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PARKINSON’S DISEASE AND CEREBROVASCULAR CHANGES: A CLINICO-EPIDEMIOLOGICAL AND NEUROIMAGING STUDY

321.05 CLINICAL NEUROLOGY

Summary of the Habilitation Thesis in Medicine

Chișinău, 2025

The thesis was developed in the Laboratory of Functional Neurology, “Diomid Gherman” Institute of Neurology and Neurosurgery, Laboratory of Neurobiology and Medical Genetics, "Nicolae Testemițanu" State University of Medicine and Pharmacy.

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The defense will take place on 15.10.2025, 14:00, at the “Nicolae Testemițanu” State University of Medicine and Pharmacy, 165 Ștefan cel Mare și Sfânt Boulevard, Office 205, during the session of the Doctoral Thesis Public Defense Committee, approved by the decision of the Scientific Council of the Consortium dated 26.08.2025 (Minutes No. 6/13).

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THE CONCEPTUAL FRAMEWORK OF THE RESEARCH

Relevance of the Topic. Parkinson's disease (PD), which is experiencing a global increase in prevalence [1], is frequently associated with vascular risk factors (hypertension, diabetes mellitus, dyslipidemia) that contribute not only to cerebrovascular morbidity but also potentially to the initiation or progression of neurodegenerative processes [2-4]. Evidence supporting the interaction between subclinical cerebral ischemia, vascular dysfunction, and dopaminergic degeneration underpins the hypothesis of a vasculo-neurodegenerative co-evolution [5-6]. Investigating these shared mechanisms may facilitate the identification of common biomarkers and enable early differential diagnosis between idiopathic PD and vascular parkinsonism [7-8]. Clinically, the association of PD with vascular lesions correlates with cognitive impairment, more severe motor symptoms, and reduced responsiveness to levodopa, suggesting a significant functional and prognostic impact [9-13]. Incorporating the vascular profile into the evaluation of PD patients provides a foundation for personalized therapies and secondary prevention interventions, thereby mitigating disability progression and socio-economic burden [13-14]. In a transitioning healthcare system such as that of the Republic of Moldova, local clinical-epidemiological research is essential for adapting screening policies, treatment approaches, and interdisciplinary management of PD [2], [14].

Description of the Study Field and Identification of Research Problems. Despite progress in recent decades, the relationship between Parkinson's disease (PD) and cerebrovascular disease (CVD) remains incompletely understood, with multiple unresolved issues: (1) common pathogenic mechanisms — evidence for the involvement of microcirculatory impairment, chronic inflammation, and oxidative stress remains indirect [4,15-16]; (2) the role of chronic subclinical cerebral ischemia and its impact on PD progression and therapeutic response is still insufficiently studied; advanced methods such as diffusion-weighted imaging (DWI) and MRI perfusion may aid in early detection [4], [17]; (3) there remains a lack of specific biological or imaging markers for mixed PD–CVD forms, limiting differential diagnosis; (4) characterization of micro- and macrostructural vascular lesions through comparative studies between PD patients and the general population is needed [18], [11]; (5) particularities of vascular risk factors remain unclear — the extent to which the expression of hypertension, diabetes mellitus, or dyslipidemia differs in PD patients compared to the general population is unknown [8], [19]; (6) the influence of therapeutic adherence on PD progression in the context of vascular risk is poorly documented; (7) the impact of CVD on non-motor symptoms of PD — including cognitive impairment, depression, and apathy — requires further investigation to clarify causal relationships [9], [20]; (8) knowledge, attitudes, and practices (KAP) studies on patient and physician perceptions regarding PD–CVD comorbidity could provide a basis for educational and organizational intervention strategies [21]; (9) the absence of clear integrated management guidelines at both international and regional levels complicates treatment of patients with PD and cerebrovascular comorbidities.

Approaches to addressing the issues outlined above include longitudinal clinical-epidemiological studies, multimodal brain imaging (advanced MRI, PET), analysis of

inflammatory and genetic markers, KAP surveys, and the development of composite risk scores for PD–CVD. In the Republic of Moldova, the lack of epidemiological and clinical-imaging data concerning PD and vascular comorbidities justifies the need for an integrative study to guide public health policies and enable treatment personalization [14, 22-23].

Research Aim: To investigate the clinical-epidemiological, imaging, and management characteristics of patients with Parkinson's disease in the population of the Republic of Moldova, through analysis of the association between vascular risk factors and cerebral vascular neuroimaging changes, evaluation of imaging heterogeneity to assess its clinical impact, and development of personalized and systemic management recommendations tailored to the specific needs of this patient group.

Research Objectives:

1. To conduct a clinical-epidemiological evaluation of patients with Parkinson's disease in the population of the Republic of Moldova to identify an integrative clinical-epidemiological profile and the medico-social particularities of these patients.
2. To phenotype Parkinson's patients based on the nature of the association (comorbidity or causality) with cerebrovascular disease, as well as according to the dominant clinical-evolutionary syndrome, to develop personalized management recommendations tailored to patient needs.
3. To investigate the presence and extent of vascular involvement in patients with Parkinson's disease and its impact on the clinical manifestations of Parkinson's disease.
4. To assess vascular risk factors in Parkinson's disease patients, their pharmacological management, and their influence on clinical manifestations of Parkinson's disease, as well as to study the correlation between these factors and cerebral neurovascular imaging lesions.
5. To evaluate the association of Parkinson's disease with neurovascular imaging lesions and to investigate their role in the clinical manifestations of Parkinson's disease.
6. To study the management of Parkinson's disease patients within the healthcare system of the Republic of Moldova through Knowledge, Attitudes, and Practices (KAP) analysis and to identify existing barriers.
7. To develop institutional and national recommendations regarding the comprehensive diagnosis of Parkinson's disease and the interdisciplinary management of these patients.

Summary of Research Methodology and Justification of Chosen Methods.

Fundamental research and clinical studies in the field of Parkinson's disease have served as the theoretical and scientific methodological foundation, demonstrating that Parkinson's disease is a pathology with considerable impact on the patient, their immediate entourage, and society [24], as well as a condition that demands significant involvement of the healthcare system [25]. The selection of research methods and interpretation of results were guided by recent studies indicating associations between Parkinson's disease and cardiovascular and cerebrovascular pathology, which

negatively affect the progression and clinical manifestations of Parkinson's disease [26]. The current research considered neuroimaging studies from recent years highlighting the presence and role of cerebral vascular lesions in the onset and evolution of Parkinson's disease [27]. Cerebral vascular lesions and vascular risk factors are investigated from the perspective of potential aggravating factors for Parkinson's disease [4].

The study's aim and objectives were addressed through clinical and neuroimaging methods, as well as through interviews with physicians and patients to elucidate their knowledge, attitudes, practices, and encountered barriers. Data collection was performed both qualitatively and quantitatively via questionnaires and assessment scales covering epidemiological, medico-social, motor and non-motor clinical aspects, as well as psycho-affective and cognitive domains. Additionally, internationally approved neuroimaging protocols for evaluating patients with Parkinson's disease were applied, in accordance with international recommendations aimed at optimizing Parkinson's disease research [28].

Novelty and Scientific Originality:

- The novelty of the conducted research lies in the complex, multidimensional, and interdisciplinary innovative approach to patients with Parkinson's disease in the Republic of Moldova — a neurodegenerative disorder potentially strongly influenced by vascular pathophysiological mechanisms.
- The study provides an integrative concept of Parkinson's disease within the population of the Republic of Moldova, highlighting the clinical heterogeneity of PD and presenting the patient's profile in relation to family, society, and healthcare services.
- The in-depth investigation of neurovascular imaging changes identified greater severity of vascular impairment and specific patterns of cerebral vascular lesion localization in PD patients.
- The research found that cerebrovascular changes impact the progression and severity of Parkinson's disease, functional disability caused by both conditions, quality of life, development of neuropsychiatric symptoms, and cognitive impairments, which consequently affect family and societal integration through reduced work capacity, disability, workforce dropout, and increased burden on healthcare systems.
- The study emphasizes the necessity of early detection of vascular risk factors to enable comprehensive, multidisciplinary, early, and proactive management.

Significant Problem Addressed in the Field. This study is the first and only research in the Republic of Moldova to phenotype the medico-social aspects and clinical particularities of patients with Parkinson's disease from the country, as well as to map the barriers to specialized medical care for these patients. The study's findings identified an aggravating effect of the association and burden of vascular risk factors and cerebrovascular lesions on the clinical severity of Parkinson's disease. These results enable the optimization of personalized management for patients with Parkinson's disease in the Republic of Moldova.

Theoretical Significance. The results of this research extend and deepen the existing knowledge regarding the role of vascular mechanisms in the neurodegenerative processes of Parkinson's disease and their impact on the clinical-evolutionary severity of the disease. The study identified an aggravating effect of the presence and burden of vascular risk factors, as well as the presence and severity of cerebral vascular lesions, on the severity of motor and non-motor symptoms of Parkinson's disease, patients' functional status, and their quality of life.

Applied Value. The importance of a multidisciplinary approach to patients with Parkinson's disease was established, emphasizing early and proactive detection of vascular risk factors—key mediators of the relationship between Parkinson's disease and cerebrovascular disease. This study is the first in the Republic of Moldova to evaluate the management of Parkinson's disease patients from both the perspective of healthcare service beneficiaries and providers. Barriers to access specialized medical services for Parkinson's disease patients were identified, aiming to improve patient-centered access to care. Preferences of both patients and healthcare providers regarding Parkinson's disease management were assessed to formulate tailored recommendations.

Main Results Submitted for Defense:

1. The clinical-epidemiological and medico-social pattern of patients with Parkinson's disease in the Republic of Moldova varies according to biological criteria and disease progression.
2. The nature of the association — comorbidity or causality — between cerebrovascular disease and parkinsonism results in particular clinical-evolutionary phenotypes of the disease, necessitating differentiated management for these patients.
3. The dominant clinical syndrome of Parkinson's disease may be indicative of a specific clinical-evolutionary phenotype, which determines the specific needs for personalized patient management.
4. Vascular risk factors are more prevalent in the population of patients with Parkinson's disease.
5. The presence and burden of vascular risk factors are associated with greater severity of motor and non-motor symptoms.
6. Cerebrovascular lesions are more prevalent in the population of patients with Parkinson's disease and exhibit a specific pattern of localization.
7. The presence and severity of cerebrovascular lesions are associated with distinct clinical features, onset, and progression of Parkinson's disease.
8. Barriers exist in the management of Parkinson's disease within the healthcare system of the Republic of Moldova, both at the level of patients and specialized service providers.

Approval of the Study Results. The main results of the research were communicated and discussed at various national and international scientific forums, including the European Academy of Neurology Day in the Republic of Moldova, held jointly with the Congress of Neurologists of the Republic of Moldova (Chișinău, 16–18 September 2021); the National Alzheimer's Disease Conference (CNALZ) (Iași,

Romania, 23–26 February 2022, invited lecturer); the 4th Edition of the National Conference on Modern Neurosciences “Parkinson’s Disease & Other Movement Disorders” (Iași, Romania, 6–8 April 2023, invited lecturer); the 6th International Conference on Nanotechnologies and Biomedical Engineering (Chișinău, Republic of Moldova, 20–23 September 2023, invited lecturer); the 6th National Congress of Neurosciences (Iași, Romania, 9–12 October 2024, invited lecturer); the National Conference on Modern Neurosciences "Parkinson’s Disease and Other Movement Disorders" (Iași, Romania, 11–13 April 2024 and 11–13 April 2025, invited lecturer); the 26th World Congress on Parkinson’s Disease and Related Disorders (Amsterdam, Netherlands, 1–4 May 2021); the European Academy of Neurology Congress MDS (Copenhagen, Denmark, 27–31 August 2023); and the International Headache Congress (on-line, audio presentation, 8-12.09.2021).

The thesis was discussed and approved at the joint meeting of the Functional Neurology Laboratory of the INN, Neurology Departments 1 and 2 of the Nicolae Testemițanu State University of Medicine and Pharmacy, and the Brain Health Center on 22 May 2025 (Minutes No. 7); as well as at the Scientific Seminar of specialties 312 Physiology; 321 General/Specialized Medicine: 312.02 Neurosciences (including Psychophysiology), 321.05 Clinical Neurology, 321.21 Neurosurgery, minutes dated 1 July 2025.

Publications on the Thesis Topic. A total of 42 publications have been produced on the thesis topic, including: 1 national monograph, 1 chapter in an international monograph (SCOPUS indexed), 1 chapter in a national monograph, 5 SCOPUS-indexed articles, 1 article in other international journals, 1 national article category A, 4 national articles category B+, 3 national articles category B, 4 national articles category C, 4 other articles from the Republic of Moldova, 8 national abstracts, 11 international abstracts, as well as 4 innovations, 4 implementation acts, and 3 copyrights.

Volume and Structure of the Thesis: The thesis contains an introduction, six chapters of original results and discussions, conclusions and recommendations, a bibliography of 455 titles, 24 appendices, 265 pages of main text, 74 figures, and 42 tables. The research results have been published in 42 scientific works.

Keywords: Parkinson’s disease, vascular risk factors, cerebrovascular changes, levodopa responsiveness, functionality, quality of life, knowledge, attitudes, practices.

CONTENTS OF THE THESIS

1. THE RELATIONSHIP BETWEEN PARKINSON’S DISEASE AND CEREBROVASCULAR CHANGES (ANALYSIS OF THE CURRENT STATE OF THE FIELD)

The investigation of the association and shared mechanisms between Parkinson’s disease and cerebrovascular disease represents a highly relevant and evolving topic. Despite ongoing efforts, the relationship between Parkinson’s disease and cerebrovascular disease remains incompletely elucidated. The hypothesis of a common pathogenesis is still uncertain, as it is unclear to what extent cerebrovascular disease contributes to the initiation or acceleration of dopaminergic neurodegeneration. Differential diagnosis between Parkinson’s disease and vascular parkinsonism is hindered by the lack of specific biomarkers for mixed forms. The role of vascular risk

factors in the progression of Parkinson's disease remains controversial, and their therapeutic management within the context of Parkinson's disease is not well defined. Cerebrovascular lesions, which are common in the elderly, have variable predictive value for the development and progression of Parkinson's disease due to the absence of standardized quantification criteria. Moreover, the integrated treatment of these two conditions is insufficiently developed, with no clear protocols available for the combined management of neurodegenerative and vascular pathology.

From this perspective, comorbid cerebrovascular disease warrants investigation as a potential factor influencing the clinical severity, progression, and therapeutic response in Parkinson's disease. It may allow for the identification of distinct clinical phenotypes of the neurodegenerative disease, requiring tailored clinical, therapeutic, and management approaches. The identification of clinically silent ischemia through advanced cerebral diffusion imaging techniques (DWI) supports the need for early and proactive management of vascular risk factors, as well as differentiated therapeutic strategies for the neurodegenerative disease.

2. MATERIALS AND METHODS

The research was conducted at the "Diomid Gherman" Institute of Neurology and Neurosurgery and consists of several component studies:

1. **Study of the Epidemiological and Medico-Social Aspects of Patients with Parkinson's Disease** (observational, descriptive, cross-sectional, selective, PD group *n*=1741) — *Study 1*. The aim was to analyze epidemiological and medico-social data from a representative cohort of patients with Parkinson's disease in the Republic of Moldova.
2. **Study of the Clinical Features of Patients with Parkinsonism and Cerebrovascular Changes** (observational, descriptive, cross-sectional, selective, *n*=409) — *Study 2*. The aim was to describe the clinical and evolutionary features of patients with parkinsonism associated with cerebrovascular changes, to phenotype vascular parkinsonism, and to classify patients based on the dominant clinical syndrome.
3. **Study of Clinical Features in Patients with Parkinson's Disease Associated with Various Types of Cerebrovascular Changes** (observational, descriptive, cross-sectional, selective, *n*=397) — *Study 3*. The aim was to characterize the clinical and evolutionary manifestations of patients with Parkinson's disease and concomitant cerebrovascular changes, in comparison with those without such changes.
4. **Study of Vascular Risk Factors in Patients with Parkinson's Disease** (*PD group n*=397, *control group n*=306) — *Study 4*. The aim was to analyze the frequency of vascular risk factors in Parkinson's disease patients versus a control group.
5. **Study of Neuroimaging Changes in Patients with Parkinson's Disease** (*PD group n*=160, *control group n*=555) — *Study 5*. The aim was to analyze cerebrovascular neuroimaging changes (both macrostructural and microstructural, including diffusion imaging) and neurodegenerative changes in patients with Parkinson's disease compared to controls.

6. **KAP Study (Knowledge, Attitudes, Practices) of Physicians (*n*=105) and Patients (*n*=103) Regarding the Management of Parkinson's Disease in the Republic of Moldova** — *Study 6*. The aim was to evaluate the knowledge, attitudes, and practices of patients and healthcare providers related to the management of Parkinson's disease in Moldova, in order to identify their needs and the barriers they face within the national healthcare system.

The inclusion and exclusion criteria are presented separately for each individual study.

