ISSN 2663-9092 (Online)

Ukrainian Neurosurgical Journal

Том 32, №2, 2026

Науково-практичний журнал (спеціалізоване видання для лікарів)
Заснований у квітні 1995 року. Виходить 4 рази на рік.
Свідоцтво про державну реєстрацію КВ №23771-13611ПР від 14 лютого 2019 р.

Журнал входить до Переліку наукових фахових видань України, в яких можуть бути опубліковані результати дисертаційних робіт на здобуття наукових ступенів доктора наук, кандидата наук та ступеня доктора філософії (Наказ МОН України від 10.12.2024 № 1721)
Ідентифікатор у Реєстрі суб'єктів у сфері медіа: R40-07048.
Журнал включено до наукометричної бази Scopus.

Всі рукописи, що надходять до редакції, обов'язково рецензуються

Засновники
Інститут нейрохірургії ім. акад. А.П. Ромоданова НАМН України
Українська Асоціація Нейрохірургів
Національна академія медичних наук України

Видавець
Інститут нейрохірургії ім. акад. А.П. Ромоданова НАМН України

Адреса видавця та редакції
вул.Платона Майбороди, 32, Київ, 04050, Україна
Тел. +380 44 483-91-98
Факс +380 44 489-35-61
E-mail: unj.office@gmail.com
http://theunj.org

Підписано до публікації
з оригінал-макета 27.03.2026

Головний редактор
Педаченко Євгеній Георгійович • *Київ, Україна*

Заступник головного редактора
Білошицький Вадим Васильович • *Київ, Україна*

Заступник головного редактора
Васюта Віра Анатоліївна • *Київ, Україна*

Завідувач редакції
Никифорова Анна Миколаївна • *Київ, Україна*

Редакційна колегія
Армонда Рокко А. • *Вашингтон, Сполучені Штати*
Арраез Мігель А. • *Малага, Іспанія*
Валадка Алекс Б. • *Даллас, Сполучені Штати*
Вукич Мирослав • *Загреб, Хорватія*
Гаврилюк Грегорі В. Дж. • *Клівленд, Сполучені Штати*
Газіоглу Нурпері • *Істанбул, Туреччина*
Гук Андрій Петрович • *Київ, Україна*
Ендрюс Рассел Дж. • *Лос Гатос, Сполучені Штати*
Зельман Володимир • *Лос-Анджелес, Сполучені Штати*
Земскова Оксана Володимирівна • *Київ, Україна*
Калангу Казаді • *Хараре, Зімбабве*
Карієв Гайрат Маратович • *Ташкент, Узбекистан*
Като Йоко • *Тойоаке, Японія*
Крегг Роман • Лондон, Велика Британія
Малишева Тетяна Андріївна • *Київ, Україна*
Медведєв Володимир Вікторович • *Київ, Україна*
Меламед Ізраїль • *Беер Шева, Ізраїль*
Нетлюх Андрій Михайлович • *Львів, Україна*
Райнов Микола • *Мюнхен, Німеччина*
Расуліч Лукас Грюіца • *Белград, Сербія*
Розуменко Володимир Давидович • *Київ, Україна*
Рутка Джеймс • *Торонто, Канада*
Сірко Андрій Григорович • *Дніпро, Україна*
Смоланка Володимир Іванович • *Ужгород, Україна*
Смрчка Мартін • *Брно, Чеська Республіка*
Фіщенко Яків Віталійович • *Київ, Україна*
Шлобін Натан А. • *Нью-Йорк, Сполучені Штати*
Хижняк Михайло Віталійович • *Київ, Україна*
Цимбалюк Віталій Іванович • *Київ, Україна*

Оригінал-макет журналу затверджений і рекомендований до друку та поширення через Інтернет на спільному засіданні Редакційної колегії Ukrainian Neurosurgical Journal та вченої ради Інституту нейрохірургії ім. акад. А.П. Ромоданова НАМН України (протокол №3 від 27.03.2026)

Відповідальність за зміст рекламних матеріалів несе рекламодавець

Усі права стосовно опублікованих статей належать їх авторам

Усі права стосовно будь-яких інших публікацій, крім авторських статей, належать видавцеві

Видання використовує ліцензію Creative Commons - CC BY - Зазначення Авторства - https://creativecommons.org/licenses/by/4.0/.
Ця ліцензія дозволяє іншим розповсюджувати, редагувати твір, вносити в нього зміни, і брати його за основу для інших творів, навіть для використання з комерційною метою, за умови зазначення авторства.

Перша сторінка обкладинки

Рисунок до статті Nhat D. H. Nguyen, Huy A. Pham, Phi D. Nguyen "Single-Stage Salvage for Recurrent Carpal Tunnel Syndrome and Delayed Guyon's Canal Syndrome Following Open Release: A Case Report" , стор. 105-111

Зміст

Оглядова стаття

М.В. Хижняк, І.Г. Васильєва, Ю.Г. Гафійчук
Нейрозапалення: молекулярні механізми, тригери та біомаркери клінічної стратифікації 3-11

Б.В. Задорожна, В.М. Шевага
Посттравматичні напади та посттравматична епілепсія після черепно-мозкової травми: сучасні підходи до профілактики, діагностики та прогнозування 12-15

Оригінальна стаття

О.А. Жернов, О.І. Ковальчук, М.П. Комаров
Первинна реконструкція дефектів склепіння черепа після опіків 16-22

Ю.Ю. Чомоляк, Ю.Г. Химинець, А.Д. Іващенко
Чинники, що впливають на якість життя пацієнтів після тубулярної мікродискектомії 23-31

Yaroslav D. Bondarenko, Oksana I. Kauk
Predicting the risk of neurodegenerative diseases based on clinical microsignals 32-50

О.М. Тарасенко, Д.В. Кучер, Т.М. Тарасенко
Redcord Neurac-терапія в нейрореабілітації пацієнтів із помірними та глибокими парезами після поперекових мікродискектомій 51-57

Huu Huynh Hai Nguyen, Phi Duong Nguyen, Khang Trien Truong
Use of C reactive protein (CRP) and creatine kinase (CK) as predictors of early postoperative infection after minimally invasive transforaminal lumbar interbody fusion 58-63

К.Р. Костюк, А.О. Лісяний
Значення МРТ-трактографії у визначенні мішені стереотаксичного втручання при хірургічному лікуванні хвороби Паркінсона 64-72

Loi Nguyen Dang, Thi Cao, Ly Minh Ngo, Khang Trien Truong, Thach Ngoc Nguyen
Side-specific and sex-related computed tomography morphometric variations of the atlas (C1) and axis (C2) in Vietnamese adults: Implications for safe posterior atlantoaxial fixation 73-79

О.В. Боміхов, В.В. Яринка, Т.І. Петрів, З.К. Меліков, Н.В. Войтенко, В.В. Медведєв, П.В. Білан
Вплив виду загальної анестезії та операційної процедури на відновлення функції сідничого нерва щура після його перетину та шовного відновлення 80-92

Спостереження з практики

Olukorede Olabanji Adekunle, Nurudeen Abiola Adeleke, Olakunle Michael Adegboye, Oghenevwoke Enaworu, Hakeem Ayinde Yeqeen, Akingbade Adebayo Akin-Dosumu, Gbenga Timothy Oyegbami, Oluwafemi Nehemiah Akeredolu, Nnara Onyeka Stanley
Occult Klippel-Feil syndrome unmasked by cervical spine trauma: A case report and literature review 93-96

Prakash Mahantshetti, Nikhita Kalyanshetti, Chandan Miriyala
Illustrative case of acromegaly caused by sparsely granulated somatotroph adenoma 97-104

Nhat D. H. Nguyen, Huy A. Pham, Phi D. Nguyen
Single-Stage Salvage for Recurrent Carpal Tunnel Syndrome and Delayed Guyon's Canal Syndrome Following Open Release: A Case Report 105-111

Tetiana V. Lymanets, Ganna S. Maslova, Yelizaveta O. Stadnik, Iuliia O. Gusachenko, Oleksandr L. Havlovskyi
A clinical dilemma for treatment choice of extramedullary spinal plasmacytoma in patients with multiple myeloma: chemotherapy or surgery? A double-case clinical report 112-118

Tuan Anh Phan, An Hoang Dai, Minh Hoang Nguyen, Khang Trien Truong, Phi Duong Nguyen, Thi Cao
Osteochondroma of inferior articular process in lumbar spine causing spinal stenosis: a case report 119-125

О.Є. Скобська, О.С. Готін, А.О. Дядечко, Д.В. Драганчук [1]
Випадок пізньої посттравматичної парадоксальної назальної ліквореї: мультидисциплінарний підхід до діагностики та лікування 126-130

Original article

Ukrainian Neurosurgical Journal. 2026;32(2):32-50
doi: 10.25305/unj.341180

Predicting the risk of neurodegenerative diseases based on clinical microsignals

Yaroslav D. Bondarenko [1,2], Oksana I. Kauk [3]

[1] Third Faculty of Medicine, Kharkiv National Medical University, Kharkiv, Ukraine
[2] Medical faculty, Friedrich-Alexander University of Erlangen–Nuremberg, Erlangen, Germany
[3] Department of Neurology with a course in Neurosurgery, Kharkiv National Medical University, Kharkiv, Ukraine

Received: 12 October 2025
Accepted: 12 January 2026

Address for correspondence:
Yaroslav D. Bondarenko, Third Faculty of Medicine, Kharkiv National Medical University, Nauky Avenue, 4, Kharkiv, 61000, Ukraine, e-mail: bondarenkoyaroslav2017@gmail.com

Background: Neurodegenerative diseases, in particular Parkinson's disease, remain difficult to diagnose due to the late manifestation of classical motor symptoms, when significant neuronal degeneration has already occurred. A growing body of evidence suggests that subtle non-motor prodromal symptoms — so-called phenotypic microsignals (PMS) may precede the clinical manifestation of neurodegenerative diseases by several years. These symptoms reflect early neurochemical disturbances and disruptions of neural networks, especially in evolutionarily ancient brain structures vulnerable to α-synuclein pathology.

Objective: To identify and systematize early clinical phenotypic microsignals observed during initial outpatient visits and potentially associated with neurodegenerative processes, as well as to develop a clinical risk stratification tool for the prodromal stage based on retrospective analysis and prospective observation.

