, may inhibit renin release [21]. Dopamine agonists, which are currently used to treat motor symptoms, stimulate both D2 and D3 receptors. Plasma renin activity is decreased in drug naive PD patients, when compared to

healthy subjects [22] and its release after upright and diuretic stimulation is attenuated [23]. Levodopa may lower PRA, but inhibitors of dopa-decarboxylase can attenuate this effect [24]. Levodopa decreases BP though, probably due to baroreflex sympathetic noradrenergic impairment, regardless of presence of autonomic dysfunction as reported by Earl and colleagues [25]. We also have found an association between orthostatic drop of DBP and levodopa dose [11] and renin concentration. This may suggest that due to autonomic denervation in PD along with dopaminergic therapy, PRA in this group of patients is decreased and renin release inadequate, therefore this mechanism is insufficient in maintaining stable BP, causing increase in BPV.

4.1. Strengths and limitations

Main strength is a selected study population. Patients with cardiovascular diseases or taking medications affecting RAS were excluded from the study to show, if PD itself may influence the RAS activity. The psychological assessment was detailed and fulfilled the formal criteria for MCI and dementia. Groups did not differ in terms of size and dopaminergic therapy. Furthermore, not only plasma renin concentration was assessed but also its activity. The shortcoming of our study was a relatively small sample size and cross-sectional design, what limited the statistical power of our analyses and strength of our conclusions. Additionally, our study did not measure plasma concentrations or enzymes activities of alternative RAS pathway components.

5. Conclusions

However peripheral RAS was not correlated with dementia or MCI in PD patients according to Litvan or Emre criteria, it may have an impact on selected cognitive domains. Low levels of renin and decreased PRA in patients with cardiovascular dysautonomia, may contribute to an increase in BPV, assessed as average real variability of systolic blood pressure. Further longitudinal studies are needed to investigate the relationship between peripheral RAS, short-term BPV and cognition in PD.

CRedit authorship contribution statement

Magdalena Kwaśniak-Butowska: Writing – original draft, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. Agnieszka Skrzybkowska: Writing – review & editing, Software, Methodology, Investigation, Formal analysis, Data curation. Agnieszka Konkel: Writing – review & editing, Methodology, Investigation, Formal analysis, Data curation. Dariusz Wiczorek: Writing – review & editing, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. Marta Tomczyk: Writing – review & editing, Methodology, Investigation, Data curation. Monika Bialecka: Writing – review & editing, Supervision, Project administration, Methodology, Conceptualization. Ryszard T. Smoleński: Writing – review & editing, Supervision, Methodology, Conceptualization. Jarosław Sławek: Writing – review & editing, Supervision, Project administration, Methodology, Funding acquisition, Formal analysis, Conceptualization.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.parkreldis.2025.108073>.

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XII. OŚWIADCZENIA WSPÓŁAUTORÓW

Gdańsk, dnia 5.03.2026

dr hab. n. med. Jarosław Dulski
(tytuł zawodowy, imię i nazwisko)

OŚWIADCZENIE

W związku z ubieganiem się lek. Magdaleny Kwaśniak-Butowskiej o stopień doktora w dyscyplinie nauki medyczne oświadczam, że jestem współautorem publikacji pt. „Cardiovascular dysautonomia and cognition in Parkinson's Disease - a possible relationship” opublikowanej w 2021r. w Neurologii i Neurochirurgii Polskiej.

Mój udział w przygotowaniu tej publikacji polegał na napisaniu podrozdziału, edycji pierwszej wersji manuskryptu.

Jednocześnie wyrażam zgodę na przedłożenie w/w publikacji jako część rozprawy doktorskiej w formie spójnego tematycznie zbioru artykułów opublikowanych w czasopismach naukowych.

dr hab. n. med. Jarosław Dulski
specjalista neurolog
5.3.2026

.....

(podpis współautora)

Gdańsk, dnia 01.04.2026

prof. dr hab. n. med. Jarosław Sławek
(tytuł zawodowy, imię i nazwisko)

OŚWIADCZENIE

W związku z ubieganiem się lek. Magdaleny Kwaśniak-Butowskiej o stopień doktora w dyscyplinie nauki medyczne oświadczam, że jestem współautorem publikacji pt.

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4. „Peripheral renin-angiotensin system and cognitive decline in Parkinson's disease patients without co-morbidities" opublikowanej w 2025r. w *Parkinsonism&related disorders*.

Mój udział w przygotowaniu tych publikacji polegał na opracowaniu założeń metodologicznych, edycji pierwszej wersji manuskryptu, nadzorze merytorycznym nad publikacjami.

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KIEROWNIK
Klinicznego Oddziału Udarowego i Oddziału Neurologicznego
Gdańskiego Uniwersytetu Medycznego

prof. dr hab. n. med. Jarosław Sławek
specjalista neurolog

947847

(podpis współautora)

Gdańsk, dnia 01.04.2026

mgr Agnieszka Konkel
(tytuł zawodowy, imię i nazwisko)

OŚWIADCZENIE

W związku z ubieganiem się lek. Magdaleny Kwaśniak-Butowskiej o stopień doktora w dyscyplinie nauki medyczne oświadczam, że jestem współautorem publikacji pt.