Research Methods Used:

1. **Clinical Method:**

A series of questionnaires were used, including: the Semi-Structured Questionnaire for Patients with Parkinson's Disease, the Unified Parkinson's Disease Rating Scale (UPDRS), the Non-Motor Symptoms Scale (NMS), the Parkinson's Disease Questionnaire (PDQ-39) for assessing quality of life, the SCOPA-PS (Scales for Outcomes in Parkinson's Disease – Psychosocial Functioning) for evaluating psychosocial dysfunction, the Montreal Cognitive Assessment (MoCA) for quantifying cognitive impairment severity, the Beck Depression Inventory for assessing depression severity, the Apathy Scale, the Visual Analog Scale for pain, the QRISK3 risk calculator, and the KAP Questionnaire (Knowledge, Attitudes, Practices).
These tools allowed for the evaluation of:

- **Demographic characteristics** (presence of vascular risk factors, Parkinson's disease risk markers);
- **Characterization of non-motor symptoms** (neuropsychiatric and autonomic);
- **Assessment of signs suggestive of pyramidal tract involvement** (exaggerated, asymmetric deep tendon reflexes, paresis);
- **Clinical characteristics of Parkinson's disease**, including:
    - Disease duration and age at onset;
    - Onset features (insidious, acute progressive, delayed progressive);
    - **Phenotype classification** (Tremor score / Akinetic-rigid score: >1.16 – tremor-dominant; 0.9–1.15 – intermediate; <0.8 – akinetic-rigid);
    - **Disease severity** (UPDRS Part 3: ≤32 – mild; 33–58 – moderate; ≥59 – severe);
    - **Asymmetry index** (Right/Left and Upper/Lower Limb Asymmetry Index: values between -1 and 1 indicate symmetric parkinsonism; values ≤ -2 indicate asymmetric parkinsonism);
    - **Motor complications** (presence, severity, latency in relation to disease duration and treatment);
    - **Previous and current medication** (levodopa doses, dopamine agonists, levodopa-equivalent dose);
    - **Levodopa responsiveness** (comparison of UPDRS Part 3 motor score in OFF vs. ON phase; responsiveness = percentage difference between UPDRS Part 3 scores in OFF and ON state, as well as the ON-state score itself);

- **Other tremor types** (postural, kinetic);
- **Diagnostic certainty** (definite PD, probable PD, vascular parkinsonism).

The **QRISK3 calculator**, using input data on vascular risk factors, determined the QRISK3 score and the relative risk of future cardiovascular or cerebrovascular events [84].

The **KAP Questionnaire** for both physicians and patients assessed knowledge, attitudes, practices, barriers, and needs related to the management of Parkinson's disease in the healthcare system of the Republic of Moldova, using both open- and closed-ended questions with single and multiple responses.

2. **Instrumental Method:**

Brain imaging was performed using 1.5 Tesla MRI, including T1, T2, FLAIR, DWI, and SWI sequences. The following parameters were assessed:

- **Presence and type of neurovascular lesions**: lacunar infarcts, gliotic foci, dilatation of Virchow-Robin perivascular spaces, widening of cerebral sulci, ventricular system enlargement, and cerebral microbleeds;
- **Lesion localization**: territorial infarcts (anterior/posterior circulation) or lacunar infarcts; gliotic foci located periventricularly or in deep white matter;
- **Lesion severity**: Fazekas scale (grades 0–3); total small vessel disease score by Staals (0–4);
- **Strategic brain regions implicated in parkinsonism**: external globus pallidus, substantia nigra pars compacta, ventrolateral thalamic nucleus, and extensive frontal lobe infarcts;
- **Qualitative measures of neurodegeneration**: signal intensity of the dorsal substantia nigra in SWI (susceptibility-weighted imaging);
- **Qualitative assessment of clinically silent chronic subthreshold ischemia**, not visible on conventional imaging: diffusion-weighted imaging (DWI) and apparent diffusion coefficient (ADC) mapping.

3. **Statistical Methods:**

Statistical analysis was performed using the Epi Info Stat software. Descriptive statistics included the mean and standard error, and differences between groups were assessed using the Student's t-test, with a significance threshold of $p < 0.05$. Pearson's correlation coefficient was used to determine the strength of associations between variables. All continuous variables were evaluated for normality of distribution. In cases where the data did not follow a normal distribution, non-parametric tests (such as the Mann–Whitney U test) were applied. Differences between two or more groups of continuous variables were analyzed using ANOVA, with Bonferroni correction for multiple comparisons. When covariates potentially influencing the outcome were present, ANCOVA was applied. For multiple variables, MANOVA and MANCOVA were used accordingly.

3. RESULTS OF THE STUDY ON THE EPIDEMIOLOGICAL AND MEDICO-SOCIAL ASPECTS OF PARKINSON'S DISEASE IN THE REPUBLIC OF MOLDOVA

For the study of demographic, medical, and social aspects, 1741 patients were examined (45.1% (786) women and 54.9% (955) men), with a mean age of 69.33 ± 7.62 years, mean age at disease onset of 60.31 ± 5.54 years and disease duration of 9.02 ± 5.58 years; selected based on inclusion criteria (1 Patient with parkinsonism; 2 Cooperative patient; 3 Informed consent) and exclusion criteria (1 Patient with atypical parkinsonism or non-vascular secondary parkinsonism; 2 Non-cooperative patient; 3 Lack of informed consent).

The demographic and social profile determined in the cohort of patients from the Republic of Moldova was characterized by aspects of age majority >60 years (88.7%), frequent onset >50 years (93.2%); sex balanced male–female distribution (ratio 1.22 : 1), similar to literature data [273]; place of residence balanced urban-rural (53.9% vs. 46.1%), with significantly higher exposure to toxic factors in rural areas (24.69% vs. 13.95%, $p<0.05$); education predominantly secondary vocational (68.3%), occupational status majority retired (76.9%); work capacity many declared unfit for work/daily activities (41%).

The clinical profile determined in the cohort of patients from the Republic of Moldova reflects disease severity majority (77.1%) present severe forms of the disease, disease phenotype majority (77.2%) with akinetic-rigid phenotype, discrepancy between symptom prevalence and use of specific antiparkinsonian treatments (tremor vs treatment with dopamine agonists: 23% vs 16.1%, $p<0.000$, dyskinesias vs antidyskinetic treatment: 39.6% vs 13.1%, $p<0.000$), and psychotropic (depression vs antidepressant treatment: 54.1% vs 30%, $p<0.000$), frequent vascular comorbidities (72.6%), with suboptimal therapeutic management (hypertension vs antihypertensive treatment: 60.7% vs 29.6%, $p<0.000$, dyslipidemia vs lipid-lowering treatment: 43% vs 14.1%, $p<0.000$, atrial fibrillation vs anticoagulant treatment: 10.9% vs 8.5%, $p<0.05$) (Figure 1), proportion of vascular parkinsonism 1.2%.

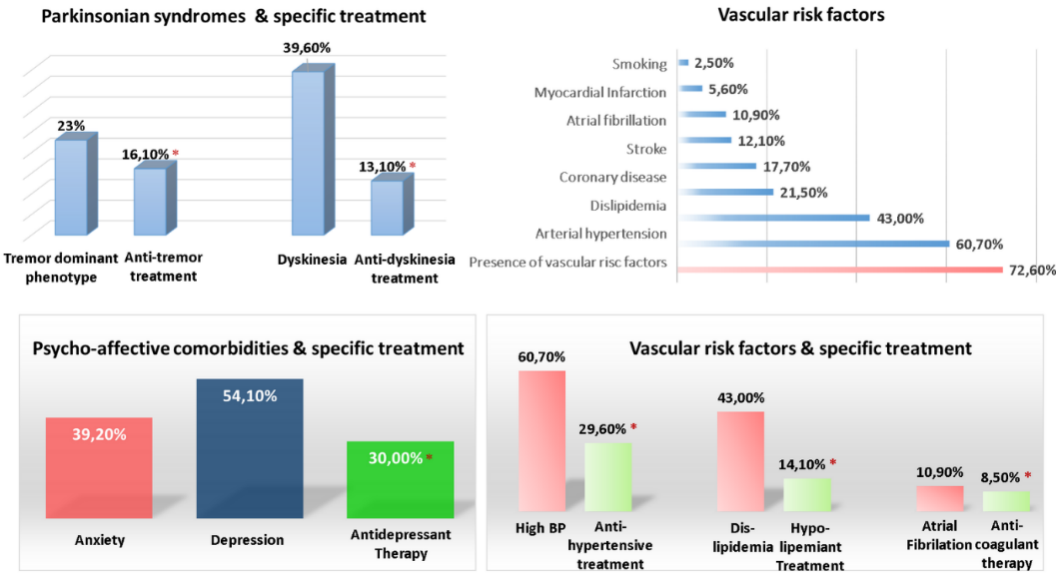

Figure 1. The Gap Between Symptom Prevalence and the Use of Specific Treatments

Stratifications of the study cohort outlined biologico-evolutionary differences based on sex: women presented with significantly more frequent fluctuations (56.1% vs. 33.4%, p=0.000) and dyskinesias (50% vs. 31.1%, p=0.000), requiring specific treatments (17.7% vs. 9.3%, p=0.000), although underutilized. Men, on the other hand, were more frequently exposed to toxic noxae (24.4% vs. 12.2%, p=0.000), exhibited higher levels of anxiety (42.3% vs. 35.5%, p=0.004), and required anxiolytic medication (32% vs. 27.5%, p=0.040). Additionally, they more often presented cardiovascular diseases (coronary artery disease (26.9% vs. 15%, p=0.000), hypertension (70.3% vs. 49.1%, p=0.000), myocardial infarction (8.5% vs. 2.2%, p=0.000)) associated with additional risks.

Based on the age criterion: patients >60 years more frequently had severe forms of the disease (50.4%, Df=2, p=0.000), predominantly with the akinetic-rigid phenotype (56.7%, Df=2, p=0.000), longer disease duration (39.4%, Df=2, p=0.000) and greater therapeutic need (levodopa in increased doses and intakes: 1128.59±567.2 vs. 632.78±439.64, p=0.000 and 4.95±2.02 vs. 3.30±1.68, p=0.000), while being more affected by vascular comorbidities (74.4% vs. 58.9%, p=0.000) and requiring symptomatic treatments (constipation). Diagnosis of vascular parkinsonism was encountered exclusively in this category.

Patients with disease onset before the age of 50 presented significantly more often with a degree of disability (45.4% vs. 4.7%, p=0.000), frequently unfit for professional or daily activities (42.9%). They more frequently manifested the severe form (56.3%) and akinetic-rigid phenotype (52.1%) of the disease, with increased prevalence of motor fluctuations (91.6% vs. 40.1%, p=0.000) and dyskinesias (89.1% vs. 36%, p=0.000). Consequently, they more frequently used amantadine (84% vs. 7.9%, p=0.000) and dopaminergic agonists (38.7% vs. 14.4%, p=0.000), the latter in significantly higher doses (1.96±0.69 vs. 1.75±0.79, p=0.48), while levodopa was administered less often and in lower doses compared to other age categories.

Patients with motor fluctuations in this cohort were significantly older (71.16±8.97 vs. 67.92±6.01, p=0.000) than those without such complications, the majority (86.2%) being over 60 years. Disease onset was at a younger age (58.38±6.42 vs. 61.81±4.17, p=0.000), generally (85.7%) after 50 years, and disease duration was longer (12.78±5.02 vs. 6.12±4.04, p=0.000), in most cases (70.5%) exceeding 10 years. They were predominantly women (58%), with disability grade (14.9%) and unfitness for work (70.9%), presenting the severe form (77.1%) and akinetic-rigid phenotype (77.2%) of the disease. They also frequently associated depression (65.8%) which required specific treatment. Compared to patients without motor complications, they required higher daily doses of levodopa (1371.59±606.89 vs. 793.22±392.02, p=0.000) and a greater number of daily administrations (5.96±2.22 vs. 3.84±1.28, p=0.000).

Therefore, the typical patient with Parkinson's disease in the Republic of Moldova (an adult over 60 years old, retired, with disease onset after 50 years, frequently residing in rural areas and with a history of exposure to toxic substances [pesticides, solvents], with an akinetic-rigid phenotype and severe form of the disease, with frequent vascular comorbidities [hypertension, coronary artery disease], suboptimal therapeutic management, frequent motor complications [fluctuations and

dyskinesias] despite a relatively short disease duration, with functional disability, with non-motor symptoms [depression, constipation] suboptimally treated, with levodopa-centered treatment often insufficient relative to the case complexity), requires a personalized, multidisciplinary approach integrating: adequate management of comorbidities, control of motor and non-motor symptoms, and treatment adaptation according to phenotype and disease severity.

4. RESULTS OF THE PHENOTYPING STUDY OF PARKINSONISM BASED ON THE ASSOCIATION WITH CEREBROVASCULAR DISEASE AND THE DOMINANT CLINICAL SYNDROME

This study included 409 patients, selected based on the inclusion/exclusion criteria described in Chapter 3; with a mean age of 64.61±6.63 years and mean age at disease onset of 60.22±6.94 years, with a mean disease duration of 52.88±37.12 months; 50.1% female and 49.9% male; the majority (92.4%) with disease onset after 50 years of age; the majority (70.9%) with disease duration up to 5 years. The aim of this study was to determine the particularities of:

- vascular parkinsonism,
- patients with vs. without stroke,
- patients with disease duration <5 years vs. 5–10 years vs. >10 years,
- patients with mild vs. moderate vs. severe disease severity,
- patients with vs. without cognitive impairment,
- patients with severe vs. mild non-motor symptoms,
- patients with vs. without motor complications.

Typical characteristics of all patients with vascular parkinsonism, exclusive features, and characteristic symptoms of patients with vascular parkinsonism were determined (Figure 2).

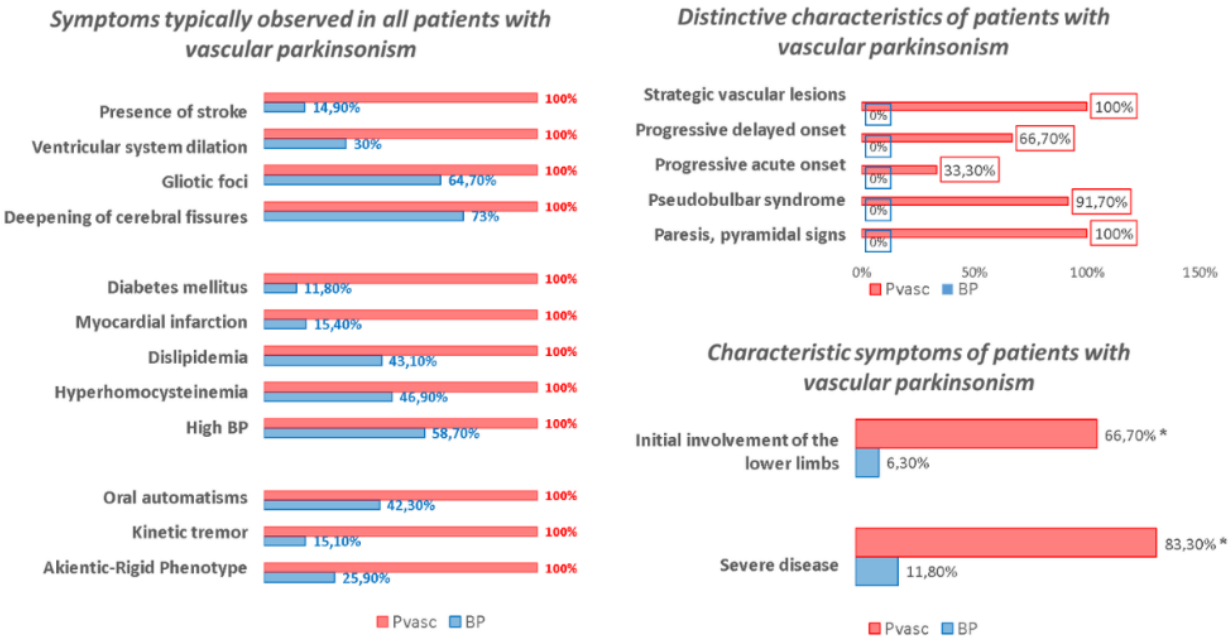

Figure 2. Typical, Exclusive, and Characteristic Features of Patients with Vascular Parkinsonism

- **The study outlined the profile of patients with vascular parkinsonism (versus idiopathic Parkinson's disease):**
  • Prevalence: 2.9% of the cohort
  • Age and onset: significantly higher (71.92±4.56 vs. 64.39±6.57, p=0.000; 69.67±4.47 vs. 59.93±6.81, p=0.000)
  • Disease duration: shorter (21.58±20.58 vs. 53.82±37.11, p=0.003)
  • Clinical form: exclusively akinetic (100%, Df=2, p=0.000), most frequently severe (83.3%, Df=2, p=0.000)
  • Tremor: kinetic tremor present in all patients (100%, Df=1, p=0.000), overall low tremor scores (0.39±0.28 vs. 1.12±0.63, p=0.000)
  • Onset: frequently in lower limbs (66.7%, Df=1, p=0.000), predominantly lower limb involvement (Superior_Inferior Asymmetry Index: -3.66±6.59 vs. 10.99±5.82, p=0.000)
- **Motor and non-motor characteristics:**
  • Increased akinesia-rigidity (AR_Score: 3.73±0.32 vs. 1.03±0.84, p=0.000), increased motor impairment (UPDRS_3_OFF: 71.58±11.08 vs. 46.38±12.24, p=0.000) and increased non-motor symptoms (NMS Score: 165.5±20.94 vs. 49.76±26.54, p=0.000)
  • Severe depression, apathy, and cognitive impairment (Beck Depression Inventory: 38.42±12.72 vs. 13.37±9.25, p=0.000; Apathy Scale: 21.17±6.96 vs. 10.98±7.20, p=0.000; MoCA: 14.83±3.53 vs. 22.52±3.90, p=0.000)
  • Significantly decreased quality of life (PDQ39: 106.5±22.92 vs. 44.39±27.73, p=0.000)
- **Therapeutic response:**
  • High doses of levodopa (LEDD: 1902.17±191.83 vs. 726.14±358.37, p=0.000), decreased responsiveness (Levodopa responsiveness, %: 16.30±4.13 vs. 67.47±8.75, p=0.000), increased residual ON deficit (UPDRS_3_ON: 60.0±10.40 vs. 15.23±6.11, p=0.000)
- **Vascular profile:**
  • All patients with vascular parkinsonism (PVasc) had hypertension (HTA), diabetes mellitus (DM), myocardial infarction (MI), and hyperhomocysteinemia
  • All patients with PVasc showed on imaging: stroke (CVA), gliotic foci, external cerebral atrophy, and ventricular dilation

The vascular etiology of parkinsonism likely influenced independently: the severity of motor impairment (UPDRS_3_OFF), patients' daily motor functionality (UPDRS_2), residual motor deficit during the ON phase (UPDRS_3_ON), the severity of non-motor symptoms (NMS), and cognitive impairment (MoCA).