Materials and methods: A combined retrospective-prospective observational study conducted at Kharkiv National Medical University during the period from January 2020 to August 2025. The study involved 112 patients aged 48 to 76 years, who were divided into three groups: group 1 (n=28, prodromal/non-manifest pathology), group 2 (n=56, manifest pathology (Alzheimer's disease (n=16), Parkinson's disease (n=28), dementia with Lewy bodies (n=9), progressive supranuclear palsy (n=3)), group 3 (control, n=28, individuals without clinical signs of neurodegenerative pathology, matched by age and sex). A 48-point PMS scale was developed and validated, assessing 30 clinical markers across cognitive, motor, autonomic, sensory and affective domains. Patients underwent comprehensive neurological examination, cognitive testing (MMSE — Mini-Mental State Examination, MoCA — Montreal Cognitive Assessment, FAB — Frontal Assessment Battery), magnetic resonance imaging and standardized assessment of non-motor symptoms. ROC analysis was used to evaluate the predictive accuracy of the scale.

Results: Patients with manifest neurodegenerative diseases had significantly higher PMS scale scores (mean value – 27.8±6.3 points) compared with the prodromal group (11.4±3.8, $p<0.001$) and control (2.8±2.1). ROC analysis demonstrated excellent diagnostic accuracy for comparison of manifest pathology with control (area under the curve (AUC) – 0.982, sensitivity – 96.4%, specificity – 92.9% at a threshold value ≥13 points), good accuracy for prodromal pathology compared with control (AUC – 0.956, sensitivity – 89.3%, specificity – 89.3% at a threshold value ≥7 points) and for differentiation of manifest and prodromal pathology (AUC – 0.891, sensitivity – 78.6%, specificity – 85.7% at a threshold value ≥21 points). Risk stratification identified three categories: low risk (0–12 points, <5% probability of conversion within 24 months), moderate risk (13–24 points, 20–30% conversion) and high risk (≥25 points, >50% conversion). In the prodromal group, the most frequent microsignals were REM sleep behavior disorder (67.9%), hyposmia (71.4%), chronic constipation (78.6%), subjective cognitive decline (82.1%), reduced arm swing during walking (46.4%) and hypomimia (42.9%).

Conclusions: The PMS scale is a clinically effective and low-cost tool for identifying individuals at risk of developing neurodegenerative diseases years before the manifestation of classical symptoms. Its use does not require specialized equipment and is feasible at the level of primary medical care through history taking, observation and basic neurological examination. The scale demonstrates high psychometric properties and provides risk stratification, enabling individualized monitoring and early intervention strategies. This approach marks a transition to proactive diagnostic models in neurology. It has significant value for screening programs among middle-aged and older individuals with subclinical neurobehavioral complaints. Early detection using PMS assessment allows timely application of neuroprotective and preventive interventions, potentially altering the course of the disease before irreversible neuronal loss.

Keywords: *prodromal symptoms; early diagnosis; risk stratification; α-synuclein; REM sleep behavior disorder; Parkinson's disease; Alzheimer's disease; dementia with Lewy bodies; progressive supranuclear palsy; phenotypic microsignals*

Copyright © 2026 Yaroslav D. Bondarenko, Oksana I. Kauk

This work is licensed under a Creative Commons Attribution 4.0 International License
https://creativecommons.org/licenses/by/4.0/

Introduction

Neurodegenerative diseases, in particular Alzheimer's disease (AD), Parkinson's disease (PD), dementia with Lewy bodies (DLB), multiple system atrophy (MSA), progressive supranuclear palsy (PSP), and corticobasal degeneration (CBD), represent one of the key problems of modern neurology due to their progressive course, irreversibility of neuronal damage, and limited possibilities for etiopathogenetic treatment [1, 2]. Despite significant progress in studying the molecular and neuroimaging mechanisms of neurodegeneration, clinical diagnosis is still based mainly on established syndromes, when the pathological process has already led to a substantial loss of neuronal networks [3, 4]. Current concepts consider neurodegeneration as a long, multiphase process with preclinical and prodromal stages that may precede the manifestation of motor or cognitive syndromes by years or decades [5, 6]. At early stages, pathological changes predominantly involve evolutionarily ancient and functionally vulnerable structures of the nervous system—the olfactory pathways, brainstem nuclei, autonomic nervous system, limbic and fronto-subcortical networks—leading to the appearance of nonspecific, mildly expressed clinical manifestations [7, 8]. The prodromal period of neurodegenerative diseases is characterized by the predominance of non-motor symptoms, in particular sleep disturbances, autonomic dysregulation, emotional–affective disorders, cognitive flexibility impairment, and sensorimotor integration deficits [9]. Although subsequent clinical evolution differs among amyloidopathies, synucleinopathies, and tauopathies, early phenotypic manifestations demonstrate substantial overlap, which complicates early nosological differentiation while simultaneously reflecting shared mechanisms of initial neuronal network destabilization.

The present study is based on the hypothesis that a structured clinical assessment of the totality of prodromal non-motor signs identified during routine outpatient visits makes it possible to stratify individuals according to their risk of developing clinically manifest disease. Such manifestations are not specific biomarkers of individual diseases; however, their cumulative presence and dynamics may serve as clinical indicators of an active neurodegenerative process at the preclinical or prodromal stage, forming a basis for further multicenter studies and the development of strategies for the early detection of neurodegeneration.

Objective of the study: To identify and systematize early clinical phenotypic microsignals observed during initial outpatient visits and potentially associated with the development of a neurodegenerative process in diseases such as Alzheimer's disease, Parkinson's disease, dementia with Lewy bodies, multiple system atrophy, progressive supranuclear palsy, and corticobasal degeneration, as well as to develop a tool for clinical risk stratification of a neurodegenerative process at the prodromal stage based on a retrospective analysis of medical documentation and prospective observation.

Materials and methods

Study participants

The initial sample consisted of 140 individuals aged 48 to 76 years (mean age 64±7.2 years) who presented with suspected prodromal or early manifestations of neurodegenerative diseases, or were included as a control group. Of these, 28 individuals were excluded from the primary analysis due to clinically significant alcohol exposure (consumption >14 alcohol units per week for men and >7 for women). The final cohort comprised 112 participants (64 men and 48 women).

Inclusion criteria

Patients were eligible if they met the following criteria: age 45–80 years; presence of at least three non-motor symptoms from different domains (cognitive, autonomic, sleep-related, sensory) lasting at least 12 months, or a combination of two non-motor symptoms with one subtle motor phenomenon; ability to provide informed consent and compliance with long-term follow-up.

Exclusion criteria

Drug-induced parkinsonism (use of neuroleptics, metoclopramide, cinnarizine during the last 6 months); significant cerebrovascular pathology on MRI (≥2 points on the Fazekas scale for white matter or >2 lacunar infarcts); severe depression (HADS-depression >15 points or major depression according to DSM-5); history of schizophrenia or other psychotic disorders in history; traumatic brain injury with loss of consciousness >30 minutes; active oncological pathology or terminal stage of somatic diseases; alcohol or psychoactive substance abuse; inability to complete neuropsychological testing due to language barrier or pronounced sensory deficit (blindness, deafness).

Group characteristics

The cohort was divided into three groups. Group 1 (prodromal/non-manifest pathology, n=28) included individuals with prodromal conditions without final nosological determination at the time of inclusion. These participants were characterized by a combination of multiple non-motor symptoms from different domains, absence of full diagnostic criteria for manifest disease, and no alternative explanation for the observed symptomatology. Group 2 (manifest pathology, n=56) included patients with a clinically established diagnosis: amyloidopathies (Alzheimer's disease, n=16), synucleinopathies (Parkinson's disease n=28, dementia with Lewy bodies n=9), and tauopathies (progressive supranuclear palsy n=3). Group 3 (control group, n=28) included individuals without clinical manifestations of neurodegenerative pathology.

Study design

The study was conducted as a single-center clinical observational study with a prospective phase, which included the development and prognostic validation of a clinical tool for detecting phenotypic microsignals of neurodegeneration. The study was carried out at the University Hospital of Kharkiv National Medical University in the period from January 1, 2020 to August 1, 2025 in accordance with the principles of the Declaration of Helsinki (2013 revision). All participants provided written

informed consent; the study protocol was approved by the local bioethics committee. Diagnosis was established by two independent neurologists specializing in movement disorders and cognitive neurology (work experience 8 and 14 years, respectively), who did not participate in the development of PMS. In case of diagnostic discrepancies (11 cases, 13.1%), an expert discussion was conducted involving a third neurologist with 22 years of experience followed by repeated blinded review of clinical data, including video materials. The final diagnosis was established according to international disease-specific criteria: NIA-AA for Alzheimer's disease (McKhann *et al*., 2011) [10], MDS Clinical Diagnostic Criteria for Parkinson's disease (Postuma *et al*., 2015) [11], consensus criteria for dementia with Lewy bodies (McKeith *et al*., 2017) [12], NINDS-PSP criteria for progressive supranuclear palsy (Höglinger *et al*., 2017) [13]. To minimize incorporation bias, the diagnosing neurologists did not have access to PMS scale scores at the time of diagnosis; PMS assessment was performed by a separate investigator, a clinical psychologist with experience in neuropsychological diagnostics, who did not participate in the diagnostic process and was blinded to the neurologists' clinical hypotheses.

Each patient underwent a standardized protocolized examination procedure. Non-motor symptoms were recorded using structured validated instruments: the RBD Single-Question Screen questionnaire (RBD1Q: "Have you ever been told, or suspected yourself, that you seem to 'act out your dreams', for example, punching, flailing your arms, running?") for screening REM sleep behavior disorder, ROME IV criteria for functional constipation (≥2 criteria: straining, hard/fragmented stool, feeling of incomplete evacuation, manual maneuvers for defecation, <3 defecations per week); Hospital Anxiety and Depression Scale (HADS; separate anxiety and depression subscales), Apathy Evaluation Scale clinical version (AES-C, 18 items, cutoff ≥37 points for clinically significant apathy) and Fatigue Severity Scale (FSS, 9 items, cutoff ≥4 mean score for pathological fatigue).