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(podpis współautora)

Szczecin, dn. 29.11.2021

prof. dr hab. n. med. Marek Drożdżik
Zakład Farmakologii Doświadczalnej i Klinicznej
Katedra Farmakologii
Pomorski Uniwersytet Medyczny
al. Powstańców Wlkp. 72, 70-111 Szczecin

OŚWIADCZENIE

Oświadczam, że w pracach:

Arterial Blood Pressure Variability and Other Vascular Factors Contribution to the Cognitive Decline in Parkinson's Disease.

(Pierzchlińska A, Kwaśniak-Butowska M, Sławek J, **Drożdżik M**, Białecka M. *Molecules*, 2021: vol. 26, nr 6, art. 1523, doi:10.3390/molecules26061523),

Effects of common functional MMP12 gene polymorphisms on PD in a Polish population.

Białecka M, Kurzawski M, Vlaykova T, Tacheva T, Dziedziejko V, A. Pierzchlińska, **Drożdżik M**. *Neurologia i Neurochirurgia Polska*, 2017: vol. 51, nr 5, s. 347-353, doi:10.1016/j.pjnns.2017.06.001)

mój udział polegał na opracowaniu końcowej wersji rękopisów ww. publikacji.

Prof. Marek Drożdżik

Gdańsk, dnia 01.04.2026

mgr Agnieszka Skrzypkowska
(tytuł zawodowy, imię i nazwisko)

OŚWIADCZENIE

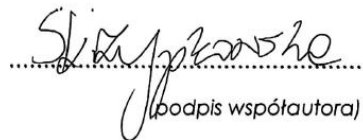
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Mój udział w przygotowaniu tych publikacji polegał na zebraniu części materiału badawczego, analizie statystycznej, interpretacji wyników badań, przygotowaniu odpowiedzi dla recenzentów.

Jednocześnie wyrażam zgodę na przedłożenie w/w publikacji jako część rozprawy doktorskiej w formie spójnego tematycznie zbioru artykułów opublikowanych w czasopismach naukowych.


(podpis współautora)

Gdańsk, dnia 30.03.2026

Dr n. med. Anna Pierzchlińska
(tytuł zawodowy, imię i nazwisko)

OŚWIADCZENIE

W związku z ubieganiem się lek. Magdaleny Kwaśniak Butowskiej o stopień doktora w dyscyplinie nauki medyczne oświadczam, że jestem współautorem publikacji pt.:

1. Genetic Polymorphisms in the HMGCR Gene and Associations with Cognitive Decline in Parkinson's Disease Patients, Int J Mol Sci 2024
2. Cardiovascular dysautonomia and cognition in Parkinson's Disease - a possible relationship, Neurol Neurochir Pol 2021
3. Arterial Blood Pressure Variability and Other Vascular Factors Contribution to the Cognitive Decline in Parkinson's Disease, Molecules 2021

Mój udział w przygotowaniu tej publikacji polegał na:

1. Przygotowaniu tekstu manuskryptu, wykonaniu badań techniką real-time PCR i analizie wyników
2. Konsultacji merytorycznej
3. Analizie literatury i przygotowaniu tekstu manuskryptu

Jednocześnie wyrażam zgodę na przedłożenie w/w publikacji jako część rozprawy doktorskiej w formie spójnego tematycznie zbioru artykułów opublikowanych w czasopismach naukowych.


.....
(podpis współautora)

Gdańsk, dnia 01.04.2026

dr hab. Marta Tomczyk
(tytuł zawodowy, imię i nazwisko)

OŚWIADCZENIE

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Katedra i Zakład Biochemii

dr hab. Marta Tomczyk

.....
Adiunkt

(podpis współautora)

Gdańsk, dnia 01.04.2026

prof. dr hab. n. med. Monika Białecka
(tytuł zawodowy, imię i nazwisko)

OŚWIADCZENIE

W związku z ubieganiem się lek. Magdaleny Kwaśniak-Butowskiej o stopień doktora w dyscyplinie nauki medyczne oświadczam, że jestem współautorem publikacji pt.

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prof. dr hab. n. med.
Monika Białecka
specjalista neurolog
1298694

.....
(podpis współautora)

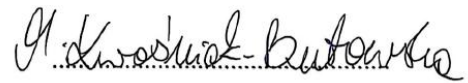
Gdańsk, dnia 31.03.2026

lek. med. Magdalena Kwaśniak-Butowska
(tytuł zawodowy, imię i nazwisko)

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(podpis współautora)

Gdańsk, dnia 31.03.2026

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(podpis współautora)

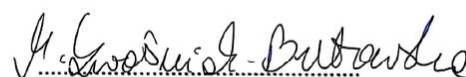
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Handwritten signature of Magdalena Kwaśniak-Butowska in blue ink, written over a dotted line.

(podpis współautora)

Gdańsk, dnia 31.03.2026

lek. med. Magdalena Kwaśniak-Butowska
(tytuł zawodowy, imię i nazwisko)

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(podpis współautora)