This study defined the profile of parkinsonism associated with cerebrovascular accident (CVA) versus parkinsonism not associated with CVA:

- Prevalence: 17.4%
- Types of CVA:
  - 11.5% territorial
  - 9% lacunar

- 2.9% in strategic structures for parkinsonism

- Clinical characteristics:
  - Older age (66.75±5.74 vs. 64.14±6.73, p=0.002) and later disease onset (62.96±6.33 vs. 59.63±6.94, p=0.000)
  - Frequent phenotype: akinetic-rigid (54.8%, Df=2, p=0.000)
  - More frequent kinetic tremor (47.9% vs. 11%, p=0.000), less frequent resting tremor (47.9% vs. 77.7%, p=0.000)
  - Onset types: acute progressive (5.5% vs. 0%), delayed progressive (11% vs. 0%), insidious (83.6% vs. 100%), Df=2, p=0.000
  - Frequently initial involvement of lower limbs (37%, Df=1, p=0.000) (Figure 3)
  - Symmetric motor impairment (Psm_simetric_Right_Left: 12.3% vs. 1.5%, p=0.000; Psm_simetric_Superior_Inferior: 12.3% vs. 0.9%, p=0.000; Asymmetry Index Superior_Inferior: 6.98±7.20 vs. 11.33±5.86, p=0.000) and severe (UPDRS_3_OFF: 52.05±14.54 vs. 46.04±12.30, p=0.000)
- Non-motor symptoms:
  - Increased severity of non-motor symptoms (NMS Score: 71.33±48.60 vs. 49.21±26.79, p=0.000)
  - More pronounced cognitive impairment (MoCA: 21.23±4.9 vs. 22.53±3.87, p=0.014)
- Dopaminergic treatment:
  - Higher doses (LEDD: 1005.90±538.85 vs. 707.36±350.36, p=0.000)
- Treatment response:
  - Reduced levodopa responsiveness (51.94±18.63 vs. 69.02±7.43, p=0.000)
  - Increased residual ON phase deficit (UPDRS_3_ON: 26.68±17.11 vs. 14.35±5.21, p=0.000)
- Vascular profile:
  - Vascular risk factors present in all patients (100% vs. 91.4%, p=0.004) and multiple risk factors per subject (Number of VRFs: 7.62±2.2 vs. 2.45±1.57, p=0.000)
  - CVA may independently influence residual post-levodopa deficit (UPDRS_3_ON).

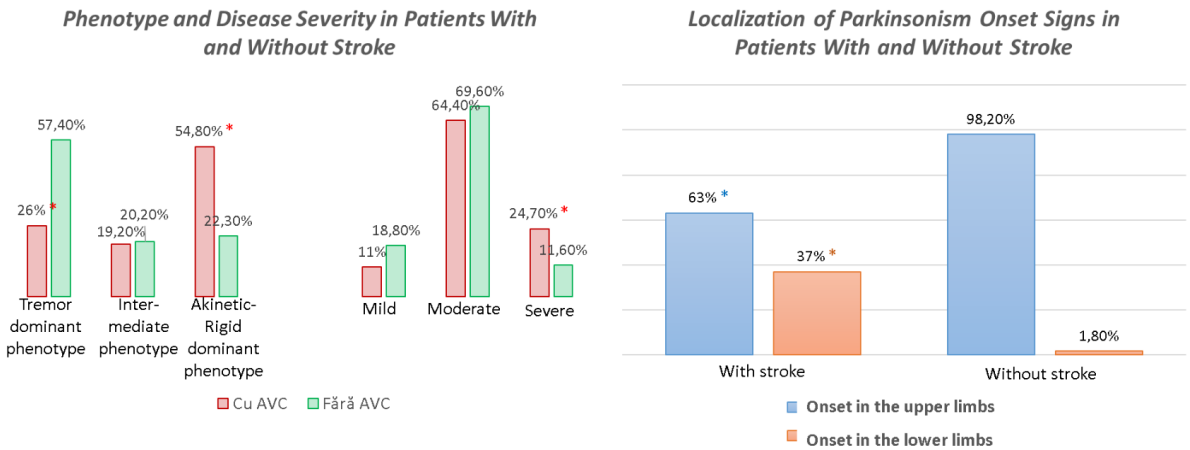

Figure 3. Phenotype, Disease Severity, and Localization of Initial Signs in Patients with and without Stroke

Based on other stratifications, it was found that the dominant clinical-evolutionary syndrome was associated with a specific phenotype of associated characteristics:

→ Longer disease duration (<5 years / 5-10 years / >10 years) was associated with:

- more severe motor impairment (UPDRS_3_ON: 45.00±12.44 vs. 52.17±13.26 vs. 52.94±7.80, p½=0.000, p⅓=0.042) and non-motor impairment (NMS: 9.96±6.38 vs. 12.18±7.17 vs. 13.63±6.06, p½=0.010)
- increased frequency (8.3% vs. 91.3% vs. 93.8%, Df=2, p=0.000) and severity of motor complications (UPDRS_4: 0.44±1.61 vs. 5.17±3.9 vs. 6.19±3.60, p½=p⅓=0.000)
- increased need for dopaminergic treatment (LEDD: 696.56±385.68 vs. 902.68±424.48 vs. 1007.9±342.32, p½=0.000, p⅓=0.007)
- possibly, independently, disease duration influenced the severity of motor complications (UPDRS_4) and cognitive impairment severity (MoCA)

→ Greater disease severity (mild / moderate / severe) was associated with:

- more severe non-motor symptoms (NMS: 26.68±15.44 vs. 47.87±18.56 vs. 112.21±35.41, p½=p⅓=p⅔=0.000) and cognitive impairment (MoCA: 22.93±3.33 vs. 22.90±3.73 vs. 18.54±4.72, p½=p⅓=p⅔=0.000)
- poorer quality of life (PDQ39: 8.27±6.12 vs. 46.30±18.75 vs. 93.09±21.86, p½=p⅓=p⅔=0.000)
- greater dopaminergic requirements (LEDD: 313.69±151.13 vs. 745.88±260.58 vs. 1390.18±421.01, p½=p⅓=p⅔=0.000)
- lower levodopa responsiveness (71.03±8.90 vs. 66.37±9.2 vs. 57.72±21.54, p½=0.008, p⅓=p⅔=0.000)
- possibly, independently, disease severity influenced non-motor symptom severity (NMS), cognitive impairment severity (MoCA), and quality of life (PDQ39)

→ Presence of cognitive impairment (with cognitive impairment / without cognitive impairment, MoCA cut-off 26) was associated with:

- significantly reduced functionality in motor aspects (UPDRS_2: 15.45±8.31 vs. 10.74±6.94, p=0.000) and non-motor aspects (UPDRS_1: 9.46±7.13 vs. 7.17±3.57, p=0.002) of daily living
- vascular profile: greater severity of cerebrovascular damage (Number of lacunes per subject: 7.79±4.95 vs. 4.00±2.39, p=0.044)
- possibly, independently, presence of cognitive impairment influenced the severity of dysfunction in motor (UPDRS_2) and non-motor (UPDRS_1) aspects of daily activities

→ Presence of motor complications (with motor complications / without motor complications) was associated with:

- significantly reduced psychosocial functionality (SCOPA_PS: 8.74±5.26 vs. 8.71±7.36, p=0.000) and quality of life (PDQ39: 54.5±30.11 vs. 42.22±28.42, p=0.000)
- cognitive impairment (MoCA: 21.29±4.16 vs. 22.79±3.98, p=0.000), possibly medication-induced

- possibly, independently, presence of motor complications influenced cognitive impairment severity (MoCA)

→ Presence of severe non-motor symptoms (NMS <40 / NMS >40) was associated with:

- significantly impaired daily functioning both in motor dimension (UPDRS_2: 17.34±8.25 vs. 8.73±4.46, p=0.000) and non-motor dimension (UPDRS_1: 10.98±7.09 vs. 5.10±2.36, p=0.000)
- higher daytime doses of dopaminergic medication (LEDD: 906.59±398.13 vs. 497.76±264.59, p=0.000)
- more frequent cardiovascular comorbidities (presence of vascular risk factors: 96.6% vs. 86.3%, p=0.000; Number of vascular risk factors per subject: 3.78±2.69 vs. 2.64±2.29, p=0.000)
- considerably lower quality of life (PDQ39: 60.26±24.65 vs. 20.91±18.69, p=0.000)
- possibly, independently, presence of severe non-motor symptoms influenced severity of dysfunction (motor (UPDRS_2) and non-motor (UPDRS_1) aspects of daily activities) and quality of life (PDQ39).

5. REZULTS OF THE STUDY ON CLINICAL PARTICULARITIES OF IDIOPATHIC PARKINSON'S DISEASE ASSOCIATED WITH CEREBROVASCULAR CHANGES

This study included 397 patients with idiopathic Parkinson's disease, with a mean age of 64.39±6.57 years, mean age at onset of 59.93±6.81 years, and disease duration of 53.83±37.11 months, selected according to inclusion criteria (1. Patient with idiopathic Parkinson's disease; 2. Cooperative patient; 3. Informed consent) and exclusion criteria (1. Patient with atypical or secondary non-vascular and secondary vascular parkinsonism; 2. Non-cooperative patient; 3. Lack of informed consent); the majority had vascular risk factors present (92.7%) and macrostructural cerebrovascular lesions (86.1%):

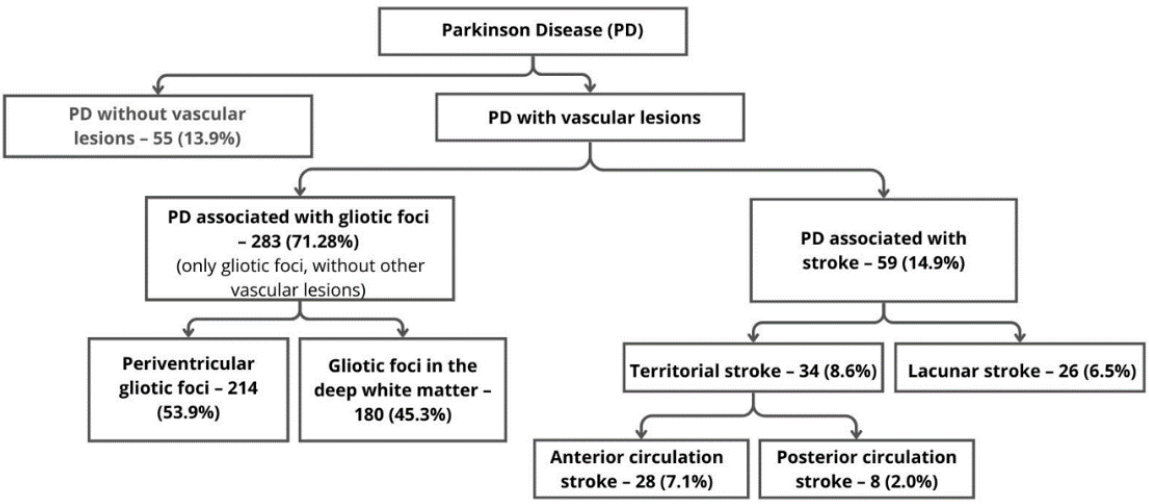

Figure 4. Types and locations of intracerebral vascular lesions in patients with Parkinson's disease

The impact of cerebrovascular disease (CVD) on Parkinson's disease (PD / PD+FG / PD+CVD) was identified as follows:

→ The presence of CVD was associated with:

‣ more severe motor impairment (UPDRS_3_OFF: 41.07±9.42 vs. 41.10±12.56 vs. 47.86±11.87, $p_{1/2} = p_{1/3} = 0.002$), including motor dysfunction in daily living activities (UPDRS_2: 9.95±4.82 vs. 14.17±7.77 vs. 14.98±8.12, $p_{1/2} = p_{1/3} = 0.001$)

‣ pronounced non-motor symptoms (NMS: 39.31±18.13 vs. 51.33±7.89 vs. 51.98±4.48, $p_{1/2} = 0.006$, $p_{1/3} = 0.03$), including depression, pain, cardiovascular symptoms, and falls

‣ increased dopaminergic doses (LEDD: 540.09±251.71 vs. 742.40±358.26 vs. 821.61±387.87, $p_{1/2} = p_{1/3} = 0.000$), decreased quality of life (PDQ39: 29.31±19.99 vs. 46.08±27.84 vs. 50.36±29.07, $p_{1/2} = p_{1/3} = 0.000$).

→ The severity of CVD was associated with:

‣ older age (62.31±8.31 vs. 64.51±6.33 vs. 65.73±5.43, $p_{1/3} = 0.016$) and later age of onset (58.05±8.73 vs. 59.94±6.15 vs. 61.68±5.74, $p_{1/3} = 0.013$)

‣ more advanced motor impairment stage (Hoehn and Yahr score: 3.04±0.18 vs. 3.18±0.49 vs. 3.34±0.60, $p_{1/3} = 0.003$)

→ The presence and severity of CVD were associated with:

‣ faster contralateral motor involvement (Time to contralateral involvement: 22.31±11.34 vs. 21.77±11.05 vs. 16.24±9.82, $p_{1/3} = p_{2/3} = 0.001$)

‣ more frequent onset with lower limb involvement (Onset involving lower limbs: 0% vs. 2.1% vs. 32.2%, Df=2, p=0.000)

‣ more severe lower limb impairment (Superior_Inferior asymmetry index: 11.92±5.5 vs. 11.24±5.92 vs. 8.91±5.22, $p_{1/3}$=0.017, $p_{2/3}$=0.015)

‣ akinetic-rigid phenotype (7.3% vs. 25.4% vs. 45.8%, Df=4, p=0.000) plus kinetic tremor (1.8% vs. 13.1% vs. 37.3%, Df=2, p=0.000)

‣ decreased levodopa responsiveness (69.46±6.79 vs. 68.86±7.61 vs. 58.97±10.56, $p_{1/3} = p_{2/3} = 0.000$), increased residual ON-phase deficit (12.51±3.97 vs. 14.77±5.41 vs. 19.98±8.19, $p_{1/2}$=0.023, $p_{1/3} = p_{2/3} = 0.000$).