Olfactory functions were assessed using a simplified odor recognition test adapted for the Ukrainian-speaking population: the patient was presented with 12 standardized odors (coffee, lemon, mint, onion, garlic, vanilla, cinnamon, fir tree, rose, vinegar, camphor, chocolate) in opaque bottles; four response options were offered for each; hyposmia was diagnosed when fewer than 9 out of 12 odors were correctly recognized (sensitivity 78±3.2%, specificity 81±2.8% according to validation data for the Eastern European population). Autonomic disturbances were determined using an active orthostatic test with measurement of blood pressure and heart rate in the supine position after 5 minutes of rest, then at the 1st and 3rd minutes of standing; orthostatic hypotension was diagnosed according to consensus criteria as a decrease of systolic pressure ≥20 mmHg or diastolic pressure ≥10 mmHg. In patients with a positive orthostatic test or clinical complaints of dizziness upon standing (n=27), the presence of compensatory tachycardia (increase in heart rate >15 bpm) was additionally recorded to differentiate neurogenic and non-neurogenic orthostatic hypotension.

Cognitive profile was determined using a standardized battery: Mini-Mental State Examination (MMSE) with correction for educational level (<9 years of education: +1 point to cutoff 24), Montreal Cognitive Assessment (MoCA) Ukrainian version 7.1 with education correction (≤12 years: +1 point to cutoff 26), Frontal Assessment Battery (FAB) to assess executive functions (cutoff <16 points for frontal dysfunction). In all patients with MoCA <26 or FAB <15 points (n=38, 33.9%), an extended neuropsychological battery was applied: Clock Drawing Test (CDT) for visuospatial and executive functions, 10-word learning test to assess verbal memory with immediate and delayed recall (after 20 minutes), phonemic (within 60 seconds words beginning with the letter "S") and categorical (naming animals) verbal fluency, Trail Making Test part A (information processing speed, norm <78±12 seconds for age 60–69 years) and part B (cognitive flexibility, norm <273±38 seconds), Luria's hand movement sequencing test for dynamic praxis. Signs of dysfunction of limbic-frontal networks were separately and structurally assessed. These included apathy not associated with depression (AES-C ≥37 points with HADS-depression <8), anhedonia according to the SHAPS subscale (Snaith-Hamilton Pleasure Scale, ≥3 points), reduction of spontaneous speech production (counting the number of words during 2 minutes of free conversation on a neutral topic "describe your typical day", norm >120 words), changes in personality traits or behavior according to a standardized questionnaire for a close relative or cohabitant addressing changes in character, interests, social activity during the last year).

Subtle motor phenomena were assessed according to a standardized protocol with obligatory video recording (Sony HDR-CX405 camera, 1920×1080, 50 fps). The following parameters were evaluated: asymmetry of arm swing while walking (assessment over a distance of 10 meters at a normal pace with three repetitions, binary assessment: symmetric/asymmetric with indication of the side of reduction), hypomimia according to a 4-point scale (0 — normal facial expression, 1 — mild reduction of facial movements noticeable only on targeted assessment, 2 — noticeable reduction of spontaneous facial expression with reduction of forehead wrinkles and infrequent blinking, 3 — mask-like face with almost complete absence of spontaneous facial movements); micrographia (writing the standard phrase "Today the weather is good" three times in a row on an unlined A4 sheet, measuring the height of five middle letters in each phrase and calculating the coefficient of progressive reduction: $(h_1 - h_3) / h_1$; a coefficient >0.10 was considered pathological); hypophonia (subjective assessment during conversation + objective measurement using a mobile decibel meter at a distance of 1 meter while reading a standard text loudly in a normal voice, normal value >55 dB), decrement during repetitive finger movements (finger tapping test: maximal rapid tapping of the index finger with the thumb for 10 seconds, separately for each hand, counting the number of taps and visual assessment of decrease in amplitude and/or speed during the test; <40 taps in 10 seconds or obvious decrement was considered pathological). All video recordings (duration 6–10 minutes per patient) were stored in anonymized form and

reviewed by two independent expert neurologists blinded to diagnosis, clinical data, and initial assessment results. Inter-expert agreement was assessed using Cohen's kappa for binary variables (arm swing asymmetry, presence of decrement) and weighted kappa for ordinal variables (degree of hypomimia).

Instrumental verification included brain MRI scanning in sagittal, axial, and coronal planes. Visual assessment was performed including medial temporal lobe atrophy according to the Scheltens scale (0–4 points, assessed separately for the hippocampus and entorhinal cortex, ≥2 points — moderate atrophy, ≥3 points — severe atrophy), global cortical atrophy according to the GCA scale (global cortical atrophy, 0–3 points), white matter lesions according to the Fazekas scale (0–3 points assessed separately for periventricular and deep lesions), presence of lacunar infarcts (>3 mm and <15 mm in diameter in deep regions), ventricular enlargement. All MRI studies were evaluated by a radiologist specializing in neuroimaging (16 years of experience) who was blinded to the clinical diagnosis. Patients with cognitive impairment (MoCA <26, n=38) underwent mandatory laboratory testing to exclude secondary causes of cognitive decline including complete blood count, determination of vitamin B12 levels (norm >200 pg/mL), folic acid (norm >3 ng/mL), thyroid-stimulating hormone (norm 0.4–4.0 mIU/L), fasting glucose, creatinine with calculation of glomerular filtration rate, serological test for syphilis (RPR or TPHA).

Development of the Phenotypic MicroSignals Scale (PMS) was carried out in several consecutive stages during 2023 and was based on the fundamental principles of network neuroscience and the clinical phenomenology of early neurodegeneration. The conceptual foundation of PMS was the hypothesis that early neurodegeneration manifests not so much as loss of function, but as loss of network plasticity, flexibility, and synchronization of neuronal systems. In contrast to classical diagnostic instruments focused on deficit and disability, PMS captures subtle disturbances of coordination between neuronal networks at the preclinical level, reflected in behavioral, autonomic, cognitive, and submotor phenomena long before the formation of classical clinical syndromes. The theoretical model of PMS is based on five neurobiological principles [14–20]. First, the evolutionary–anatomical principle of Braak proposes that pathological protein aggregates (α-synuclein, tau, amyloid-β) initially appear not in the cerebral cortex, but in phylogenetically older structures—the olfactory nuclei, the dorsal motor nucleus of the vagus nerve, the locus coeruleus, the raphe nuclei. This explains why the first clinical manifestations of neurodegeneration are hyposmia, constipation, REM sleep disorders, and depression, rather than dementia or parkinsonism. Second, the principle of network brain organization suggests that the pathological process spreads not randomly but along functionally and structurally connected neuronal networks (default mode network, salience network, fronto-striatal circuits), which leads to impaired synchronization between networks and reduced cognitive flexibility earlier than the loss of specific functions. Third, the principle of neurotransmitter cascade proposes that prodromal neurodegeneration initially affects monoaminergic systems (serotonin, noradrenaline) and the cholinergic system, which clinically manifests as disturbances of sleep, mood, autonomic regulation, and attention, and only at later stages affects the dopaminergic system with the development of motor symptoms. Fourth, the principle of the neuro-glio-vascular unit: the first to respond to the neurodegenerative process are not neurons but astrocytes and microglia leading to disruption of metabolic support of neurons, dysfunction of the blood–brain barrier, and microcirculatory changes. Clinically these alterations manifest as fatigue, symptom fluctuations, and "mental fog" earlier than structural changes on MRI. Fifth, the clinical–epidemiological principle of synergy indicates that according to prospective studies (Postuma *et al*., 2012; Berg *et al*., 2015) [21, 22], a single prodromal symptom has low prognostic value (hazard ratio 2–4), whereas a combination of symptoms from different domains increases the risk of conversion exponentially (hazard ratio >20 for 4–5 symptoms), which substantiates the cumulative principle of scale construction.

Based on a systematic analysis of the literature on prodromal neurodegeneration (systematic search in PubMed using the keywords "prodromal," "premotor," "preclinical" in combination with "Parkinson," "Alzheimer," "Lewy body," "neurodegeneration"), a review of international consensus criteria for prodromal states (MDS Research Criteria for Prodromal Parkinson's Disease 2015 [22], NIA-AA Preclinical Alzheimer's Disease 2011 [10]), and a retrospective analysis of 84 medical histories of patients with established neurodegenerative diagnoses with reconstruction of the prodromal period based on active interviews with patients and their relatives, an initial list of 42 potential phenotypic microsignals was formed. Phenotypic microsignals were included in the list provided that four criteria were simultaneously met: (1) documented temporal association in the literature with the subsequent manifestation of a neurodegenerative disease—the symptom must occur statistically significantly more often in individuals who later develop a neurodegenerative disease compared with the control group, and precede the clinical diagnosis by at least 6–12 months; (2) pathophysiological validity—the presence of evidence of involvement of specific neuronal networks, structures, or neurotransmitter systems according to neuroimaging, neurophysiological, or pathomorphological studies; (3) clinical measurability—the possibility of objective or semi-objective assessment of the symptom using validated instruments available in routine clinical practice, without the need for complex equipment; (4) inter-expert reproducibility—demonstrated in validation studies as agreement of assessment between independent researchers at the level of Cohen's kappa or ICC >0.60. A three-stage modified Delphi procedure (March–May 2023) was conducted with the participation of five independent expert neurologists. In the first round, experts assessed the clinical significance of 42 microsignals on a 9-point scale; 10 items were excluded due to low ratings or lack of consensus. In the second round, 32 microsignals were reassessed taking into account the summarized results, and consensus was achieved for all items (median ≥7, IQR ≤2). In the third round, experts determined the prognostic weight of microsignals; however, an unweighted system was

applied in the final scale to simplify clinical use and increase reliability.

Statistical analysis

The sample size calculation was based on the assumption that the conversion rate of prodromal conditions into manifest forms would be 35–45% over 24 months of follow-up (based on literature data for prodromal Parkinson's disease and mild cognitive impairment), the expected area under the ROC curve for the PMS scale would be at least 0.75, and the minimally acceptable width of the 95% confidence interval for AUC would be 0.15. Under these parameters, with α=0.05 and a power of 80%, the required sample size was 76–82 patients; the actual sample of 112 individuals (84 patients with pathology and 28 controls) provided sufficient statistical power considering possible attrition (10–15%).