The study also outlined the characteristics of Parkinson's disease (PD) associated with gliotic foci (GF) (versus PD without cerebrovascular disease (CVD) and versus PD with stroke):

Parkinson's disease with gliotic foci (GF) vs. PD without cerebrovascular disease (CVD):

- More frequent onset with rigidity (24.7% vs. 9.1%, p=0.000)
- Increased rigidity (AR_Score_OFF: 0.95±0.76 vs. 0.64±0.45, p=0.023), more symmetrical motor impairment (Right_Left Asymmetry Index: 0.049±9.22 vs. 3.87±8.76, p=0.015)
- More frequent presence of kinetic tremor (13.1% vs. 1.8%, p=0.000)
- More severe motor (UPDRS_3_OFF: 41.10±12.56 vs. 41.07±9.42, p=0.002) and non-motor symptoms (NMS: 51.33±7.89 vs. 39.31±18.13, p=0.006), including depression, pain, apathy
- Reduced quality of life (PDQ39: 46.08±27.84 vs. 29.31±19.99, p=0.000)

- Increased post-levodopa deficit (UPDRS_3_ON: 14.77±5.41 vs. 12.51±3.97, p=0.023), despite significantly higher dopaminergic doses (LEDD: 742.40±358.26 vs. 540.09±251.71, p=0.000)

Parkinson's disease with gliotic foci (GF) vs. PD with associated stroke:

- Longer latency to contralateral involvement (Time to contralateral involvement: 21.77±11.05 vs. 16.24±9.82, p=0.001)
- Less pronounced akinesia-rigidity (AR_Score_OFF: 0.95±0.76 vs. 1.75±1.06, p=0.000)
- Lower dopaminergic doses (LEDD: 742.40±358.26 vs. 821.61±387.87, p=0.000)
- Higher levodopa responsiveness (68.86±7.61 vs. 58.97±10.56, p=0.000)
- Lower residual post-levodopa deficit (UPDRS_3_ON: 14.77±5.41 vs. 19.98±8.19, p=0.000)

The study demonstrated that comorbid cerebrovascular disease, manifested as the presence of gliotic foci or stroke, is associated with a significant reduction in levodopa responsiveness in patients with Parkinson's disease. The identified negative correlations ($r = –0.349$, $p=0.000$ for cerebrovascular lesions overall and $r = –0.415$, $p=0.000$ for stroke) suggest a direct impact of cerebrovascular comorbidity on the efficacy of dopaminergic treatment. Furthermore, the presence of vascular risk factors correlated with poorer therapeutic response ($r = –0.317$, $p=0.024$), indicating a possible cumulative role of cardiovascular impairment in reducing levodopa efficacy.

6. COMPARATIVE STUDY RESULTS OF VASCULAR RISK FACTORS IN PATIENTS WITH PARKINSON'S DISEASE

This study enrolled 703 subjects: 397 patients with idiopathic Parkinson's disease (PD) and 306 control subjects matched for age and sex; the overall mean age was 63.46±8.31 years, with 49.9% males and 50.1% females. The aim of this study was to determine:

• the frequency of vascular risk factors (VRFs) in PD patients versus controls and

• the influence of sex and age variables on VRFs in PD patients versus controls.

The study identified distinct features of vascular risk factors in PD patients (versus controls):

- VRFs were more frequent in PD patients compared to controls (95.7% vs. 86.3%, p=0.000)
- Number of VRFs per subject was significantly higher in PD (3.48±2.04 vs. 2.37±1.74, p=0.000)
- Vascular risk score was higher in PD patients (2.13±4.46 vs. 1.55±1.98, p=0.000)
- VRFs significantly more prevalent in PD patients:
    - Hypertension (59.7% vs. 44.4%, p=0.000)
    - Diabetes mellitus (22.4% vs. 10.8%, p=0.000)
    - Dyslipidemia (56.4% vs. 38.6%, p=0.000)
    - Cerebral atherosclerotic stenosis (45.6% vs. 19.0%, p=0.000)

- Stroke (14.6% vs. 8.2%, p=0.009)
- Atrial fibrillation (10.1% vs. 7.8%, p=0.003)
- Chronic kidney disease (2.8% vs. 0.7%, p=0.048)
- Obesity (32.2% vs. 20.9%, p=0.001)
- Migraine (43.6% vs. 4.1%, p=0.000)

- VRFs significantly less frequent in the PD group:
  - Myocardial infarction (0.8% vs. 5.9%, p=0.000)
  - Active smoking (2.0% vs. 14.4%, p=0.000)
- A split-group analysis by sex (male/female) in both PD and control groups revealed that vascular risk factors were commonly present in both groups without significant sex differences; the study differentiated VRFs as follows:
  - No significant sex differences in either group,
  - Significant sex differences present in both groups,
  - Significant sex differences present only in the PD group:
    - More frequent in females: chronic kidney disease, rheumatoid arthritis, regular steroid treatment;
    - More frequent in males: cerebral atherosclerotic stenosis,
  - Significant sex differences present only in the control group:
    - More frequent in males: atrial fibrillation, coronary artery disease, myocardial infarction, stroke, total number of vascular risk factors, QRISK3 score.

The sex differences observed exclusively in one group (PD or control) (Figure 5) may suggest a possible interaction between neurodegeneration and vascular vulnerability, with implications for sex-differentiated homeostatic regulation. The attenuated sex differences in PD, compared to the general population, were noted for atrial fibrillation, coronary artery disease, and myocardial infarction, possibly reflecting neurodegeneration effects on the vascular system.

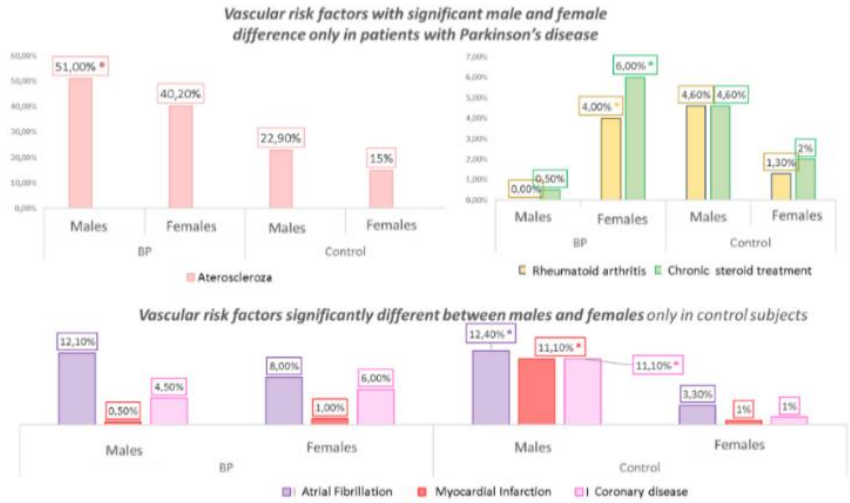

Figure 5. Sex Differences in Vascular Risk Factors, Expressed Exclusively in One of the Groups – Parkinson's Disease or Control

Women with Parkinson's disease (PD) in this study exhibited a significantly higher relative risk *compared to men* (whereas in the control group, no significant sex-related differences in relative risk were observed).

The split-group analysis by age (<60 years / >60 years), conducted in both the PD and control groups, found that vascular risk factors (VRFs) were frequently present across both groups, with no significant differences between the age categories. However, the analysis identified specific VRFs with distinct patterns:

- *With significant age-related differences observed only in the PD group:*
  - ▪ Smoking – more frequent among patients <60 years
  - ▪ Number of risk factors per subject – higher in patients >60 years
- *With significant age-related differences observed in both groups*, and more frequent or elevated in the >60 years subgroup:
  ~ Arterial hypertension (HTN)
  ~ Atherosclerosis
  ~ QRISK3 score
- *With significant age-related differences observed only in the control group:*
  ~ Migraine, rheumatoid arthritis, and chronic steroid use – more common in those <60 years
  ~ Diabetes mellitus (DM) – more frequent in those >60 years
  ~ Myocardial infarction (MI) – more frequent in those <60 years

The relative value of cardiovascular risk did not differ significantly between age groups (<60 years and >60 years) in either the PD or control group.

A low risk (<10%) predominated in the <60 years age category. Moderate (10–20%) and high risk (>20%) categories were more prevalent among individuals >60 years, in both groups.

The increased prevalence of certain vascular risk factors (e.g., diabetes mellitus, migraine) even at younger ages in patients with Parkinson's disease (Figure 6), contrary to trends observed in the general population, may support the hypothesis that these factors contribute to the early onset of neurodegeneration.

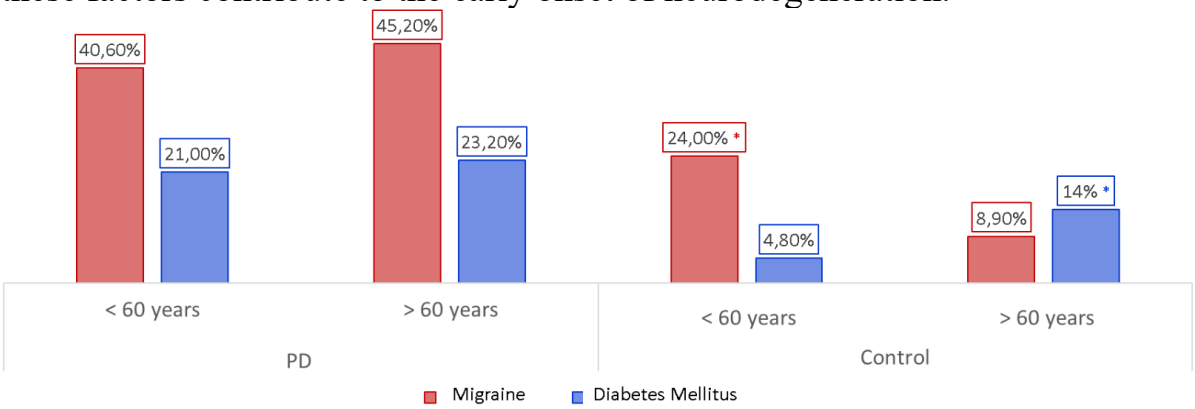

Figure 6. Migraine and Diabetes Mellitus by Age Category in Patients with Parkinson's Disease and Control Subjects

Given the distinct vascular profile associated with Parkinson's disease, which includes a blunting of physiological differences between sexes and age groups, screening for vascular risk factors (VRFs) in patients with PD should be individualized and stratified by sex and age in order to optimize cardiovascular risk assessment and management.

7. RESULTS OF THE STUDY ON CEREBROVASCULAR CHANGES IN PATIENTS WITH PARKINSON'S DISEASE

This study included 160 patients with Parkinson's disease and 555 control subjects, with a mean age of 62.29±10.87 years, selected according to specific inclusion and exclusion criteria:

Inclusion criteria for patients:

1. Confirmed diagnosis of Parkinson's disease
2. Availability of neuroimaging examination / informed consent to undergo neuroimaging

Inclusion criteria for control subjects:

1. Availability of neuroimaging examination
2. Random selection from a patient list based on age-matching criteria
3. Referral diagnosis of non-structural brain pathology
4. Absence of exclusion criteria

Exclusion criteria for patients:

1. Imaging evidence of space-occupying brain lesions

Exclusion criteria for control subjects:

1. Referral diagnosis for brain MRI suggesting an intracerebral mass lesion
2. Referral diagnosis for brain MRI suggesting stroke
3. Imaging evidence of space-occupying brain lesions

All patients underwent brain MRI using a 1.5 Tesla scanner (General Electric, SIGNA EXPLORER G3, 16-channel high-resolution head/neck coil), in order to assess:

- The types, frequency, severity, and localization of structural vascular lesions in patients with Parkinson's disease versus control subjects
- Quantitative structural parameters of neurodegeneration in patients with Parkinson's disease versus controls (midbrain area, pontine area, substantia nigra width)
- Qualitative parameters of chronic subthreshold ischemia in Parkinson's disease versus controls (DWI, ADC)

The ages of patients with Parkinson's disease (PD) and control subjects in this study were comparable: 61.79±9.22 vs. 62.43±11.31 years ($p > 0.05$). Macrostructural cerebrovascular lesions were identified in the majority of participants: 85.6% of PD patients and 71.5% of controls, with no statistically significant difference between groups ($p > 0.05$). However, statistically significant differences were found between groups regarding most types of macrostructural cerebrovascular lesions—these were significantly more frequent in patients with PD than in controls, specifically: Ischemic strokes (10.0% vs. 1.1%, $p = 0.000$); Lacunar infarcts (15.6% vs. 4.0%, $p = 0.000$); Gliotic foci (63.3% vs. 45.8%, $p = 0.000$); Virchow–Robin space dilatation (56.3% vs. 35.7%, $p = 0.000$); External cerebral atrophy (73.8% vs. 42.9%, $p = 0.000$). No significant differences were observed between groups in terms of internal cerebral atrophy (31.9% vs. 28.1%, $p = 0.374$) or microbleeds (5.6% vs. 2.7%, $p = 0.082$).

In patients with Parkinson's disease, strokes in the anterior circulation (9.4% vs. 0.5%, $p = 0.000$) and posterior circulation (2.5% vs. 0.4%, $p = 0.025$) were significantly

more frequent compared to the control group. Total anterior circulation infarcts—strategically located lesions implicated in the development of parkinsonism—were identified exclusively in PD patients (3.1%), as well as concomitant infarcts affecting both circulations (1.9%). Within the PD group, anterior circulation strokes were significantly more frequent compared to posterior circulation (Anterior: 9.4% vs. Posterior: 2.5% vs. Combined anterior and posterior: 1.9%, $p_{1/2} = p_{1/3} < 0.001$, $p_{2/3} > 0.05$).

Lacunar infarcts were significantly more frequent in patients with Parkinson's disease (15.6% vs. 4.0%, $p = 0.000$), including in the deep white matter (15.0% vs. 1.3%, $p = 0.001$) and periventricular white matter (12.5% vs. 2.9%, $p < 0.001$). The presence of lacunes in both locations—deep and periventricular white matter—was significantly more common in the PD group (11.25% vs. 0.36%, $p < 0.001$). PD patients also exhibited significantly more multiple lacunar infarcts, including cases with ≥4 locations—an aspect entirely absent in the control group. The mean number of lacunar infarcts per patient was significantly higher in the PD group compared to controls (6.68 ± 4.10 vs. 1.57 ± 0.99, $p = 0.000$). Strategically located lacunes were identified exclusively in patients with PD: within or adjacent to the substantia nigra pars compacta (SNc) in 1.3% of cases (Figure 7) and within or near the ventrolateral thalamus (VLthal) in 2.5% of cases (Figure 8). No cases showed lacunes within or near the external globus pallidus (GPe). Each patient had only one strategically affected region.

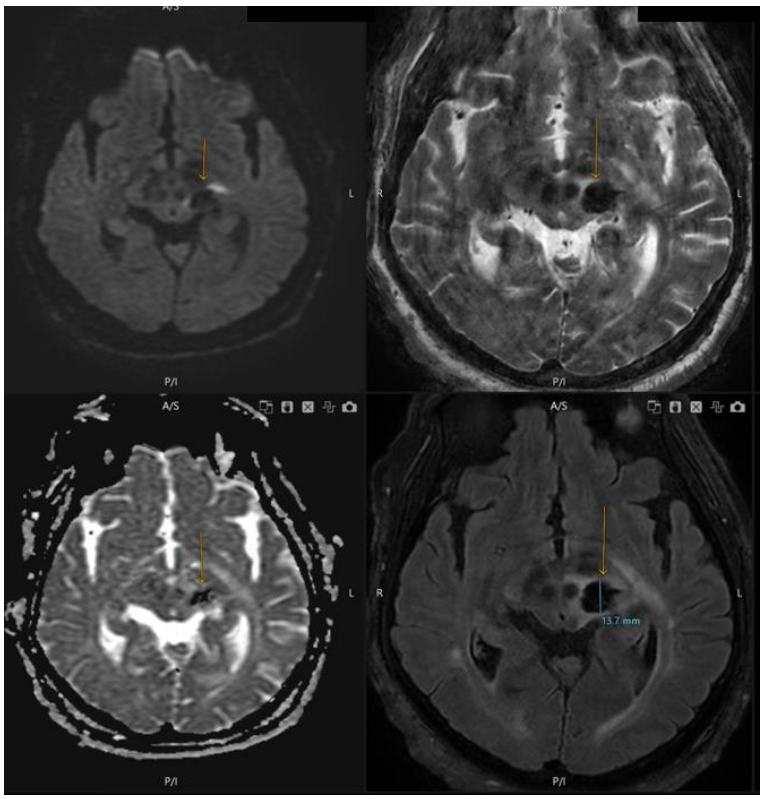

Figure 7. Subacute Lacunar Stroke in the Left Midbrain Involving the Substantia Nigra

(1-Axial DWI; 2 -Axial T2w; 3 -Axial ADC; 4 -Axial FLAIR)

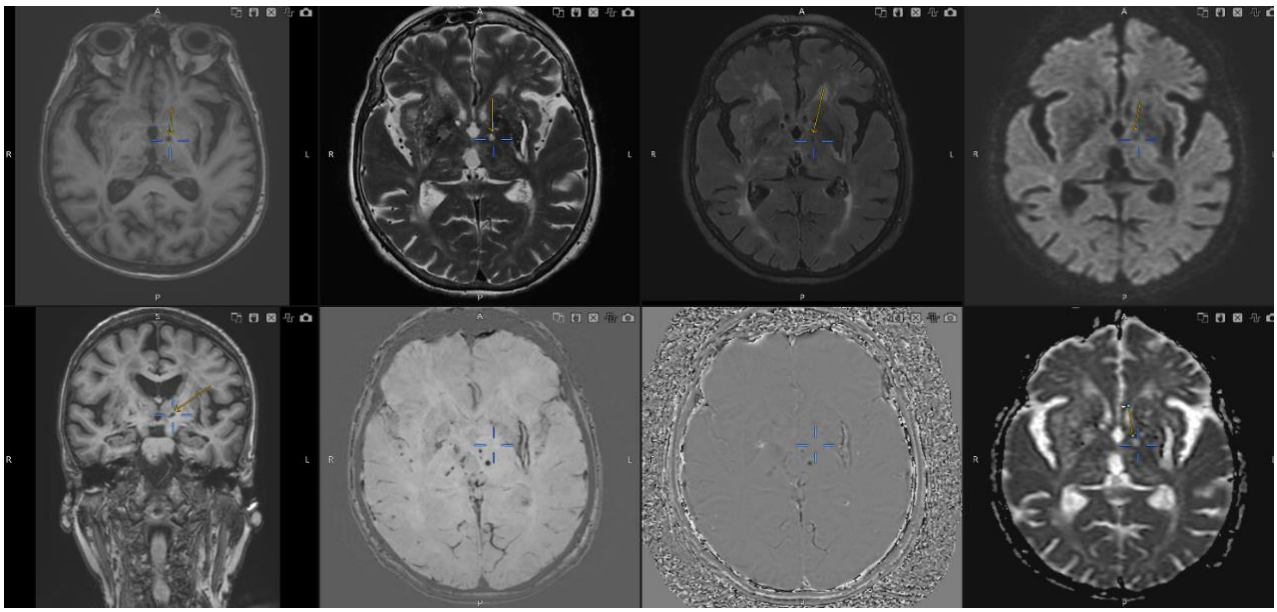

Figure 8. Post-Stroke Lacune in the Left Ventral Thalamus
(1 -Axial T1w; 2 -axial T2w; 3 -Axial FLAIR; 4 -Axial DWI; 5 -Coronal T1w; 6 - Axial FSBB/SWI; 7 -Axial FSBB reconstructie "phase"; 8 – Axial ADC.)