To empirically verify the domain structure of PMS and reduce the number of items, an exploratory factor analysis (principal component method with varimax rotation to maximize interpretability of factors) was conducted on the baseline dataset of 84 patients from groups 1 and 2 (period January–June 2023). Before performing factor analysis, data adequacy was confirmed. The Kaiser–Meyer–Olkin criterion showed a value of 0.71±0.04 (>0.60 acceptable, >0.70 good), indicating sufficient correlation between variables for factorization. Bartlett's test of sphericity showed a statistically significant result (χ^2=394.7±18.3, df=496, p<0.001), rejecting the null hypothesis of non-correlated variables. The number of factors for extraction was determined based on three criteria: (1) Kaiser criterion—eigenvalue >1.0 (9 factors extracted), (2) scree plot analysis with identification of the "elbow" (visually at the 7th–8th factor), (3) criterion of interpretability and clinical meaningfulness of factors. The optimal solution was found to include 7 factors, which explained 68.4±3.2% of the total variance (factor 1: 18.2±2.1%, factor 2: 12.7±1.8%, factor 3: 10.1±1.5%, factor 4: 9.3±1.4%, factor 5: 7.8±1.2%, factor 6: 5.6±0.9%, factor 7: 4.7±0.8%). Microsignals were included in a domain provided that the factor loading was >0.50 on the corresponding factor (high loading) and <0.35 on all other factors (low cross-loading), thereby ensuring a clear domain structure. ROC analysis was performed for three comparisons (manifest vs. control, prodromal vs. control, manifest vs. prodromal) to assess the diagnostic accuracy of the PMS scale. Correlation and multiple regression analyses were used to identify predictors of the total PMS score.

Results

The clinical cohort that was empirically analyzed consisted of 112 patients. The age range of the sample was from 48 to 76 years, with a mean age of 64.0 ± 7.2 years, indicating a predominant concentration of participants in the period of late middle age and early old age. Gender distribution showed a moderate predominance of men—57.1% (n=64), whereas women accounted for 42.9% (n=48). Although this distribution does not reach ideal symmetry, it is not methodologically critical and is consistent with typical epidemiological patterns observed in population studies of chronic neurodegenerative processes [23, 24]. The observation period lasted from January 1, 2020 to August 1, 2025, with prospective monitoring designed to track the conversion of prodromal states into manifest neurodegenerative diseases over 24 months. This protocol monitoring ensured consistency of dynamic observation without excessive burden on participants. During the full cycle of prospective monitoring, the cohort demonstrated high retention rates, providing a reliable basis for further analytical interpretations.

Frequency and spectrum of detected phenotypic microsignals at the baseline visit. During the initial clinical examination of individuals included in the study, a wide spectrum of phenotypic microsignals was identified, showing a high degree of variability both in clinical profile and in severity. The main domains with phenotypic microsignals are presented in ***Table 1***. For analysis, participants were divided into three groups: Group 1 (prodromal/non-manifest pathology, n=28), comprising individuals with prodromal states without definitive nosological determination; Group 2 (manifest pathology, n=56), including patients with clinically established diagnoses of neurodegenerative diseases: Alzheimer's disease (n=16), Parkinson's disease (n=28), dementia with Lewy bodies (n=9), progressive supranuclear palsy (n=3). Group 3 (control group, n=28), consisting of individuals without clinical manifestations of neurodegenerative pathology. Prodromal cases were characterized by a combination of multiple non-motor symptoms from different domains without full correspondence to the criteria of manifest disease and in the absence of alternative explanations for the symptomatology. In most cases, these symptoms did not reach the threshold necessary for a formal diagnosis, however, their pattern and sequence suggested latent neurovegetative dysfunction with potential prognostic significance. Risk assessment and comparisons were performed using the newly introduced Phenotypic MicroSignals Scale (PMS).

Characteristics of Group 1 (prodromal/non-manifest pathology (NM pathology), n=28). In the first group, which included 28 individuals with prodromal conditions without definitive nosological determination at the time of inclusion, phenotypic microsignals according to the developed PMS scale were detected in 92.9% (n=26) of patients with a total score ≥1. This cohort was characterized by a combination of multiple non-motor symptoms from different domains without full correspondence to the criteria of manifest disease and in the absence of alternative explanations for the symptomatology. The mean age of participants was 63.2±6.8 years (range 51–74 years) with a gender distribution of 57.1% (n=16) men and 42.9% (n=12) women. The mean duration of symptoms from the onset of the first complaints to inclusion in the study was 4.7±2.3 years (range 1.2–9.5 years).

The most common findings were disturbances of sleep architecture with a predominance of behavioral disorders during rapid eye movement (REM) sleep. According to the RBD1Q questionnaire [25], positive responses regarding episodes of nocturnal motor activity associated with dreaming (shouting, arm flailing, striking movements) were recorded in 67.9% (n=19) of the examined individuals, which represented the highest rate among all domains. At the same time, in 42.1% (n=8 of 19) of cases relatives reported injuries during sleep (bruises on the partner's limbs, falling

out of bed), and in 31.6% (n=6 of 19) — vocalizations of varying intensity. The mean frequency of episodes was 2.8±1.4 per week (range 1–6). Excessive daytime sleepiness with an Epworth Sleepiness Scale score >10 was noted in 53.6% (n=15) of patients, with a mean score of 12.4±2.6 (range 11–18), accompanied by complaints of an overwhelming need for daytime rest regardless of the duration of nighttime sleep. Disturbances of the circadian sleep–wake rhythm in the form of phase inversion or fragmentation of nighttime sleep with multiple awakenings (>3 per night) were recorded in 60.7% (n=17) of individuals, with the mean number of awakenings per night being 4.6±1.8 (range 3–9).

Olfactory dysfunction was found to be the second most frequent phenotypic microsignal. According to the results of the simplified 12-odour identification test, hyposmia (correct identification of <9 odours) was diagnosed in 71.4% (n=20) of the group participants. The mean number of correctly recognized odours was 6.8±1.9 (range 3–11), which was significantly below the threshold value of 9 points. At the same time, 35.0% (n=7 of 20) patients with hyposmia were unaware of the presence of this disorder before testing, emphasizing the latent nature of the symptom. Anosmia (recognition of ≤3 odours) was recorded in 14.3% (n=4) of the examined individuals, with a mean value of 2.3±0.5 odours. The most frequently unrecognized were subtle odours including rose (82.4% errors), camphor (76.5%) and fir tree (71.8%), whereas intense odours were recognized better, including vinegar (31.2% errors), onion (35.3%) and garlic (38.8%).

Visual-perceptual phenomena in the form of episodic visual illusions (misperception of objects in the peripheral visual field, especially at dusk) were noted in 17.9% (n=5) of participants, with a frequency of 1.8±0.9 episodes per month, while formed visual hallucinations were absent. Central pain syndromes of unclear etiology (chronic pain in the limbs or trunk without a structural substrate on MRI) were observed in 21.4% (n=6) of patients, with an intensity of 4.3±1.2 points on the visual analogue scale (range 3–6).

Gastrointestinal manifestations were dominated by chronic constipation meeting the ROME IV criteria in 78.6% (n=22) of individuals. The mean frequency of defecation was 2.4±0.8 per week (range 1–4), with constipation duration exceeding 5 years in 68.2% (n=15 of 22), median 6.8 years (range 5.2–14.3 years), and exceeding 10 years in 31.8% (n=7 of 22), median 11.9 years (range 10.1–18.2 years). Accompanying symptoms included morning nausea in 39.3% (n=11), with a frequency of 3.4±1.6 episodes per week, and episodes of aerophagia in 28.6% (n=8) of cases.

Dysuric disorders were recorded in 60.7% (n=17) of patients: nocturia (≥2 episodes per night) in 50.0% (n=14), with a mean frequency of 2.8±0.9 episodes per night (range 2–5); imperative urges in 35.7% (n=10), with a frequency of 4.2±2.1 episodes per day; episodes of urgent urinary incontinence in 17.9% (n=5), with a frequency of 1.4±0.7 episodes per week. Orthostatic hypotension according to the active orthostatic test was found in 28.6% (n=8) of the examined participants, with mean systolic pressure decrease of 26.3±8.4 mmHg (range 20–44) and diastolic decrease of 13.7±4.2 mmHg (range 10–22). In 75.0% (n=6 of 8) of cases adequate compensatory tachycardia (increase in heart rate >15 bpm) was observed, with a mean increase of 21.8±5.3 bpm, indicating a non-neurogenic pattern, whereas in 25.0% (n=2) an insufficient tachycardic response with an increase of 8.5±2.1 bpm was characteristic of the neurogenic form.

Persistent hyperhidrosis without thermal or endocrine substrate was recorded in 46.4% (n=13) of individuals, predominantly localized in the head and upper trunk region (92.3%, n=12 of 13), less often in the palms (30.8%, n=4 of 13).

Psychoemotional disturbances were characterized by polymorphism of manifestations. Anxiety according to the HADS-anxiety subscale ≥8 points (subclinical or clinical level) was detected in 64.3% (n=18) of patients, with a mean score of 9.2±3.1 (range 8–16). Of these, a subclinical level (8–10 points) was observed in 55.6% (n=10 of 18), whereas clinical (≥11 points) in 44.4% (n=8 of 18). Depressive symptoms (HADS-depression ≥8 points) were recorded in 53.6% (n=15) of individuals, with a mean score of 8.7±2.8 (range 8–15), but no case reached the criteria of major depressive disorder according to DSM-5. Apathy not associated with depression (AES-C ≥37 points with HADS-depression <8) was found in 39.3% (n=11) of the examined individuals, with a mean score of 41.3±4.8 (range 37–52). Anhedonia according to the SHAPS scale ≥3 points was noted in 42.9% (n=12) of patients, with a mean score of 4.7±1.9 (range 3–9). Resistance to standard antidepressant therapy (lack of response to ≥2 drugs from different classes for >8 weeks) in the history was present in 28.6% (n=8) of individuals; the mean number of ineffective treatment attempts was 2.6±0.7 (range 2–4). Pathological fatigue with FSS ≥4 of the mean score was found in 57.1% (n=16) of participants, with a mean value of 5.2±1.1 points (range 4.1–7.3), accompanied by complaints of asthenia disproportionate to physical exertion for 5.3±1.8 hours per day.