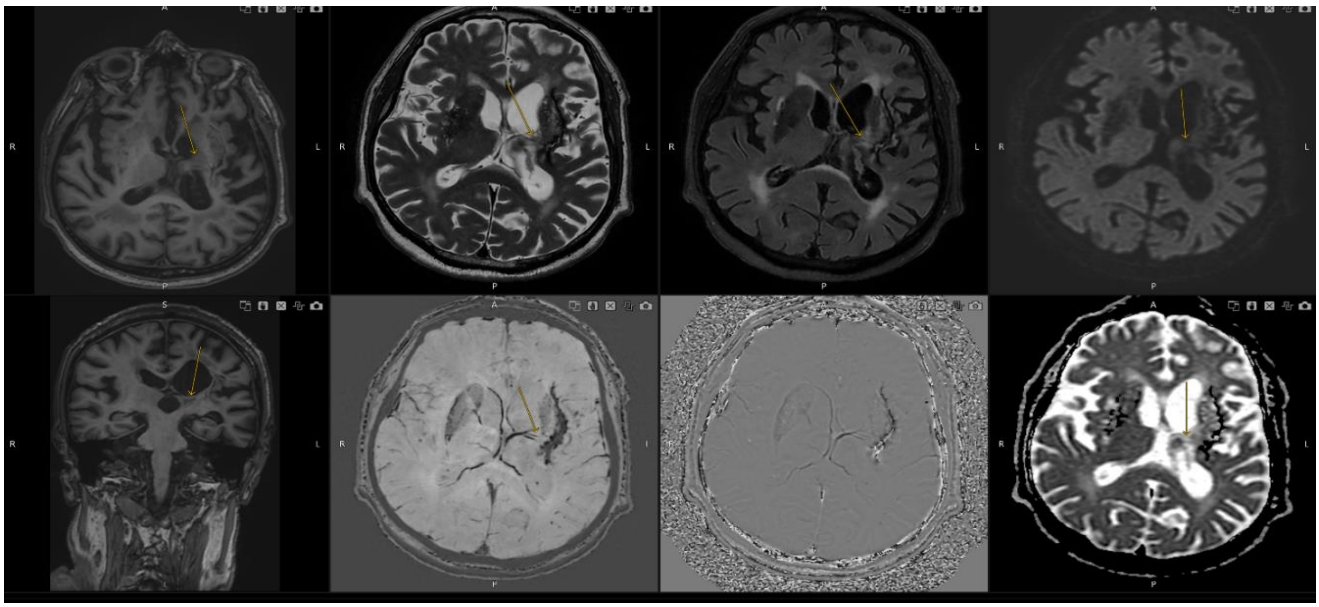

Figure 9. Gliotic Focus at the Level of the Left Globus Pallidus and Adjacent Area
(1 -Axial T1w; 2 -axial T2w; 3 -Axial FLAIR; 4 -Axial DWI; 5 -Coronal T1w; 6 - Axial FSBB/SWI; 7 -Axial FSBB reconstruction "phase"; 8 – Axial ADC.)

Gliotic foci were significantly more prevalent in patients with Parkinson's disease (66.3% vs. 45.8%, $p = 0.000$). In the deep white matter, their frequency was similar between groups (46.9% vs. 45.8%, $p = 0.857$); however, in the periventricular white matter, gliotic foci were significantly more frequent in PD patients (53.1% vs. 30.8%, $p = 0.000$). Combined localizations (both deep and periventricular) were also significantly more common in the PD group (33.8% vs. 23.1%, $p = 0.007$). Gliotic foci in the deep white matter showed comparable severity between groups ($Df = 3$, $p = 0.060$), with Fazekas grade I predominating (PD: 24.4% vs. Control: 25.4%). In contrast, periventricular foci were significantly more severe in PD patients ($Df = 3$, $p = 0.000$), with a higher proportion of Fazekas grade II (26.9% vs. 11.4%) and grade III (11.9% vs. 2.7%)

compared to controls. Gliotic foci within or near strategic brain structures were identified in 11.88% of PD patients versus 3.24% of controls ($p = 0.006$). Specifically, in the external globus pallidus (GPe; Figure 9): 10.0% in PD vs. 2.0% in controls ($p < 0.001$); in the substantia nigra pars compacta (SNc; Figure 10): identified only in PD patients (1.3%); and in the ventrolateral thalamus (VLthal; Figure 11): 0.6% in PD vs. 1.3% in controls, not statistically significant ($p = 0.691$). Among PD patients with strategic gliotic foci, localization in the GPe was significantly more frequent ($p < 0.001$).

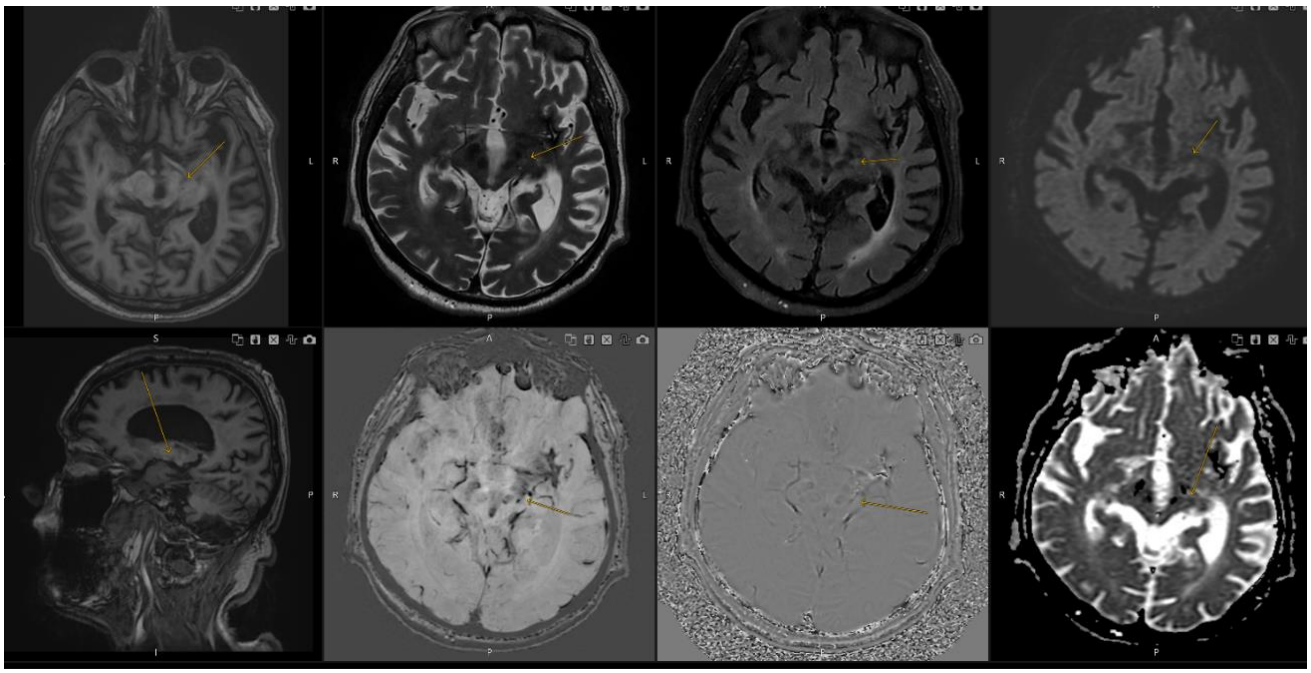

Figure 10. Gliotic Focus in the Vicinity of the Left Midbrain Substantia Nigra
(1 -Axial T1w; 2 -axial T2w; 3 -Axial FLAIR; 4 -Axial DWI; 5 -Coronal T1w; 6 - Axial FSBB/SWI; 7 -Axial FSBB reconstruction “phase”; 8 – Axial ADC.)

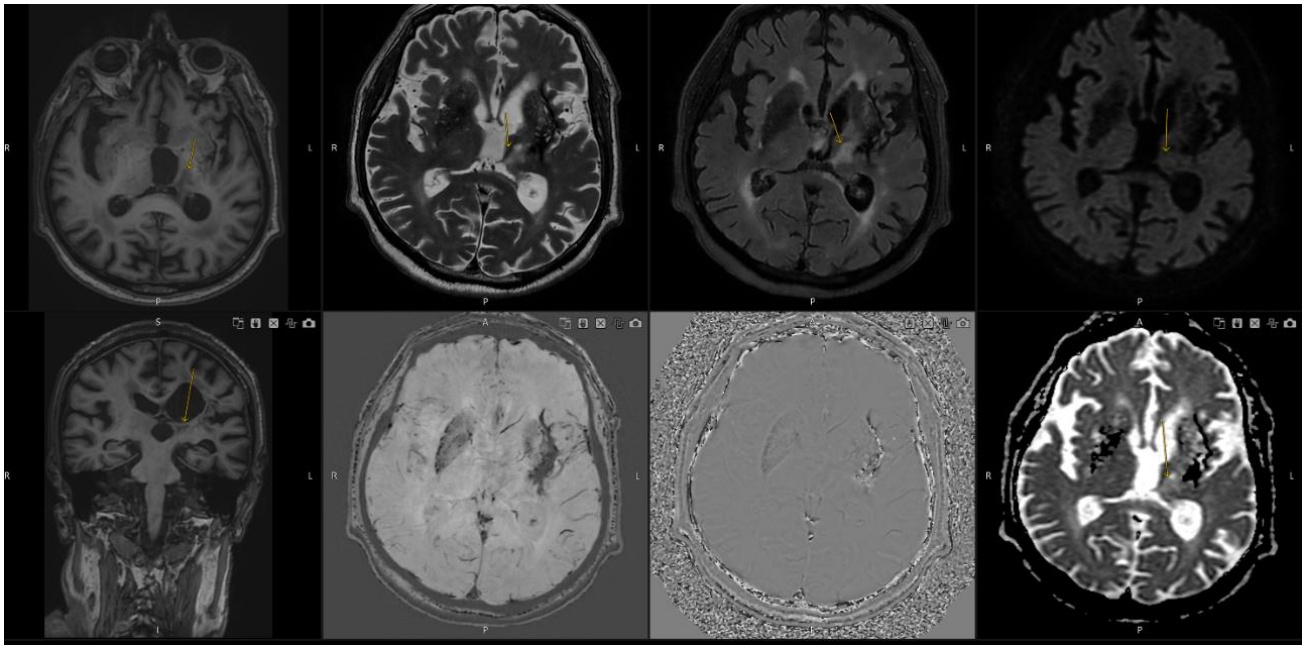

Figure 11. Gliotic Focus in the Left Thalamus Involving the Ventrolateral Nucleus
(1 -Axial T1w; 2 -axial T2w; 3 -Axial FLAIR; 4 -Axial DWI; 5 -Coronal T1w; 6 - Axial FSBB/SWI; 7 -Axial FSBB reconstructie “phase”; 8 – Axial ADC.)

The total small vessel disease score, calculated based on the number and severity of lacunes, gliotic foci, and perivascular space dilation, was significantly higher in patients with Parkinson's disease compared to controls (0.27 ± 0.50 vs. 0.087 ± 1.02, $p = 0.000$), indicating more severe cerebral vascular impairment in Parkinson's disease.

In the T1-weighted (T1w) sequence, measurements were taken along the mid-sagittal line of the substantia nigra pars compacta (SNc) width (mm), pontine and mesencephalic areas (cm^2), and the pontine-to-mesencephalic area ratio was calculated. All these values were significantly reduced in patients with Parkinson's disease compared to control subjects, supporting the involvement of the mesencephalon in the disease's pathogenesis. Furthermore, the decreased width of the SNc reflects the specific morphological substrate of Parkinson's disease, being significantly lower than in the control group (2.331 ± 0.456 vs. 2.409 ± 0.406, $p=0.038$).

The dorsal substantia nigra intensity (arbitrary units) in the susceptibility-weighted imaging (SWI) sequence was significantly higher in Parkinson's disease patients compared to controls (51.67 ± 14.87 vs. 38.63 ± 11.11, $p=0.000$), reflecting its status as a specific marker of Parkinson's disease in magnetic susceptibility imaging.

Using a standardized region of interest (ROI) method (1 cm, lesion-free white matter), cerebral diffusivity parameters (DWI and ADC) were measured in the frontal lobe, internal capsule, and corpus callosum—areas remote from the pathogenic regions of Parkinson's disease. Decreased DWI and increased ADC indicate elevated diffusivity, characteristic of chronic ischemic lesions caused by demyelination and rarefaction of white matter. In patients with Parkinson's disease, the following were observed:

- In the frontal lobe region: significantly lower DWI ($p=0.006$) and significantly higher ADC ($p=0.481$), suggesting mild but relevant ischemic involvement of the frontal white matter, consistent with the frequently observed executive cognitive decline in Parkinson's disease.
- In the internal capsule region: non-significantly lower DWI ($p=0.192$) and significantly higher ADC ($p=0.000$), indicating microstructural damage from chronic ischemic changes in the corticospinal tracts, which may be diffuse or variable.
- In the corpus callosum region: significantly lower DWI ($p=0.010$) and significantly higher ADC ($p=0.000$), suggesting pronounced chronic ischemic injury to the interhemispheric pathways.

The significant differences observed in both parameters (DWI and ADC) exclusively in the corpus callosum suggest a more pronounced chronic ischemic involvement of associative pathways compared to corticospinal tracts. These findings highlight a diffuse chronic ischemic injury profile in patients with Parkinson's disease, even in the absence of overt lesions on conventional MRI. Changes in the corpus callosum and frontal lobe may contribute to cognitive and non-motor symptoms, while internal capsule involvement supports the motor component. The observed alterations support the involvement of small vessel disease in the pathogenic substrate of Parkinson's disease in a subgroup of patients, providing opportunities for preventive vascular intervention.

Correlation analysis revealed significant associations between the total vascular score and the following variables: frontal ADC ($r = 0.199$, $p = 0.000$), corpus callosum ADC ($r = 0.356$, $p = 0.000$), subject age ($r = 0.212$, $p = 0.000$), and dorsal substantia nigra (SN) intensity on SWI ($r = 0.299$, $p = 0.000$). Thus, increased macrostructural cerebral vascular damage correlates with advancing age, altered diffusivity in white matter regions (frontal and corpus callosum), and dorsal SN hyperintensity — suggesting a possible shared ischemic-neurodegenerative mechanism.

Age stratification (<60 years / >60 years) of both cohorts showed that, in the control group, macrostructural vascular lesions were significantly less frequent in subjects under 60 years (46.3%) compared to those over 60 years (84.5%), $p = 0.000$. In contrast, among Parkinson's disease (PD) patients, these lesions were common even in those under 60 years (81.4% vs. 88.1%, $p = 0.172$), with no significant difference. This analysis suggests that younger PD patients exhibit vascular damage comparable to that of older non-PD subjects, supporting the hypothesis of early vascular involvement associated with neurodegenerative processes at the onset of Parkinson's disease. Thus, age influences the occurrence of vascular lesions in the general population, but not in PD patients, where vascular pathology appears related to the disease itself rather than aging alone.

Significant age-related differences for certain types and locations of cerebrovascular lesions were recorded only in PD patients, but not in controls: stroke (13.9% in >60 years vs. 3.4% in <60 years, $p = 0.026$), microbleeds (8.9% in >60 years vs. 0% in <60 years, $p = 0.027$), and gliotic foci in strategic regions (12.9% in >60 years vs. 0% in <60 years, $p = 0.000$). These results suggest that age over 60 in PD patients is associated with increased vulnerability to specific vascular lesions, including those in regions critical for parkinsonism, indicating a possible interaction between cerebrovascular aging and neurodegenerative mechanisms.