Subjective cognitive complaints with preserved daily functioning were reported by 82.1% (n=23) of patients, most often in the form of forgetfulness for recent events (78.3%, n=18 of 23), difficulty concentrating (69.6%, n=16 of 23), and slowing of thought processes (60.9%, n=14 of 23). Objective episodic memory impairment with rapid forgetting according to the 10-word recall test (delayed recall after 20 minutes <5 words) was detected in 25.0% (n=7) of the examined individuals, with a mean value of 3.9±0.8 words (range 2–5), whereas immediate recall was 6.4±1.3 words (range 4–9), indicating impaired memory consolidation. Fluctuations of attention and reduced mental endurance were recorded in 46.4% (n=13) of individuals, manifested by episodes of cognitive instability during the day with deterioration under stress or fatigue; the mean duration of episodes was 32.7±14.2 minutes (range 15–65).

Visuospatial disorientation according to the clock-drawing test (<7 points on the 10-point Shulman scale) was noted in 17.9% (n=5) of patients, with a mean score of 5.8±0.9 (range 4–7). Language dysfunction in the form of anomia (word-finding difficulty) and reduced fluency was found in 32.1% (n=9): the mean letter fluency score (words beginning with "S" in 60 seconds) was 11.3±3.2 (range 6–17, normative value >15), and category fluency (animals) was 13.8±2.9 (range 9–19, normative value >18).

Table 1. Phenotypic Microsignal Scoring Scale for Neurodegenerative Risk Assessment

Domain	Phenotypic microsignal	Dominant neurodegenerative association*	Score
COGNITIVE / MEMORY	Subjective cognitive decline with preserved daily functioning	AD, prodromal AD, DLB	1
	Episodic memory impairment with rapid forgetting	AD (amyloidopathy)	3
	Attention fluctuations, reduced mental endurance	DLB, PD	2
	Visuospatial disorientation, constructional apraxia	AD, DLB	2
	Language dysfunction (anomia, reduced fluency)	AD, CBD	3
EXECUTIVE / FRONTAL	Slowed information processing	PD, PSP	1
	Impaired planning and task switching	PD, PSP, CBD	2
	Behavioral disinhibition or apathy	PSP, CBD, AD	3
SUBMOTOR / MOTOR	Reduced arm swing, unilateral motor subtlety	Prodromal PD, DLB	1
	Bradykinesia with axial predominance	PD, PSP	2
	Early postural instability or falls	PSP, MSA	3
	Limb apraxia, alien limb phenomena	CBD	3
OCULOMOTOR / SPEECH	Slowed saccades	PSP	2
	Vertical gaze palsy (early or incomplete)	PSP	3
	Hypophonia, dysarthria	PD, MSA	2
AUTONOMIC	Chronic constipation	PD, MSA	1
	Urinary urgency or retention	PD, MSA	2
	Orthostatic hypotension	MSA > PD	3
SLEEP	REM sleep behavior disorder	PD, DLB, MSA	3
	Excessive daytime sleepiness	PD, DLB	1
SENSORY / PERCEPTUAL	Hyposmia or anosmia	PD, AD	1
	Visual hallucinations or illusions	DLB	3
	Central pain syndromes	PSP, CBD	2
AFFECTIVE / LIMBIC	Anxiety, emotional lability	PD, AD	1
	Depression resistant to treatment	PD, AD	2
	Apathy, loss of initiative	PSP, CBD, AD	3
PERSONALITY / SOCIAL	Social withdrawal, reduced empathy	AD, FTD spectrum	2
	Loss of insight, anosognosia	AD	3
TOTAL PMS SCORE		Maximum possible score	48

Notes: * Dominant neurodegenerative association indicates the most commonly associated condition.
Abbreviations: AD — Alzheimer's disease; PD — Parkinson's disease; DLB — dementia with Lewy bodies; PSP — progressive supranuclear palsy; MSA — multiple system atrophy; CBD — corticobasal degeneration.

Slowing of information processing on the Trail Making Test Part A was found in 39.3% (n=11) of patients. The mean completion time was 84.3±16.7 seconds (range 79–128, norm <78 seconds for age 60–69 years). Impairment of planning and task switching on the Trail Making Test Part B was recorded in 35.7% (n=10) of the examined individuals: mean time 312.5±52.3 seconds (range 278–432, norm <273 seconds). The B/A ratio, reflecting the specificity of executive dysfunction, was 3.8±0.9 (norm <3.0). Frontal dysfunction with FAB <16 points was identified in 28.6% (n=8) of individuals, with a mean score of 14.2±1.8 (range 11–16); the most affected subtests were conceptualization (mean 1.8±0.6 of 3 possible) and motor programming (1.6±0.7 of 3). Reduction of spontaneous speech production (<120 words in 2 minutes of free conversation on the topic "describe your typical day") was noted in 42.9% (n=12) of patients with a mean value of 98.7±18.4 words (range 68–119), which is 21.3% below the normative threshold.

Behavioral disinhibition or apathy of clinically significant degree was observed in 25.0% (n=7) of cases, with a mean score on the corresponding Frontal Systems Behavior Scale subscale of 24.3±6.2 (range 18–36, norm <15). Reduction of arm swing on one side while walking, according to video analysis, was found in 46.4% (n=13) of the examined individuals; in 76.9% (n=10 of 13) left-sided asymmetry was observed, whereas right-sided asymetry was present in 23.1% (n=3 of 13). The mean decrease in swing amplitude on the affected side was 38.6±12.4% compared to the contralateral side (range 20–65%). Inter-rater agreement for asymmetry assessment, according to Cohen's kappa was 0.82±0.07. Hypomimia ≥1 point on the 4-point scale was recorded in 42.9% (n=12) of patients: 1 point — in 28.6% (n=18 of 28 examined, which is 28.6% of the whole group or 66.7% among those who had hypomimia), 2 points — in 14.3% (n=4), 3 points were not observed in any case. Inter-rater agreement for hypomimia assessment according to weighted kappa was 0.78±0.06. Micrographia with a pathological progressive reduction coefficient >0.10 was detected in 32.1% (n=9) of individuals with a mean coefficient of 0.14±0.03 (range 0.11–0.22), while the mean letter height in the first sentence was 4.8±0.7 mm and in the third 4.1±0.6 mm, corresponding to a 14.6% reduction. Hypophonia <55 dB during standardized text reading at a distance of 1 meter was recorded in 28.6% (n=8) of the examined individuals with a mean value of 51.8±3.2 dB (range 46–55), which is 5.8% below the normative threshold. A decrement on the finger tapping test was found in 35.7% (n=10) of patients: the mean number of taps in 10 seconds was 36.4±5.1 (range 28–39, norm ≥40), with a decrease in frequency during the test of 18.3±6.7%. Inter-rater agreement for decrement assessment according to Cohen's kappa was 0.74±0.08. Bradykinesia with axial predominance (slowing when turning in bed, rising from a chair, turning while walking) was noted in 21.4% (n=6) of cases, with a score of 1–2 points according to item 3.14 of the MDS-UPDRS Part III. Early postural instability or falls were recorded in 10.7% (n=3) of individuals: in 2 cases (7.1%) — episodes of instability without falls, in 1 case (3.6%) — falls with a frequency of 2 episodes over 6 months. Limb apraxia and "alien hand" phenomena were absent in all examined participants. Slowing of saccades on clinical testing (slow eye movements when shifting gaze between two targets at a distance of 30 cm with an interval of 90 degrees) was detected in 17.9% (n=5) of patients; the mean saccade duration was 0.28±0.04 seconds (norm <0.20 seconds), which exceeds normative values by 40%. Early or incomplete vertical ophthalmoplegia was not recorded in any case. Hypophonia and dysarthria, in addition to the previously described cases of reduced voice loudness, included elements of monotony of intonation in 25.0% (n=7), with a perceptual analysis score of 2.3±0.6 points on a 5-point scale, and difficulty in phrase initiation in 21.4% (n=6) of the examined participants, with a latency of 2.8±0.9 seconds (norm <1.5 seconds). Social withdrawal and reduced empathy according to a standardized questionnaire for close relatives were identified in 35.7% (n=10) of patients, manifested by a 42.3±18.7% decrease in the frequency of social contacts compared with the previous year, loss of interest in former hobbies in 60.0% (n=6 of 10) of cases, and a reduced emotional response to the problems of others according to relatives' assessment by 3.8±1.2 points on a 10-point scale. Loss of insight and anosognosia were not recorded in any case.

According to brain MRI, moderate atrophy of the medial temporal structures (≥2 points on the Scheltens scale) was found in 32.1% (n=9) of patients. The mean score for the hippocampus was 1.8±0.9 (range 0–3), for the entorhinal cortex 1.6±0.8 (range 0–3). Global cortical atrophy according to GCA ≥1 point was noted in 39.3% (n=11), with a mean score of 1.4±0.6 (range 1–2). White matter lesions according to Fazekas were found in 50.0% (n=14): periventricular lesions of 1 point — in 28.6% (n=4 of 14), 2 points — in 21.4% (n=3 of 14); deep lesions of 1 point — in 35.7% (n=5 of 14), whereas no case reached the exclusion criterion of ≥2 points. Lacunar infarcts were detected in 7.1% (n=2) of patients (one infarct in each case, 4–5 mm in diameter in the basal ganglia).

Laboratory parameters in patients with cognitive impairment (n=10, 35.7% of the group) were within normal limits. The mean vitamin B12 level was 342.7±118.3 pg/mL (range 210–598, norm >200), folic acid 6.8±2.4 ng/mL (range 3.2–12.1, norm >3), TSH 2.1±0.9 mIU/L (range 0.6–3.8, norm 0.4–4.0), fasting glucose 5.3±0.6 mmol/L (range 4.4–6.2), eGFR 78.4±12.7 mL/min/1.73m² (range 62–98). Serological tests for syphilis were negative in all cases.

The mean total score on the Phenotypic Microsignal Scale in Group 1 was 11.4±3.8 (range 2–19 points, median 11 points) with a maximum possible score of 48 points. Based on the obtained data, we developed a risk stratification system for the development of neurodegenerative diseases, which was based on three categories: low risk (0–12 points), moderate risk (13–24 points), and high risk (≥25 points). According to this stratification, Group 1 was distributed as follows: the low-risk category included 67.9% (n=19) of patients with a mean score of 8.2±3.1 (range 2–12), which constituted 17.1% of the maximum possible score; the moderate-risk category — 32.1% (n=9), with a mean score of 16.8±2.4 (range 13–19), corresponding to 35.0% of the maximum; no patient entered the high-risk category (0%, n=0), since the maximum score in Group 1 was 19 points. Thus, 32.1% (n=9) of patients in the prodromal

group had a moderate level of risk of developing manifest neurodegenerative disease according to the developed stratification system. This finding emphasizes the clinical significance of the identified phenotypic microsignals and their potential for early identification of individuals at increased risk of neurodegenerative progression. Correlation analysis revealed statistically significant associations between the total PMS score and key clinical parameters including duration of symptoms ($r=0.52$, $p=0.004$), age of patients ($r=0.38$, $p=0.042$), and the number of affected domains ($r=0.76$, $p<0.001$). Multiple regression analysis showed that the greatest contribution to the total PMS score was made by sleep disorders ($\beta=0.34$, $p=0.002$), olfactory dysfunction ($\beta=0.28$, $p=0.008$), and autonomic disorders ($\beta=0.26$, $p=0.012$), which explained 68.4% of the variance of the total score ($R^2=0.684$, $p<0.001$). These results confirm the construct validity of the PMS scale and demonstrate that non-motor symptoms, in particular sleep disturbances, olfactory and autonomic dysfunctions, are the most significant predictors of neurodegenerative risk at the prodromal stage.

Stratification of patients by risk level for developing neurodegenerative diseases based on the Phenotypic Microsignals Scale (PMS). One of the key results of this study was the implementation of a multilevel system for stratifying patients according to the risk of developing neurodegenerative diseases (NDDs). Stratification was based on the total score obtained using the PMS, which made it possible to quantitatively assess the current phenotypic status of the patient and qualitatively predict the likelihood of transformation of the prodromal state into a clinically manifest form of the disease. Based on the obtained results, three clinically significant risk categories were identified: low (0–12 points), moderate (13–24 points), and high (≥25 points). This approach opens new opportunities for proactive clinical intervention, targeted monitoring, and personalized patient management. Summary data are presented in ***Table 2***.

Low-risk category (0–12 points). Patients classified in the low-risk category according to the total score on the Phenotypic Micro-Signals (PMS) Scale constituted the largest proportion of the prodromal cohort (67.9%, n=19 from Group 1). These individuals demonstrated isolated or multiple phenotypic manifestations, with a mean total PMS score of 8.2±3.1 (range 2–12), which accounted for 17.1% of the maximum possible score. The clinical profile was characterized by mild or moderate expression of non-motor symptoms across various domains, without sufficient accumulation to reach the moderate-risk threshold. Such symptoms included episodic sleep disturbances (REM sleep behavior disorder in some cases), olfactory dysfunction, autonomic manifestations (constipation, urinary symptoms), mild cognitive complaints with preserved daily functioning, and subtle motor phenomena. From a clinical and prognostic perspective, this phenotypic configuration was associated with a conversion rate to manifest neurodegenerative disease of less than 5% during the observation period, indicating a relatively low short-term prognostic risk. However, the presence of documented prodromal markers, even at a low cumulative level, requires further clinical attention. From a practical standpoint, this clinico-phenotypic configuration does not require immediate engagement in intensive diagnostic algorithms—specifically, extended neuroimaging, biomarker analysis, or extensive neuropsychological batteries. Management of patients in this category can be carried out within the framework of standard outpatient follow-up with periodic reassessment (annually or semiannually), focusing on basic evaluation of functional status, monitoring symptom progression, and educational interventions regarding risk factors for neurodegeneration and lifestyle modification. However, considering the potential impact of certain anamnesis risk factors (family history of neurodegenerative diseases, presence of vascular comorbidities, exposure to chronic stress or circadian rhythm disturbances), it is recommended to form an individualized clinical profile, including monitoring of possible triggers and periodic reassessment using PMS. This will allow timely detection of early signs of shift to a higher risk category and adaptation of patient management strategies to evolving clinical realities.

Moderate-risk category (13–24 points). The moderate-risk category, which included patients with a total PMS score of 13-24, encompassed 32.1% (n=9) of the prodromal cohort (Group 1) with a mean score of 16.8±2.4 (range 13–19), which accounted for 35.0% of the maximum possible score. This category was characterized by a polysymptomatic clinical profile with clear accumulation of phenotypic micro-signals across multiple domains, indicating initial signs of multi-network neurophysiological dysregulation. In most cases, a combination of affective, autonomic, cognitive, sensory, and subtle motor manifestations was observed, forming a clinically significant prodromal phenotype with internal structure and domain diversity. The affective domain in this cohort was characterized by predominance of anxiety states (HADS-anxiety ≥8 in 64.3%), depressed mood (HADS-depression ≥8 in 53.6%), apathy not associated with depression (AES-C ≥37 in 39.3%), and anhedonia (SHAPS ≥3 in 42.9%). Patients reported persistent subjective feelings of tension, loss of motivation, reduced behavioral initiative, and treatment-resistant

Table 2. Risk Stratification Based on Phenotypic Micro-Signal Scale (PMS Scale)

Risk Category	PMS Score Range	Estimated Risk of NDD Progression	Clinical Implication
Low	0-12	<5%	Routine dynamic observation
Moderate	13–24	~20–30%	Enhanced clinical monitoring
High	≥25	>50%	Comprehensive diagnostic evaluation

mood disorders (28.6% with a history of unsuccessful antidepressant therapy), indicating early signs of limbic system dysregulation. Autonomic symptoms included chronic constipation meeting ROME IV criteria (78.6%), orthostatic hypotension (28.6%), urinary dysfunction including nocturia and urgency (60.7%), and excessive sweating (46.4%). These autonomic disturbances indicated impaired sympathetic-parasympathetic balance and initial disorganization of autonomic regulation, typical of early stages of neurodegenerative processes, especially in synucleinopathies. Sleep architecture disturbances were pronounced, particularly REM sleep behavior disorder (67.9% positive responses on RBD1Q), excessive daytime sleepiness (53.6% with Epworth >10), and sleep fragmentation (60.7% with >3 awakenings per night). Cognitive symptoms in this group had not yet reached the threshold for dementia but manifested as subjective cognitive decline (82.1%), episodic memory impairment with rapid forgetting (25.0%), attention fluctuations (46.4%), slowed information processing (39.3%), and executive dysfunction (35.7%). These phenomena were detected during targeted neuropsychological testing (MoCA, FAB, Trail Making Test), even when routine screening remained within normal limits. Sensory changes were particularly frequent, including hyposmia (71.4% with correct identification of <9 out of 12 odors), with 35% of patients being unaware of their olfactory deficit prior to testing—a recognized non-motor biomarker that often precedes manifest motor symptoms in Parkinson's disease. Subtle motor phenomena included asymmetry of arm swing (46.4%), hypomimia (42.9%), micrographia (32.1%), and decrement on the finger-tapping test (35.7%). Concomitant complaints of pathological fatigue (FSS ≥4 in 57.1%) and reduced spontaneous speech production (42.9% with <120 words in a 2-minute discourse) were also characteristic of this category. The conversion rate from prodromal state to clinically manifest neurodegenerative disease in the moderate-risk category was estimated at approximately 20–30% over a 24-month observation period, significantly exceeding population baseline rates. This finding necessitates intensified dynamic monitoring with careful tracking of cognitive, emotional, autonomic, and motor parameters. Within the framework of clinical tactics, it is advisable to conduct evaluations at least twice a year with reassessment using PMS, cognitive screening (MoCA, FAB), standardized assessment of sleep architecture, autonomic function testing, and evaluation of olfactory function. In the case of detection of negative dynamics—specifically, the appearance of new symptoms, worsening of existing ones, or an increase in PMS score crossing into the high-risk territory—it is strongly recommended to implement modern instrumental diagnostic methods, including brain MRI with a focus on midbrain structures and medial temporal regions, comprehensive multidomain neuropsychological testing, and autonomic profiling. Timely stratification of patients in this risk category allows identification of individuals with an increased likelihood of neurodegenerative progression at the preclinical stage, opening opportunities for proactive clinical intervention, intensified monitoring protocols, and potential implementation of disease-modifying or neuroprotective therapeutic strategies.

High-risk category (≥25 points). Patients with a total PMS score ≥25 were classified into the high-risk category. Notably, in the prodromal cohort (Group 1), no patient reached this threshold, as the maximum observed score was 19. Therefore, this category is defined theoretically and based on extrapolation from patients with established manifest neurodegenerative diseases (Group 2), where such scores would be expected. This group would be characterized by the presence of multiple, persistent, recurrent, and mutually reinforcing phenotypic micro-signals across virtually all evaluated domains, demonstrating high chronological stability, clear progression over time, and morphofunctional interdependence. In the clinical spectrum of such patients, a predominance of a wide range of non-motor symptoms would be expected, including pronounced REM sleep behavior disorder with frequent traumatic episodes, marked hyposmia or anosmia, significant autonomic insufficiency (neurogenic orthostatic hypotension, severe constipation, urinary dysfunction), alongside clear motor phenomena such as hypomimia, bradykinesia, reduced arm swing, and possibly early postural instability. Additionally, patients in this category would be expected to exhibit clear signs of reduced cognitive flexibility, executive function and behavioral initiative impairment, visuospatial dysfunction, episodic memory deficits, and involvement of fronto-limbic structures in the pathological process, manifesting as apathy, reduced spontaneous activity, and social withdrawal. The frequency of developing neurodegenerative disease in this group would be expected to exceed 50% over 24 months, representing patients at the threshold or already meeting criteria for manifest disease. This would be confirmed by both clinical dynamic observation and instrumental methods, including MRI detecting medial temporal atrophy or midbrain changes, multi-domain neuropsychological testing demonstrating deficits in multiple cognitive domains, and pathological autonomic function tests. Given the high prognostic probability, immediate referral of patients for comprehensive diagnostic evaluation is clinically necessary, including detailed neuroimaging (MRI with volumetric analysis, potentially DaTscan if synucleinopathy is suspected), extensive neuropsychological assessment, autonomic function testing, polysomnography for suspected REM sleep disorder (RBD), and, if clinically indicated, genetic counseling, CSF biomarker analysis, or advanced imaging methods. In a high-risk situation, clinicians should consider initiating disease-specific therapeutic interventions, including neuroprotective strategies, symptomatic treatment of non-motor symptoms (RBD, autonomic dysfunction, neuropsychiatric symptoms), and comprehensive multidisciplinary care involving neurology, neuropsychology, psychiatry, and rehabilitation services.