Significant age-related differences (<60 vs. >60 years) were identified only in the control subjects (and not in Parkinson's disease patients) for: dilation of perivascular spaces (28.7% vs. 39.2%, $p = 0.015$), midbrain area (5.42 vs. 1.47 cm^2, $p = 0.003$), and frontal lobe ADC values (730.5 vs. 758.7, $p = 0.000$). The absence of age-related differences in PD patients for perivascular space dilation, midbrain atrophy, and increased ADC suggests that the observed structural and functional changes predominantly reflect neurodegenerative processes rather than physiological aging. This supports the early involvement of these structural and diffusion alterations in Parkinson's disease pathogenesis.

8. **RESULTS OF THE KAP (Knowledge, Attitudes, and Practices) STUDY OF PATIENTS AND PHYSICIANS REGARDING THE MANAGEMENT OF PARKINSON'S DISEASE IN THE REPUBLIC OF MOLDOVA**

To determine the •knowledge, •attitudes, •practices, •barriers, and •needs of both •beneficiaries and •healthcare providers regarding Parkinson's disease, a mixed descriptive study — both qualitative and quantitative — was conducted. Patient participants were enrolled during consultations at the "Diomid Gherman" Institute of Neurology and Neurosurgery as they presented for care. Physician participants were recruited through direct contact or via the professional society. A total of 103

Parkinson's disease patients and 105 neurologists and family physicians were interviewed, selected according to inclusion and exclusion criteria.

Inclusion criteria for patients:

1. Diagnosed with Parkinson's disease
2. Cooperative
3. Sufficient cognitive abilities to read, understand, and complete the questionnaire

Exclusion criteria for patients:

1. Diagnosed with parkinsonism other than Parkinson's disease
2. Non-cooperative
3. Insufficient cognitive abilities to read, understand, and complete the questionnaire

Inclusion criteria for physicians:

1. Neurologists and family physicians
2. Cooperative
3. Physicians who consult patients with Parkinson's disease

Exclusion criteria for physicians:

1. Non-cooperative
2. Physicians who do not consult patients with Parkinson's disease

For the quantitative study, structured questionnaires were used, self-administered by patients with Parkinson's disease and by physicians, focusing on the assessment of knowledge, attitudes, and practices (KAP), as well as barriers to medical care. The questionnaires were pretested and validated. The qualitative study was conducted both prior to and following the quantitative phase, through interviews and focus groups with patients and physicians, aimed at identifying relevant topics and interpreting the results.

The questionnaires for both patients and physicians included an introduction regarding the study's purpose, anonymity, and voluntary participation. The patient questionnaire consisted of closed-ended questions structured around: ▪ knowledge about the disease and treatment, ▪ attitudes towards the disease, ▪ treatment practices, ▪ barriers to access to services, ▪ suggestions for improvement, and ▪ general demographic data.

The physician questionnaire included both closed- and open-ended questions focusing on:
▪ knowledge regarding Parkinson's disease diagnosis and treatment, ▪ attitudes and management practices, ▪ barriers and needs within the healthcare system, ▪ suggestions for optimization, and ▪ general demographic data.

Results of the KAP (Knowledge, Attitudes, Practices) Study and Barriers Reported by Patients Regarding the Management of Parkinson's Disease in the Republic of Moldova:

The mean age of patients with Parkinson's disease was 65.5 ± 8.4 years; 52.4% were female, 59.2% originated from rural areas, and the average years of education was 12.6 ± 3.6. The majority of patients (75.7%) were in Hoehn-Yahr stage II, 21.4% in stage III, and 2.9% in stage I of the disease.

Assessment of patient knowledge revealed prevalent myths circulating among patients (Figure 12) as well as stigmas related to clinical manifestations, disease progression, and the patient's relationship with their family and society.

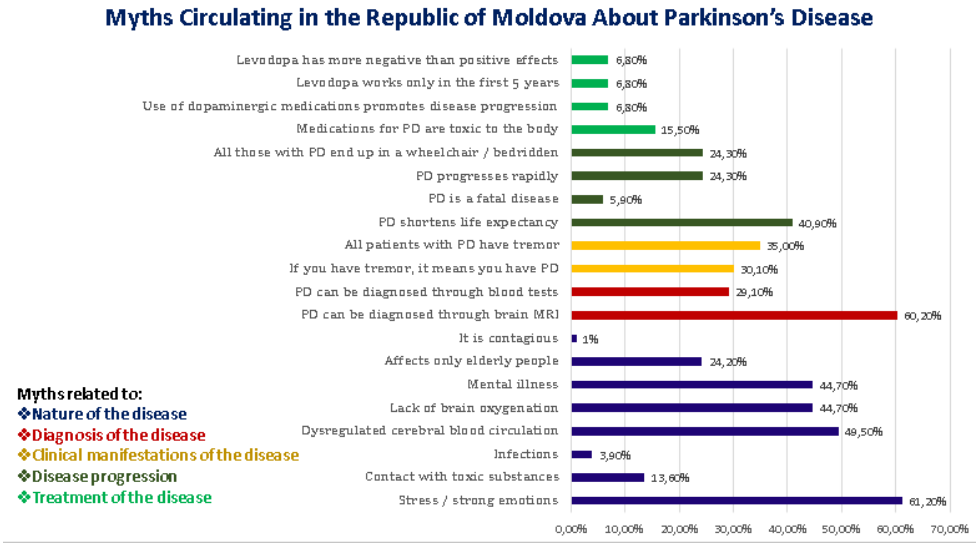

Figure 12. Patient Myths About Parkinson's Disease

The study highlighted frequent stigmas among patients with Parkinson's disease, reflected in erroneous perceptions about the illness and social fears. Some patients believed that Parkinson's disease is a mental disorder (44.7%), shortens life expectancy (40.8%), causes dementia (33%), or is contagious (1%). Socially, shame related to the illness (46.6%), fear of dependence (65%), and fear of judgment by others (44.7%) were widespread. These beliefs exacerbate stigmatization and may negatively impact quality of life and treatment adherence.

Patients exhibited both negative and positive attitudes. Negative attitudes predominated, including fear of dependence (65%), shame related to disability (49.5%) or diagnosis (46.6%), fear of social isolation (32%), and fear of community judgment (44.7%). At the same time, many patients believed they could positively influence disease progression through exercise (61.2%), healthy diet (55.3%), and an active lifestyle (42.7%).

Evaluating treatment practices of patients with Parkinson's disease using a Likert scale, the study found good treatment adherence: 42.7% never forget to take their medication, 51.5% occasionally forget, and 5.8% frequently forget. The majority (84.5%) do not question the necessity of treatment, and 87.4% do not take breaks from medication. However, some patients (25.4%) admit to skipping doses when they "feel well." Modification of the therapeutic regimen without medical consultation was reported by 26.3% of patients (1% always, 7.8% frequently, 17.5% occasionally). Financial barriers are significant, with 56.3% experiencing difficulties obtaining medications due to costs. Regarding healthcare access, 91.6% consult a neurologist, 29.1% a family doctor, while 12.6% attempt to manage symptoms without medical assistance—indicating potential deficiencies in access to adequate care.

The study identified multiple significant barriers to healthcare access for patients with Parkinson's disease (PD) in the Republic of Moldova. System-level barriers were the most frequently reported, mentioned by the majority of patients. Specifically,

84.5% indicated a lack of specialists with expertise in PD, and 88.3% reported the unavailability of essential medications within the country. Additionally, 82.5% noted the absence of reimbursement for all necessary treatments. Geographic access remains limited, with 63.1% having to travel long distances to receive consultations, and 58.3% experiencing long waiting lists for free diagnostic investigations. Patients also complained about the high frequency of visits required for prescription refills (32.0%) and the insufficient monthly quantities of reimbursed medications (30.1%). The disability certification process was considered slow (14.6%), and the associated allowance inadequate (18.4%).

Financial barriers constitute a major obstacle: 55% of patients cannot consistently afford their medications, and in 55.3% of cases, expenses are shared with relatives. Some patients (15.5%) rely exclusively on reimbursed medications or lack medical insurance. Regarding health literacy barriers, nearly half of patients (40.8%) and their relatives (48.5%) acknowledge insufficient knowledge about PD, while 36.9% state they have not received essential information from healthcare providers. Moreover, 60.2% erroneously believe that PD diagnosis must be confirmed by brain MRI, underscoring the need for health education.

Beliefs and attitudes toward treatment negatively influence adherence: 57.3% forget to take their medication, 15.5% sometimes decide to interrupt it, and a similar proportion consider it toxic. Some patients (6.8%) express misconceptions about the effects of levodopa on disease progression. The general health status of patients represents another important individual functional barrier: 97.1% are in moderate to advanced stages of the disease (Hoehn & Yahr II–III), with severe motor impairment, limiting mobility and the ability to access services.

Regarding treatment, 69.9% of patients use both reimbursed and purchased medications, 14.6% rely exclusively on purchased medications, and 25.2% bear the full cost without family support. This reflects an economic limitation in accessing necessary treatment, adversely affecting equitable and continuous access to therapies required for optimal Parkinson's disease management.

In conclusion, patients with Parkinson's disease in the Republic of Moldova face multiple barriers — systemic, financial, educational, and health-related — which profoundly impact access to diagnosis, treatment, and ongoing care. These challenges negatively affect treatment adherence and, consequently, quality of life.

Patients with Parkinson's disease included in this study expressed essential needs for improving access to and quality of care in the Republic of Moldova. The majority requested an increase in the number of specialists in PD (80.6%) as well as dedicated physiotherapy, kinesitherapy, and rehabilitation services (85.4%). Social support needs were significant: 47.6% emphasized the importance of social workers and home care services, while 45.6% called for specialized institutions for advanced stages of the disease. Access to treatment remains a major concern: 88.3% advocated for an expanded list of reimbursed medications, and 86.4% requested registration of additional medications in the country. Furthermore, 54.4% sought greater availability of surgical treatment options for PD. Patient education was found to be inadequate, with only 35.0% reporting that they received sufficient explanations from healthcare

professionals. These findings underscore the necessity of an integrated approach combining medical, social, and educational support.

Results of the KAP (knowledge, attitudes, practices) study and barriers reported by physicians regarding the management of Parkinson's disease in the Republic of Moldova: The study included 105 physicians with a mean age of 37.03 ± 11.88 years. The majority practiced in urban areas (82.9%) and were female (72.4%). Only 7.6% held an academic scientific degree. Regarding the frequency of consultations for Parkinson's disease patients, 80% saw patients monthly, 15.2% weekly, 2.9% daily, and 1.9% several times per day.

The study evaluated the knowledge of physicians in the Republic of Moldova regarding the diagnosis and management of Parkinson's disease. Although 81.0% were familiar with the clinical diagnostic criteria, only 57.1% knew the guidelines/protocols, and 56.2% were aware of the assessment scales. Training in this field during the past five years was reported by only 35.2% of respondents, most frequently through courses abroad (22.9%) or professional society lectures (21.9%). Self-assessment of knowledge related to Parkinson's disease management revealed low confidence levels: only 8.6% considered themselves prepared to manage early-stage disease, 7.6% for late-stage management, and 6.7% for Parkinson's disease with associated cognitive disorders. Conversely, approximately half of the respondents acknowledged insufficient knowledge in all these scenarios. Therefore, physicians' knowledge about Parkinson's disease is often partial or inadequate, reflecting a lack of ongoing training and negatively impacting the quality of diagnosis and treatment.

The study on physicians' attitudes toward patients with Parkinson's disease in the Republic of Moldova reveals mixed perceptions. A significant proportion of physicians (36.2%) believe that these patients consume excessive time and resources, 28.6% associate them with costly treatments, and 19% perceive them as a burden on the healthcare system—reflecting negative attitudes. At the same time, positive attitudes prevail: 80% support the need for specialized movement disorder centers, 79% advocate for adapting services to patients' needs, and 60% favor institutionalization for palliative care in advanced stages. These findings suggest that healthcare providers are open to improving care but also highlight the necessity for ongoing training to combat stigmatizing perceptions and to strengthen a patient-centered approach.

The evaluation of physicians' practices regarding the diagnosis and treatment of Parkinson's disease revealed that the majority do not fully assume responsibility for diagnosing Parkinson's disease: 63.8% establish a presumptive diagnosis and refer the patient to a tertiary institution for confirmation, 22.9% refer patients immediately, and only 13.3% make the diagnosis independently. Regarding treatment, 88.6% have the greatest experience with levodopa—a reimbursed medication considered the gold standard. Other medications are prescribed infrequently: cyclodol (32.4%), dopamine agonists (29.5%), amantadine (10.5%), and selegiline (6.7%). Prescribing experience is limited, with 81.9% prescribing levodopa less than once per month; the situation is even more restricted for other medications. Only 19.0% of physicians initiate and monitor treatment independently, while over 80% involve tertiary institutions. Only

half (51.4%) monitor treatments prescribed by tertiary specialists. These findings confirm that most physicians in this study avoid establishing the diagnosis or fully managing treatment for patients with Parkinson's disease, reflecting a lack of experience, confidence, and training in managing this pathology.

The study also identified multiple barriers faced by physicians in the Republic of Moldova when managing Parkinson's disease patients. Clinical barriers were most frequently reported (99.0%), particularly in managing late-stage disease (61.9%), non-motor symptoms (46.7%), and treatment planning (41.0%). Some physicians reported difficulties in diagnosis (33.3%) and in initiating dopaminergic therapy with levodopa (27.6%) or agonists (24.8%). Communication-related barriers were reported by 25.7% of respondents, and systemic barriers by 72.4%, including the lack of a Specialized Center (61.0%) and social support services (46.7%). These results indicate a need for continuous professional education as well as structural reforms in neurological care, including the development of specialized medical infrastructure adapted to the complexity of Parkinson's disease.

Physicians included in the study reported the need for additional training regarding both pharmacological (68.6%) and non-pharmacological (67.6%) treatment of Parkinson's disease, therapy complications and late-stage management (62.9%), clinical evaluation (70.5%), as well as communication with patients (60.0%) and their families (55.2%). Over 69.5% believe that any physician could manage Parkinson's disease provided they receive appropriate training, and 81.9% emphasize the shortage of specialists in movement disorders. As potential solutions, 33.3% propose establishing a separate specialization, 21.0% suggest open training in movement disorders for any interested physician, and 45.7% support a combination of both approaches. The majority (71.4%) advocate for the establishment of a Specialized Center and a multidisciplinary approach, the implementation of standardized management algorithms, specific neurorehabilitation programs, availability of essential medications, and access to advanced therapies.

GENERAL CONCLUSIONS AND RECOMMENDATIONS

Conclusions:

1. Cartografierea clinico-epidemiologică și medico-socială a pacienților cu boala Parkinson din Republica Moldova a evidențiat o preponderență a afectării persoanelor peste 60 de ani, cu debutul bolii cel mai frecvent după vârsta de 50 de ani, fără diferențe semnificative legate de sex sau mediul de reședință. Majoritatea pacienților prezentau un tip akinetic-rigid sever, cu impact funcțional important. Criteriile biologice și evolutive ale bolii au influențat patternul clinico-epidemiologic și medico-social: bărbații au raportat semnificativ mai frecvent expunerea la substanțe nocive, în timp ce femeile au dezvoltat mai frecvent complicații motorii. Pacienții vârstnici au fost mai frecvent afectați de fenotipul akinetic-rigid sever și au necesitat doze mai mari de levodopa. Debutul precoce al bolii a fost asociat cu incapacitate de muncă și dizabilitate mai frecvente.
2. În funcție de relația dintre boala cerebrovasculară și boala Parkinson, această cercetare a identificat fenotipuri clinico-evolutive distincte. Astfel, asocierea bolii Parkinson cu

accidentul vascular cerebral (comparativ cu boala Parkinson neasociată cu AVC) și relația cauzală dintre boala cerebrovasculară și parkinsonismul vascular (în contrast cu boala Parkinson idiopatică) determină fenotipuri parkinsoniene semnificativ mai severe, caracterizate prin predominanță akinetică, răspuns redus la tratamentul cu levodopa, prezența deficitelor persistente post-tratament și un impact funcțional mult mai sever.

3. At the same time, the dominant clinico-evolutionary syndrome may indicate certain associated constellations of characteristics: longer disease duration is associated with more severe motor and non-motor impairment, increased frequency and severity of motor complications, and decreased levodopa responsiveness of symptoms; greater disease severity is associated with more severe non-motor and cognitive symptoms, poorer quality of life, higher need for dopaminergic drugs, and lower levodopa responsiveness; the presence of cognitive disorders is associated with significantly reduced functionality in the motor aspects of daily living; and the presence of motor complications is associated with significantly reduced psychosocial functionality and quality of life, as well as with cognitive disorders, possibly medication-induced.
4. The research demonstrated a more frequent presence of vascular risk factors and a significantly higher number of vascular risk factors per subject in patients with Parkinson's disease compared to controls. Sex stratification of both groups (PD and control) revealed attenuated sex differences in PD, unlike in the general population (atrial fibrillation, coronary artery disease, and myocardial infarction), possibly due to the effects of neurodegeneration on the vascular system. The high prevalence of certain vascular risk factors (diabetes mellitus, migraine), including at younger ages in PD patients (contrary to known data for the general population), could indicate their pathogenetic implications in the onset of neurodegeneration in Parkinson's disease.
5. Patients with severe non-motor symptoms significantly more frequently had vascular risk factors; the presence and number of vascular risk factors per subject increased significantly with the severity of Parkinson's disease.
6. According to the results of this research, cerebrovascular lesions were frequent in the population of patients with Parkinson's disease (85.6%). Significantly more frequent compared to controls, patients with PD had strokes in the anterior circulation, lacunar infarcts (in significantly higher number and more locations), gliotic foci in the white matter, dilation of perivascular spaces, external cerebral atrophy; with quantitatively greater macrostructural vascular involvement (expressed by the total small vessel disease score) and chronic ischemic injury detectable by dedicated imaging techniques (reduced diffusivity); and exhibited a specific localization pattern – vascular lesions in cerebral regions strategic for the development of parkinsonism were detected exclusively in patients with PD. Young patients with PD showed mesencephalic atrophy (a sign of neurodegeneration) and reduced cerebral diffusivity (a sign of chronic ischemic injury) comparable to those of older PD patients and older non-PD subjects – indicating neurodegeneration and chronic ischemic injury in PD patients starting from young ages.
7. As a result of this study, the presence and severity of cerebrovascular lesions were associated with specific characteristics of Parkinson's disease: At onset (onset manifestation – significantly more frequent bradykinesia; onset localization –

significantly more frequent in the lower limbs); In progression (rate of involvement of other limbs – significantly faster); Clinical features (dominant phenotype – significantly more frequently akinetic; tremor type – significantly more frequently kinetic; predominant involvement of a specific body part – significantly more frequently the lower hemibody; degree of limb involvement symmetry – significantly lower; severity of motor and non-motor impairment – significantly higher); Treatment response (levodopa responsiveness – significantly reduced); Functional impact of the disease (daily functioning in motor and non-motor domains – significantly diminished); Quality of life (significantly lower).

8. This research confirms that, for the management of Parkinson's disease within the healthcare system of the Republic of Moldova, barriers exist both at the level of beneficiaries and healthcare providers. Thus, patients with Parkinson's disease in the Republic of Moldova demonstrate insufficient knowledge regarding their condition, harbor erroneous beliefs about the disease, experience stigma both within the family environment and society at large, and face barriers in accessing medical services—due to inability to request care, difficulties in qualification for services, as well as financial constraints. Additionally, there is a reported lack of availability of certain service and a mismatch between the healthcare services provided by the system and the patients' actual needs. On the other hand, physicians—as providers of medical services to patients with Parkinson's disease—report deficiencies in their knowledge and skills; they emphasize the need for additional theoretical and practical training, including in communication with patients and their caregivers, aimed at overcoming negative attitudes towards these patients. In summary, the barriers faced by physicians in delivering dedicated services are clinical, communicational, and systemic in nature.

Recommendations:

Based on the demographic, social, and medical characteristics of the patients from the study on the epidemiological and medico-social aspects of Parkinson's disease in the Republic of Moldova, a three-stage patient management algorithm is proposed for Parkinson's disease in the Republic of Moldova: 1. Screening and diagnosis stage conducted at the level of the family physician, 2. Diagnostic confirmation stage carried out by the general neurologist, 3. Treatment initiation and monitoring stage managed by the general neurologist or tertiary-level neurologist, depending on disease severity (Figure 13).

The clinical study on parkinsonism phenotyping based on its association with cerebrovascular disease (causality or comorbidity) (Figure 14) and according to the dominant clinical syndrome (Figure 16) allowed the formulation of suggestions for differentiated management of these patients.

The results of the study on the association between Parkinson's disease and cerebrovascular disease outlined clinical features suggestive of this association's diagnosis, which require a dual therapeutic approach targeting both pathologies and allow the identification of negative prognostic factors (Figure 16).

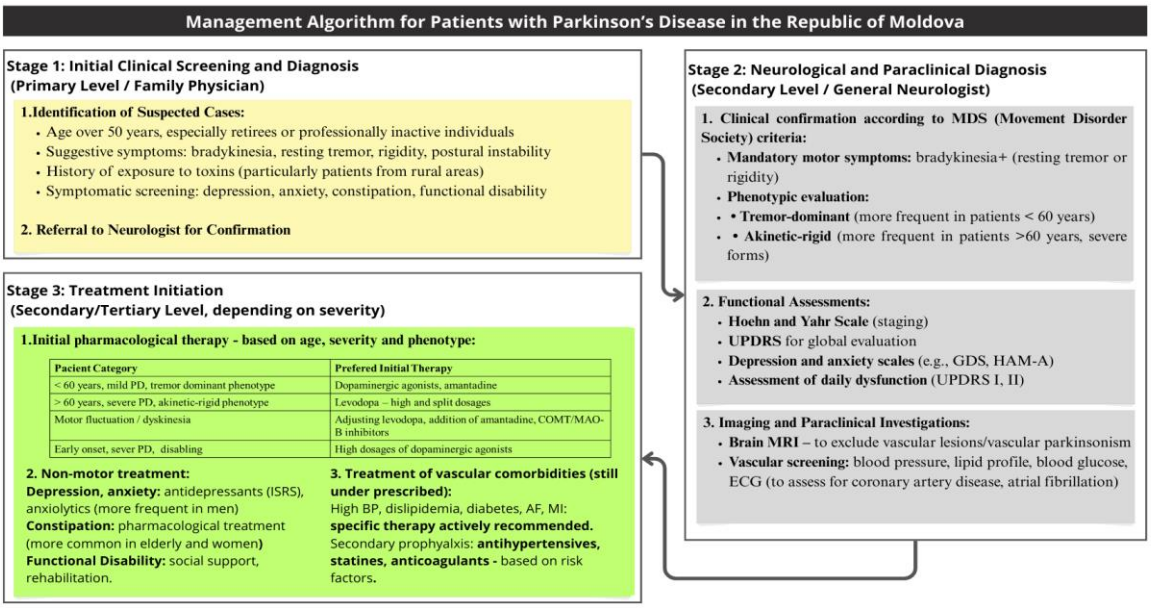

Figure 13. Management Algorithm for Patients with Parkinson's Disease in the Republic of Moldova

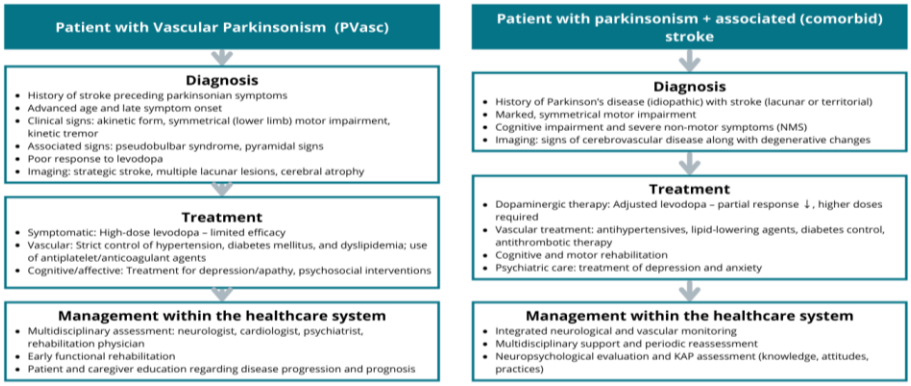

Figure 14. Differential management algorithm for the patient with parkinsonism, according to the association with cerebrovascular disease (causality/comorbidity).

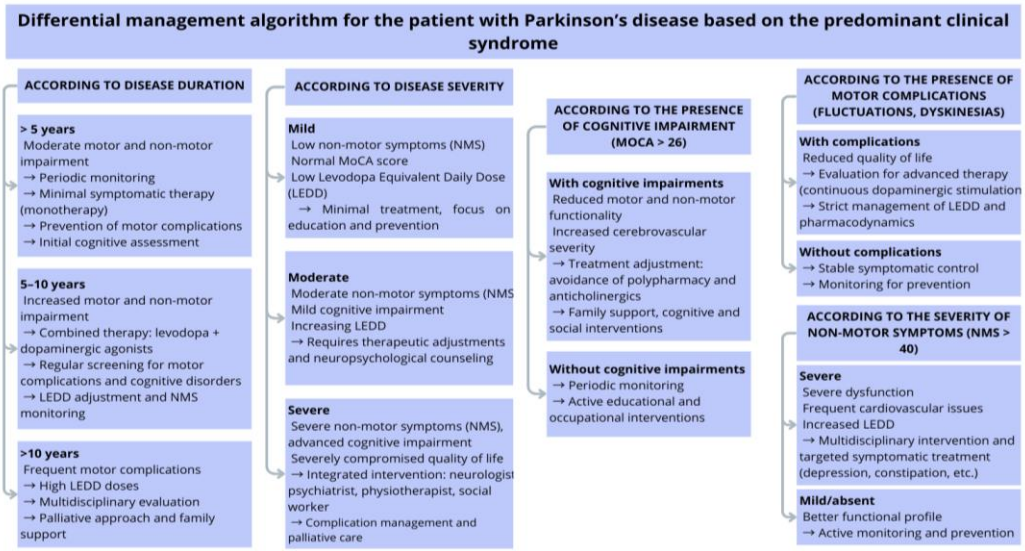

Figure 15. Differential management algorithm for the patient with Parkinson's disease, based on the predominant clinical syndrome.

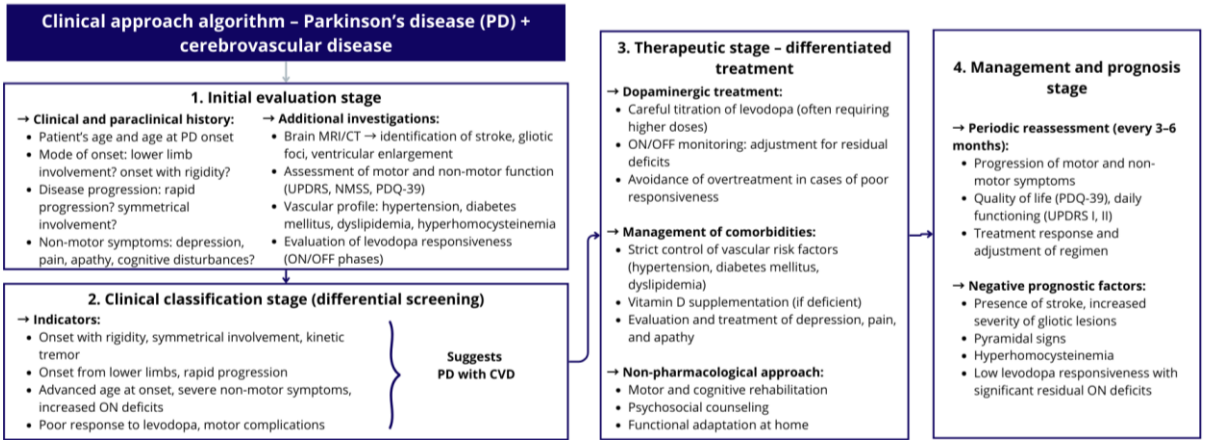

Figure 16. Clinical Management Algorithm for Patients with Idiopathic Parkinson's Disease and Coexisting Cerebrovascular Disease

Based on the results of the comparative study of vascular risk factors in patients with Parkinson's disease versus control subjects, and following the split-group analysis of these cohorts according to sex and age criteria, general recommendations for vascular screening in patients with Parkinson's disease have been formulated, along with differentiated recommendations according to age and sex (Figure 17).

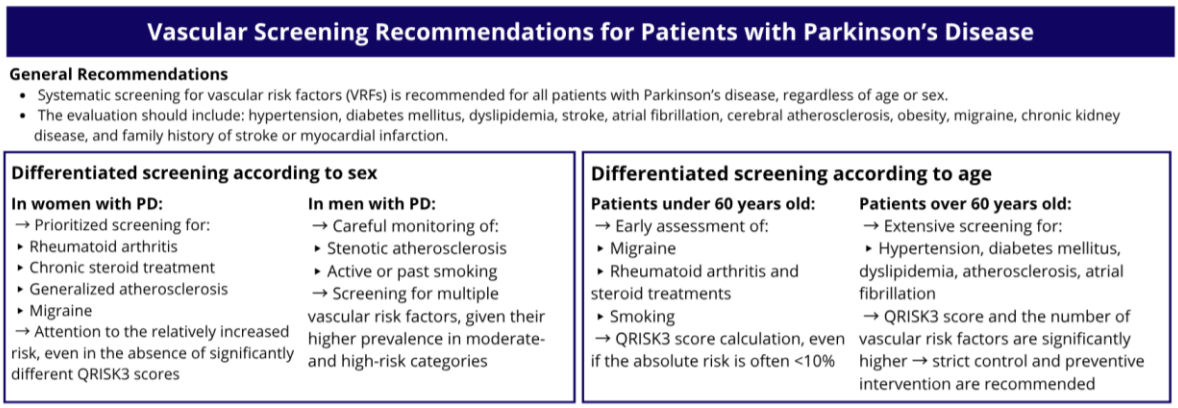

Figure 17. Vascular Screening Recommendation Algorithm for Patients with Parkinson's Disease

The results of the study on cerebrovascular neuroimaging changes in patients with Parkinson's disease versus controls suggest the need for evaluation of Parkinson's disease patients using both traditional methods and diffusion MRI to visualize subclinical chronic ischemia, including in younger patients (Figure 18).

Based on the CAP study, which highlights multiple barriers in the management of Parkinson's disease in the Republic of Moldova—both on the part of patients and healthcare providers—an intervention algorithm is proposed to counteract patients' barriers to accessing health services. This algorithm operates on three levels: family physician, neurologist, and healthcare system (Figure 19).

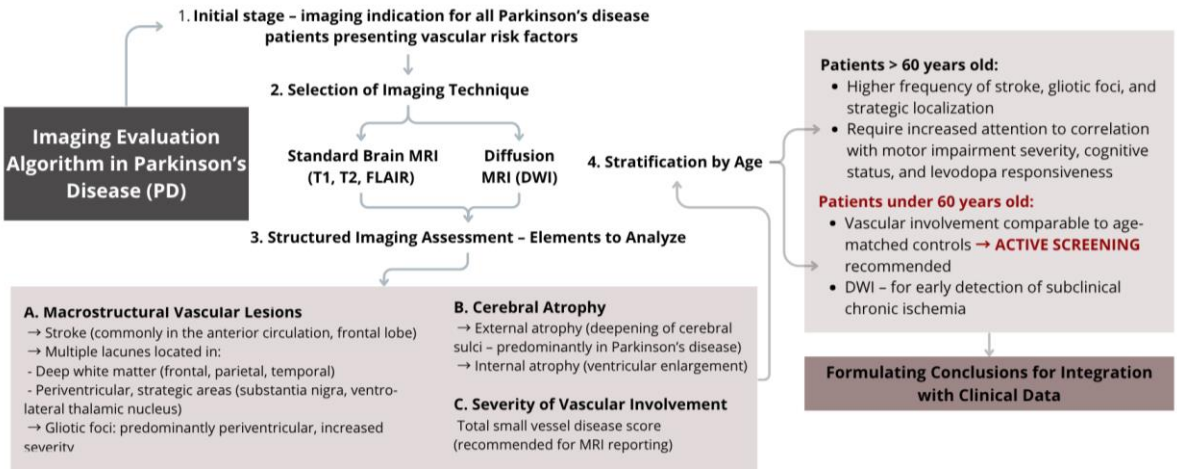

Figure 18. Imaging Evaluation Algorithm in Parkinson's Disease

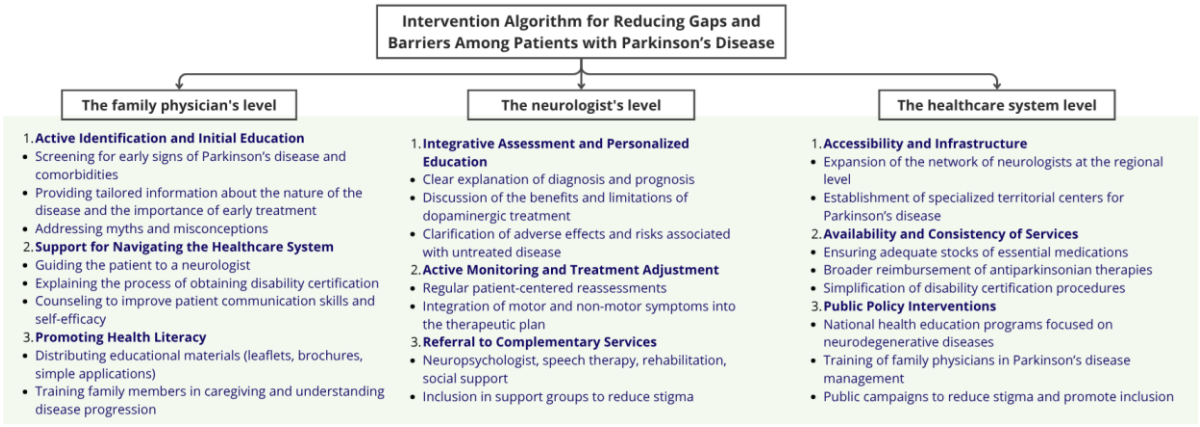

Figure 19. Intervention Algorithm for Reducing Gaps and Barriers Among Patients with Parkinson's Disease

The proposed intervention algorithm at the healthcare system level to support physicians in caring for patients with Parkinson's disease includes continuous professional training, development of specialized infrastructure, as well as systemic organizational interventions (Figure 21).