Characteristics of Group 2 (manifest pathology, n=56). The second group included 56 patients with clinically established diagnoses of neurodegenerative diseases, verified by two independent neurologists according to international disease-specific criteria. The mean age of participants was 68.4±6.9 years (range 52–77 years), which was 5.2 years older than the mean age of the prodromal group (p=0.003). Gender distribution showed a predominance of men — 60.7%

(n=34) versus 39.3% (n=22) women. The mean disease duration from the onset of initial motor or pronounced cognitive symptoms to study inclusion, was 3.8±2.6 years (range 0.5–11.2 years). According to nosological structure, the group was distributed as follows: amyloidopathies (Alzheimer's disease) — 28.6% (n=16), synucleinopathies (Parkinson's disease — 50.0%, n=28; Lewy body dementia — 16.1%, n=9), and tauopathies (progressive supranuclear palsy) — 5.4% (n=3). All patients underwent comprehensive clinical-instrumental evaluation with mandatory MRI verification of diagnosis.

Alzheimer's disease (n=16, 28.6% of Group 2). The subgroup of patients with Alzheimer's disease included 16 individuals, representing 28.6% of Group 2. The mean age of the examined patients was approximately 70 years, with a slight predominance of women. The average disease duration did not exceed three years, with mild and moderate stages of dementia predominating. The clinical picture was characterized by universal impairment of episodic memory with pronounced consolidation deficits, reduction in global cognitive scores, and significant executive dysfunction. Visuospatial, language, and attention deficits, as well as affective and behavioral symptoms, were common. Social functioning and insight into condition were substantially reduced in a significant portion of patients. Neuroimaging data showed predominant atrophy of the medial temporal structures combined with generalized cortical atrophy and vascular changes in the white matter. Key clinical-demographic, neuropsychological, and MRI parameters are presented in ***Table 3***.

The mean total PMS score in the subgroup of patients with Alzheimer's disease was 28.6±5.4 points (range 19–38 points, median — 29 points). Analysis of the distribution by risk categories showed no patients with low risk (0–12 points). Moderate risk (13–24 points) was found in 18.8% of patients (n=3) with a mean score of 21.3±2.1 points, whereas the vast majority of examined patients — 81.3% (n=13) — belonged to the high-risk category (≥25 points) with a mean score of 31.2±4.8 points.

Parkinson's disease (n=28, 50.0% of Group 2). The subgroup of patients with Parkinson's disease was the largest in Group 2 and included 28 individuals with a mean disease duration of over four years. The clinical profile corresponded to the typical idiopathic form of Parkinson's disease, with predominance of the akinetic-rigid phenotype and stages III–IV according to Hoehn–Yahr. Motor symptoms were characterized by universal presence of bradykinesia, a high frequency of rigidity and resting tremor, and a significant prevalence of postural instability. Non-motor symptoms were observed in all patients and demonstrated marked heterogeneity with early onset. The most common manifestations were sleep disturbances with REM sleep behavior disorder, olfactory dysfunction, autonomic disturbances, and affective disorders. Cognitive impairments were recorded in most patients; however, in the vast majority of cases, they did not reach the level of dementia and displayed a fronto-striatal profile. Key demographic, clinical, cognitive, and neuroimaging parameters are presented in ***Table 4***.

Table 3. Key clinical-neuropsychological and neuroimaging parameters of patients with Alzheimer's disease (n = 16)

Parameter	Value	Parameter	Value
Demographics and Global Cognitive Scales			
Age, years	70.2 ± 4.8	MMSE, points	20.3 ± 4.2
Female, n (%)	9 (56.3)	MoCA, points	16.8 ± 5.1
Disease duration, years	2.9 ± 1.8		
Cognitive Profile and Executive Functions			
Episodic memory impairment, %	100	TMT-A, s	126.7 ± 34.2
Immediate recall (10- word test)	4.2 ± 1.3	TMT-B, s	418.3 ± 98.6
Delayed recall	1.8 ± 1.1	B/A ratio	5.8 ± 2.1
Forgetting rate, %	57.1 ± 18.4	Unable to complete TMT-B, %	31.3
Language, Visuospatial Functions, and Affective-Behavioral Disturbances			
Visuospatial impairment, %	81.3	Apathy (AES-C ≥37), %	62.5
Clock Drawing Test, points	4.6 ± 2.1	Anxiety (HADS-A ≥8), %	68.8
Letter fluency, words/min	8.4 ± 3.6	Depression (HADS-D ≥8), %	62.5
Neuroimaging (MRI)			
Medial temporal atrophy, %	81.3	Hyposmia/anosmia, %	100
Hippocampal atrophy score	3.2 ± 0.8	Sleep disturbances, %	75.0
Total cortical atrophy, %	75.0	Orthostatic hypotension, %	25.0
Fazekas ≥1, %	68.8		

Table 4. Key clinical and neuropsychological characteristics of patients with Parkinson's disease (n = 28)

Parameter	Value	Parameter	Value
Demographics, Disease Course and Motor Symptoms			
Age, years	67,8 ± 6,3	Bradykinesia, %	100
Male, n (%)	17 (60,7)	MDS-UPDRS III (rigidity)	2,4 ± 0,8
Disease duration, years	4,2 ± 2,8	Resting tremor, %	78,6
Akinetic-rigid form, %	60,7	Postural instability,%	42,9
Hoehn–Yahr III–IV, stage %	75,0	Freezing of gait, %	35,7
Speech-Motor Manifestations and Non-Motor Symptoms			
Hypomimia ≥2 points, %	75	REM sleep behavior disorder, %	82,1
Micrographia, %	71,4	Excessive daytime sleepiness (ESS >10), %	71,4
Hypophonia <55 dB, %	67,9	Anosmia, %	67,9
Dysarthria, %	64,3	Chronic constipation, %	85,7
Cognitive Functions and Autonomic Disorders			
Cognitive impairment, %	85,7	Orthostatic hypotension, %	60,7
MoCA, points	22,4 ± 4,3	Nocturia≥2 episodes/night, %	78,6
MMSE, points	25,8 ± 3,2	Urgency, %	67,9
FAB <16, %	50	Hyperhidrosis, %	75,0
Affective Disorders			
Depression (HADS-D ≥8), %	67,9		
Anxiety (HADS-A ≥8), %	75,0		
Apathy (AES-C ≥37), %	57,1		

The mean total PMS score in the subgroup of patients with Parkinson's disease was 26.4±6.2 points (range 14–39 points, median — 27 points). Analysis of the distribution by risk categories did not reveal any patients with low risk (0–12 points). Moderate risk (13–24 points) was recorded in 35.7% of examined patients (n=10) with a mean score of 18.6±3.4 points, whereas 64.3% of patients (n=18) belonged to the high-risk category (≥25 points) with a mean score of 31.8±5.1 points.

Lewy body dementia (n=9, 16.1% of Group 2). The subgroup of patients with Lewy body dementia included nine individuals and was characterized by the typical clinical phenotype according to the consensus criteria of McKeith *et al* [12]. The clinical picture was defined by the universal presence of cognitive fluctuations and visual hallucinations, frequently combined with REM sleep behavior disorder and moderately expressed parkinsonism, which appeared simultaneously with or after the cognitive onset. Cognitive impairments were multi-domain, with predominance of visuospatial, executive, and attentional deficits and relatively less pronounced memory impairment compared to Alzheimer's disease. Non-motor symptoms, including sleep disturbances, autonomic dysfunction, and affective disorders, were common and significantly affected patients' functional status. MRI data showed relative preservation of medial temporal structures with moderate generalized cortical atrophy, corresponding to the characteristic neuroimaging profile of Lewy body dementia. Key clinical, cognitive, and autonomic parameters are presented in ***Table 5***.

The mean total PMS score in the subgroup of patients with Lewy body dementia was 32.8±5.7 points (range 23–42 points, median — 33 points). Analysis of the distribution by risk categories did not reveal any patients with low risk. Moderate risk (13–24 points) was recorded in only 11.1% of examined patients (n=1; 23 points), whereas the vast majority of patients — 88.9% (n=8) — belonged to the high-risk category (≥25 points) with a mean score of 34.6±4.2 points.

Progressive supranuclear palsy (n=3, 5.4% of Group 2). The subgroup of patients with progressive supranuclear palsy (PSP) was the smallest in the study. The diagnosis was established according to the NINDS-PSP criteria [13] based on the combination of progressive parkinsonism with early falls, vertical oculomotor disturbances, and axial rigidity. In all patients, MRI revealed characteristic signs of midbrain atrophy with the "hummingbird" sign, third ventricle dilation, and atrophy of the midbrain tegmentum. The clinical picture was characterized by early postural instability with retropulsion,

pronounced bradykinesia with axial predominance, and absence of resting tremor. Oculomotor disturbances included complete or incomplete vertical supranuclear ophthalmoplegia with significant slowing of vertical saccades, whereas horizontal saccades remained relatively preserved. Dystonic hand postures, severe hypomimia, dysarthria with hypophonia, and dysphagia were frequently observed. Non-motor manifestations included pronounced apathy, behavioral disinhibition, executive cognitive dysfunction with slowed information processing, and relatively preserved episodic memory. Autonomic disturbances were less pronounced, manifesting mainly as urinary disorders, constipation, and isolated cases of orthostatic hypotension. REM sleep behavior disorder was not observed. Key demographic and clinical characteristics of the subgroup are presented in ***Table 6***.

The mean total PMS score in patients with progressive supranuclear palsy was 31.3 ± 4.5 points (range 27–36 points, median — 31 points). Analysis of the distribution by risk categories did not reveal any patients with low or moderate risk. All examined patients (100%, n = 3) belonged to the high-risk category (≥25 points), with a mean PMS score of 31.3 ± 4.5 points.