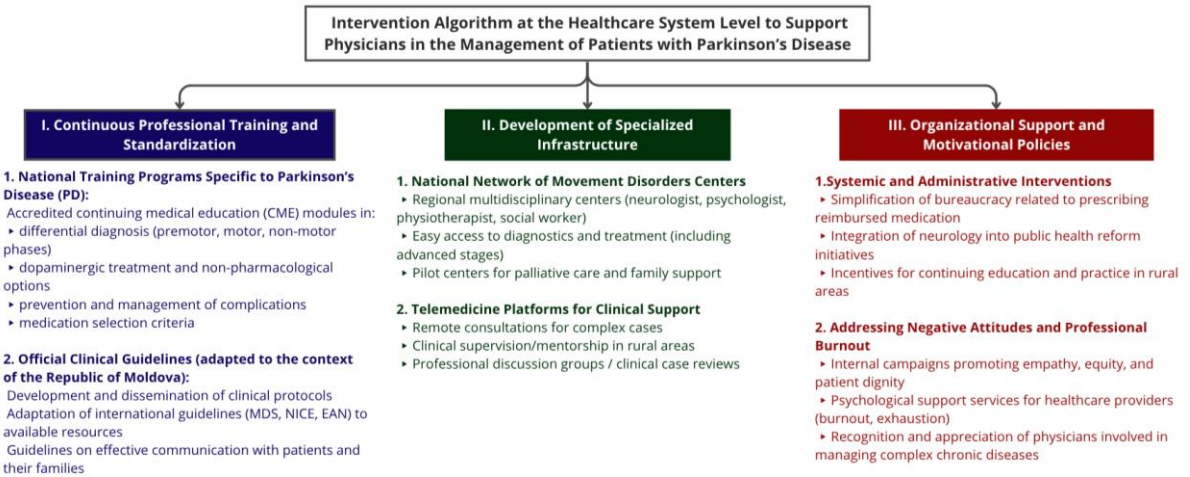

Figure 20. Intervention Algorithm at the Healthcare System Level to Support Physicians in the Management of Patients with Parkinson's Disease

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within the postdoctoral project
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- **Monographs:**
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- **Patents, registration certificates, materials at invention fairs:**
  - ✓ **copyright:**

1. **Rotaru, L**. Grosu, O., Moldovanu, I., Odobescu, S., Gavriliuc, O., Maticiuc, V., Misic, O., Timirgaz, Cebuc, M., Vovc, V., Lozovanu, S., Lupușor, A., Dragan, B., Ganenco, A., Ojog, V., Timotin, I., Sangheli, M., Șimon, V., Groppa, S. *Boala*

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1. **Rotaru, L.**, Grosu, O., Pleșcan, T., Moldovanu, M., Odobescu, S., Moldovanu, I., Groppa. S. *Protocol de evaluare a modificărilor vasculare cerebrale la pacienții cu boală Parkinson*. Certificat Inovator USMF Nicolae Testemițanu 6302 din 22.11.2024
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3. **Rotaru, L.**, Grosu, O., Odobescu, S., Moldovanu, I., Șimon, V., Gherghelegiu, E., Costru-Tașnic, E., Groppa. S *Metodă de evaluare a cunoștințelor, atitudinilor, practicilor și barierelor medicilor în prestarea serviciilor medicale pacienților cu boala Parkinson prin Chestionar specializat*. Certificat Inovator USMF Nicolae Testemițanu 6307 din 27.11.2024
4. **Rotaru, L.**, Grosu, O., Odobescu, S., Moldovanu, I., Sangheli, M., Manole, E., Istrati, N., Groppa. S. *Metodă de evaluare a cunoștințelor, atitudinilor, practicilor și barierelor pacienților cu boala Parkinson prin Chestionar specializat*. Certificat Inovator USMF Nicolae Testemițanu 6308 din 27.11.2024

ACTIVE PARTICIPATION IN SCIENTIFIC FORUMS:

- **Participation with *communications* at scientific forums:**

✓ **international:**

1. **Rotaru L.** Parkinson's Disease Dementia. Preliminary results of a cohort study in Moldova. Raport în plen. *European Academy of Neurology day in Republic of Moldova joined whith Congres of Neurologist of Republic of Moldova,* Chișinău, 16-18.09.2021**.**
2. **Rotaru, L**. Demența bolii Parkinson. Raport, lector invitat (24.02.2022) la: *Conferința Națională de Boală Alzheimer (CNALZ) din Romania cu participare internațională, Ediția 12, cu genericul: "Anticiparea și reducerea impactului pandemiei COVID19 asupra bolii Alzheimer și demențelor conexe"*, Iași, Romania, 23-26.02.2022

3. **Rotaru, L**. Declinul cognitiv asociat bolii Parkinson. Epidemiologie, patofiziologie și management. Raport, lector invitat (7.04.2023) la: *Ediția IV-a a Conferinței Naționale de Neuroștiințe Moderne "Boala Parkinson & Alte Tulburări de Mișcare"*, 6-8 Aprilie 2023, Iași, Romania.
4. **Rotaru, L**. The Peculiarities of Circadian Rhythms and their Implications on Parkinson's Disease. Raport, lector invitat (20.09.2023) la: *6th International Conference on Nanotechnologies and Biomedical Engineering*, September 20-23, Chișinău, Republic of Moldova.
5. **Rotaru L**. Parkinson disease and vascular risk factors. Raport, lector invitat (10.10.2024) la: *The 6th National Congres of Neurosciences*, 9-12 October 2024, Iași, Romania.
6. **Rotaru L**., Grosu O., Pleșcan T., Groppa S. Modificarile cerebrovasculare asociate bolii Parkinson. Raport, lector invitat (11.04.2024) la: *Conferința Națională de Neuroștiințe Moderne "Boala Parkinson și alte Tulburări de Mișcare"*. 11-13 aprilie 2024, Iași, România.
7. **Rotaru L**. Parkinsonism associated with cerebrovascular disease. Clinical features and management. Raport, lector invitat (11.04.2025) la: *Conferința Națională de Neuroștiințe Moderne "Boala Parkinson și alte Tulburări de Mișcare"*. 11-13 aprilie 2025, Iași, România.

✓ **national:**

1. **Rotaru, L.** Simptomele non-motorii ale bolii Parkinson. Raport la: *Congresul USMF consacrat aniversării de 75 ani de la fondare***,** 21-23 octombrie 2020.
2. **Rotaru, L.** Tulburările cognitive în boala Parkinson. Raport în plen la: *Conferința științifică „Arii comune și diverse în domeniul neuropsihiatriei"*, eveniment online organizat de Societatea Psihiatrilor, Narcologilor, Psihoterapeuților și Psihologilor Clinicieni din Republica Moldova în parteneriat cu Societatea Neurologilor din Republica Moldova, Chișinău, 11.11.2020.
3. **Rotaru, L.** Demențe neurodegenerative – criterii de diagnostic, management diferențiat. Raport la: *Societatea Neurologilor din Republica Moldova*, 04.03.2021.
4. **Rotaru, L.** *Vascular risk factors in patients with Parkinson's disease. Clinical and neuroimaging associations.* Comunicare la: *Congresul 7 al Neurologilor și Neurochirurgilor din Republica Moldova*, 18.09.2021, secțiunea postere moderate.
5. **Rotaru, L.** Factorii toxici de mediu și modelul clinic al bolii Parkinson. Comunicare la: *Conferința anuală științifică USMF*, 21.10.2021.
6. **Rotaru, L.** Managementul farmacologic al bolii Parkinson avansate. Raport la: *Conferință științifico-practică INN "Bolile neurodegenerative și managementul neurochirurgical"*, 19.11.2021, organizată on-line în cadrul proiectului 20.80009.8007.39.
7. **Rotaru, L.** Tulburările cognitive asociate bolii Parkinson. Cum abordăm un pacient cu boală Parkinson și tulburări cognitive asociate. Raport la: *Conferință națională, interdisciplinară: Tulburările cognitive în bolile neurologice și psihiatrice*. 30.06.2022. https://conferinte.stiu.md/event_page/394
8. Lupușor, A., **Rotaru, L.** Grosu, O. Rolul tulburărilor de ritm circadian în dezvoltarea maladiilor neurodegenerative. Raport la: *Conferință națională,*

interdisciplinară: Tulburările cognitive în bolile neurologice și psihiatrice. 30.06.2022. https://conferinte.stiu.md/event_page/394

9. **Rotaru, L.** Diagnosticul și managementul tulburărilor cognitive neurodegenerative. Raport la: *Conferință națională, lansare de carte: Monografia „Tulburări cognitive majore (demență) la pacienții cu patologie neurogenerativă și vasculară. Fiziopatologie, diagnostic, tratament"*. Chișinău, 14.12.2023.
10. **Rotaru, L.** Durerea musculo-scheletală din boala Parkinson. Raport la: *Conferință națională, lansare de carte: Monografia „ Durerea cronică: clasificarea, patofiziologie și management personalizat"*; în comun cu Societatea Neurologilor din Republica Moldova; Chișinău, 26.10.2023.
11. **Rotaru, L.** Parkinsonismul și modificările cerebrovasculare. Raport la: *Conferință națională cu participare internațională: Săptămâna medicală Balcanică, ediția a XXXVII-a*, 7.06.2023.
12. **Rotaru, L.** Examinarea pacientului cu tulburări de mișcare. Raport la: Conferință națională. *Școala de Neuroștiințe 2023*, Orhei, Moldova, 30 septembrie 2023.

- **Participation with *posters* at scientific forums:**
  - ✓ **international:**

1. **Rotaru, L**. Cerebral vascular lesions in Parkinson's disease patients. Preliminary results of Moldovan PD cohort study. *World Congress on Parkinson's Disease and Related Disorders*. Ediția a 26-a, 1-4 mai 2021, Hamburg. Amsterdam, Netherlands:
2. **Rotaru, L.**, Cebuc, M., Lupuşor, A., Grosu, O., Odobescu, S., Gavriliuc, O., Moldovanu, I. Sleep disorders in Parkinson's disease patients. A case-control study. *European Academy of Neurology Congress MDS*. 27-31 august 2023, Copenhagen. Copenhagen.
3. **Rotaru, L.**, Grosu, O. Practices of neurologists in the management of Parkinson's disease patients in the Republic of Moldova. *European Academy of Neurology Congress MDS*. 27-31 august 2023, Copenhagen.
4. **Rotaru, L**. Is there any impact of cardiovascular risk factors and migraine comorbidity on Parkinson's disease severity? Preliminary data of the Moldovan Parkinson's disease cohort. *International Headache Congress*. 8-12 septembrie 2021(on-line, poster + audio presentation).

ADNOTARE

Lilia Rotaru. "Boala Parkinson și modificările cerebrovasculare: studiu clinico-epidemiologic și neuroimagistic".
Teza de doctor habilitat în medicină, Chişinău, 2025.

Structura tezei: lucrarea conţine introducere, șase capitole de rezultate proprii şi discuţii, concluzii şi recomandări, bibliografie din 455 titluri, 24 anexe, 265 pagini de text de bază, 74 figuri şi 42 tabele. Rezultatele cercetării au fost publicate în 42 lucrări ştiinţifice.

Cuvintele-cheie: boală Parkinson, factori de risc vascular, modificări cerebrovasculare, levodopa-responsivitate, funcționalitate, calitate a vieții, cunoștințe, atitudini, practici.

Domeniul de studiu: neurologie, neuroimagistică.

Scopul şi obiectivele tezei: evidenţierea particularităţilor medico-sociale, clinice, neuroimagistice și de management ale pacienților cu boală Parkinson din Republica Moldova, în raport cu factorii de risc vascular și modificările cerebrovasculare comorbide.

Noutatea şi originalitatea lucrării: în premieră s-a efectuat cartografierea pacienților cu boală Parkinson din RM pe un eșantion reprezentativ, care însumează circa o treime din pacienții potențiali cu boală Parkinson din RM, sub aspect medico-social și clinico-neuroimagistic; au fost determinate cunoștințele, atitudinile practicile și barierele, atât ale pacienților cu boală Parkinson, cât și ale medicilor pentru primirea / prestarea serviciilor medicale în cadrul acestei nozologii; a fost obținută imaginea pacientului cu BP în raport cu societatea și serviciile medicale.

Problema ştiinţifică importantă soluţionată în domeniul respectiv. Studiul a cuantificat impactul comorbidității cardio- și cerebrovasculare asupra simptomelor motorii și non-motorii psiho-afective și cognitive ale bolii Parkinson, precum și asupra levodopa-responsivității ei și a constatat efectul agravant al prezenței și severității factorilor de risc vascular și modificărilor cerebrovasculare asupra manifestărilor clinice și răspunsului la tratament al bolii Parkinson; a permis fenotiparea pacienților în funcție de acești parametri; a constatat barierele în calea asistenței medicale dedicate BP, ceea ce ar permite optimizarea managementului acesteia.

Semnificaţia teoretică a cercetării. Rezultatele cercetării extind cunoştinţele existente despre rolul factorilor de risc vascular și a leziunilor vasculare în evoluţia bolii Parkinson, aceștea constituind factori agravanți pentru evoluţia şi severitatea clinică a BP, influenţând levodopa-responsivitatea.

Valoarea aplicativă a tezei. A fost stabilită importanţa constatării la pacienţii boală Parkinson a modificărilor cerebrovasculare și a factorilor de risc vascular, ce necesită o strategie de management precoce și proactiv. Determinarea barierelor în asistența medicală specializată ar putea servi drept bază pentru elaborarea strategiilor de ameliorare a ei.

Implementarea rezultatelor ştiinţifice: Institutul de Neurologie şi Neurochirurgie, USMF „N. Testemiţanu", Centrul de Diagnostic German, Clinica Internațională MedPark.

SUMMARY

Lilia Rotaru. "Parkinson's disease and cerebrovascular lesions: clinical-epidemiological and neuroimaging study". Thesis for the degree of doctor habilitate in medicine, Chisinau, 2025.

Structure of the thesis: the work contains an introduction, six chapters of own results and discussions, conclusions and recommendations, a bibliography of 455 titles, 24 annexes, 265 pages of basic text, 74 figures and 42 tables. The results of the research were published in 42 scientific papers.

Keywords: Parkinson's disease, vascular risk factors, cerebrovascular lesions, levodopa-responsiveness, functionality, quality of life, knowledge, attitudes, practices.

Field of study: neurology, neuroimaging.

The purpose and objectives of the thesis: highlighting the medico-social, clinical, neuroimaging and management pecularities of Parkinson's disease patients in the Republic of Moldova, in relation to vascular risk factors and comorbid cerebrovascular disorder.

The novelty and originality of the work: for the first time, the mapping of patients with Parkinson's disease in the Republic of Moldova was carried out on a representative sample, which amounts to about a third of potential Parkinson's disease patients in RM, from a medico-social and clinical-neuroimaging aspect; the knowledge, attitudes, practices and barriers of both patients with Parkinson's disease and doctors for receiving / providing medical services within this nosology were determined; the image of PD patient in relation to society and medical services was obtained.

Important scientific problem solved in the respective field. The study quantified the impact of cardio- and cerebrovascular comorbidity on the motor and non-motor psycho-affective and cognitive symptoms of Parkinson's disease, as well as on its levodopa-responsiveness and found the aggravating effect of the presence and severity of vascular risk factors and cerebrovascular disease on the clinical PD manifestations and response to treatment; it allowed patients phenotyping according to these parameters; found the barriers to medical care dedicated to PD, which allows optimizing its management.

Theoretical significance of the study. The research results expand the existing knowledge about the role of vascular risk factors and vascular lesions in the evolution of Parkinson's disease, these being aggravating factors for the evolution and clinical severity of PD, influencing levodopa-responsiveness.

Applicative value of the work. The importance of detecting cerebrovascular changes and vascular risk factors in Parkinson's disease patients was established, requiring early and proactive management strategys. Determining the barriers in specialized medical care could serve as a basis for developing strategies to improve it.

Implementation of scientific results: Institute of Neurology and Neurosurgery, USMF "N. Testemiţanu", German Diagnostic Center, MedPark International Clinic

ROTARU LILIA

PARKINSON'S DISEASE AND CEREBROVASCULAR CHANGES: A CLINICO-EPIDEMIOLOGICAL AND NEUROIMAGING STUDY

321.05 CLINICAL NEUROLOGY

Summary of the Habilitation Thesis in Medicine

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