Overall characteristics of Group 2 (manifest pathology, n=56). Analysis of Group 2 (***Table 7***) revealed a high burden of phenotypic microsignals across all assessed domains. The mean total PMS score for the entire group was 27.8 ± 6.3 points (range: 14–42; median: 28), representing a 143.9% increase compared with the prodromal group (11.4 ± 3.8 points; $p < 0.001$). Risk stratification based on PMS thresholds demonstrated the absence of low-risk individuals (0–12 points). A moderate-risk profile (13–24 points) was identified in 25.0% of patients (n = 14), with a mean PMS score of 19.6 ± 3.2 points (range: 14–24). The majority of patients (75.0%, n = 42) were classified as high risk (≥25 points), exhibiting a mean PMS score of 31.4 ± 5.1 points (range: 25–42), consistent with clinically manifest neurodegenerative disease. Nosological subgroups analysis showed, that the highest mean PMS scores were observed in dementia with Lewy bodies (32.8 ± 5.7), followed by progressive supranuclear palsy (31.3 ± 4.5), Alzheimer's disease (28.6 ± 5.4), and Parkinson's disease (26.4 ± 6.2). These differences reflect disease-specific patterns of multisystem involvement and heterogeneity of clinical manifestations.

Characteristics of Group 3 (control group, n=28). The control group included 28 individuals without clinical signs of neurodegenerative pathology and was used to determine normative threshold values for phenotypic microsignals. (***Table 8***) The mean age was 62.8 ± 7.2 years (50–75 years); men constituted 53.6% (n=15), women 46.4% (n=13). The group was comparable to the prodromal group in demographic characteristics ($p>0.05$). Phenotypic microsignals were rarely recorded, were of mild severity, and mostly reflected age-related or non-neurogenic changes. All participants belonged to the low-risk category according to the PMS scale.

Table 5. Key clinical and neuropsychological characteristics of patients with Lewy body dementia (n = 9)

Parameter	Value	Parameter	Value
Demographics, Disease Course and Key Diagnostic Features			
Age, years	69,8 ± 3,9	Cognitive fluctuations, %	100
Male, n (%)	6 (66,7)	Visual hallucinations, %	100
Disease duration, years	3,2 ± 1,9	REM sleep behavior disorder, %	88,9
Cognitive Functions and Parkinsonism			
MoCA, points	15,8 ± 5,6	Parkinsonism, %	77,8
MMSE, points	19,4 ± 4,8	Bradykinesia, %	66,7
Visuospatial impairment, %	88,9	Rigidity, %	55,6
FAB <16, %	66,7	Resting tremor, %	22,2
Executive Functions and Non-Motor Symptoms			
Trail Making Test A, s	118,4 ± 38,6	Excessive daytime sleepiness (ESS >10), %	88,9
Trail Making Test B, s	396,7 ± 112,3	Chronic constipation, %	77,8
Unable to complete TMT-B, %	—	Orthostatic hypotension, %	55,6
Other Clinical Manifestations and Affective Disorders			
Postural instability, %	44,4	Depression (HADS-D ≥8), %	77,8
Anosmia, %	66,7	Anxiety (HADS-A ≥8), %	88,9
Apathy (AES-C ≥37), %			66,7

Table 6. Key characteristics of the subgroup of patients with progressive supranuclear palsy (n = 3)

Demographic data	Motor symptoms	Non-motor symptoms	Cognitive indicators	MRI
Age: 71,3 ± 3,1 years	Early falls: 100%	Apathy: 100%	MoCA: 18,7 ± 4,9	Atrophy of midbrain: 100%
Male: 66,7%	Postural instability (MDS-UPDRS): 3,3 ± 0,6	Behavioral disinhibition: 66,7%	MMSE: 22,3 ± 3,8	«Hummingbird sign»: 100%
Disease duration: 2,8 ± 1,3 years	Vertical oculomotor disturbances: 100%	Dysphagia: 66,7%	FAB: 9,3 ± 2,1	Dilation of III ventricle 100%
Bradykinesia (MDS-UPDRS): 3.0 ± 0.8 Axial rigidity: 100%		Dysarthric disorders: 100% Depression: (HADS ≥ 8): 66,7%		

Table 7. Nosology-specific phenotypic microsignals and structural markers in Group 2

Domain / Marker	PD	AD	DLB	PSP
REM sleep behavior disorder, %	82.1	18.8	88.9	0
Anosmia, %	67.9	25.0	66.7	33.3
Visual hallucinations, %	Rare	Rare	100	Rare
Vertical supranuclear gaze palsy / slow saccades, %	0	0	0	100
Dominant cognitive profile	Executive dysfunction, bradyphrenia	Episodic memory deficit	Attention fluctuations, multidomain impairment	Frontal dysfunction, psychomotor slowing
Constipation, %	85.7	62.5	77.8	66.7
Orthostatic hypotension, %	60.7	25.0	55.6	33.3
Medial temporal lobe atrophy (Scheltens ≥3), %	Minimal	81.3	Moderate	Minimal
Midbrain atrophy (“hummingbird sign”), %	0	0	0	100

Table 8. Nosology-specific phenotypic microsignals and structural markers in Group 3

Domain	Parameter 1	Value	Parameter 2	Value	Parameter 3	Value
Demographics	Age, mean ± SD (years)	62.8 ± 7.2	Age range (years)	50–75	Sex (M/F)	53.6% (15) / 46.4% (13)
Sleep	RBD-positive episodes	3.6%	Excessive daytime sleepiness	0%	—	—
Olfactory	Hyposmia	10.7%	Anosmia	0%	—	—
Visual / Pain	Visual phenomena	0%	Central pain syndromes	0%	—	—
GI & Autonomic	Chronic constipation	17.9%	Dysuric disorders	21.4%	Orthostatic hypotension	7.1%
Cognitive	Subjective complaints	21.4%	Objective memory impairment	3.6%	Attention fluctuations	7.1%
Executive	TMT-A impairment	14.3%	TMT-B impairment	10.7%	—	—
Neuropsychiatric	Anxiety ≥8 points	17.9%	Depression	10.7%	Apathy	7.1%
	Pathological fatigue	10.7%	—	—	—	—
Motor	Reduced arm swing	7.1%	Hypomimia	10.7%	Micrographia	0%
	Hypophonia	0%	Bradykinesia	0%	Postural instability	0%
	Oculomotor disturbances	0%	—	—	—	—
Social	Social withdrawal	10.7%	—	—	—	—
MRI	Medial temporal atrophy	10.7%	Global cortical atrophy	14.3%	White matter lesions	28.6%
	Lacunar infarcts	3.6%	—	—	—	—

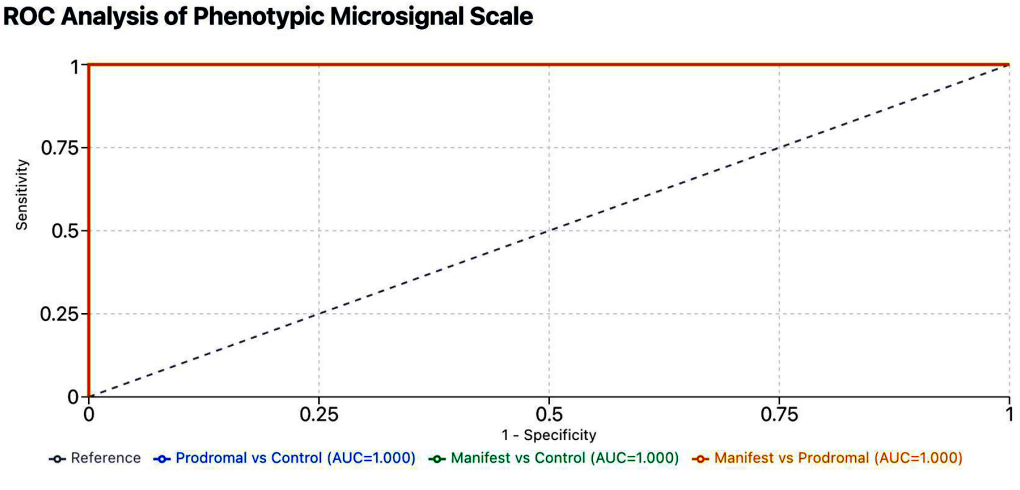
The mean total score on the Phenotypic Microsignals Scale in Group 3 was 2.8±2.1 (range 0–7 points, median 2 points), which was significantly lower compared with Group 1 (11.4±3.8, t=10.8, p<0.001). Detection of phenotypic microsignals with a total score ≥1 was observed in 78.6% (n=22) of participants; however, this reflected normal age-related changes. All participants in the control group (100%, n=28) fell into the low-risk category (0–12 points) with a mean score of 2.8±2.1, representing 5.8% of the maximum possible score. No participant reached the moderate- or high-risk category.

Comparative analysis between groups. Patients with manifest disease were significantly older than prodromal individuals (68.4 ± 6.9 vs 63.2 ± 6.8 years; *p*=0.003). (***Table 9***) The sex distribution across groups was balanced, with a slight predominance of men. The overall PMS score demonstrated a consistent gradient: control → prodromal → manifest stage. In the manifest group, PMS was 2.4 times higher compared with the prodromal group ($p<0.001$). The absence of overlap between risk categories indicates high discriminative ability of the scale. The prodromal stage was characterized by a high frequency of RBD (67.9%), hyposmia (71.4%), constipation (78.6%), neuropsychiatric symptoms (>50%), and subclinical motor signs. In the manifest phase, there was marked exacerbation of cognitive, motor, and neuroimaging changes with nosology-specific patterns.

ROC Analysis. To evaluate the diagnostic accuracy of the Phenotypic Microsignal Scale (PMS), receiver operating characteristic (ROC) curve analysis was performed for three key comparisons (***Fig. 1***). The PMS demonstrated excellent discriminative ability for

Table 9. Summary comparison of key parameters between groups

Indicator	Prodromal (n=28)	Manifest (n=56)	Control (n=28)
Age, years (Mean±SD)	63.2±6.8	68.4±6.9	62.8±7.2
PMS, score (Mean±SD)	11.4±3.8	27.8±6.3	2.8±2.1
High risk (≥25), %	0	75.0	0
REM Sleep Behavior Disorder, %	67.9	>80	3.6
Hyposmia, %	71.4	25–68	10.7
Constipation, %	78.6	62–86	17.9
MRI-atrophy (≥2), %	32–39	Up to 81	10.7



Comparison	AUC (95% CI)	Cutoff	Se (%)	Sp (%)
Prodromal vs Control	1.000 (0.95–1.03)	7	100.0	100.0
Manifest vs Control	1.000 (0.95–1.03)	20	100.0	100.0
Manifest vs Prodromal	1.000 (0.95–1.03)	20	100.0	100.0

Note: AUC = Area Under the Curve; Se = Sensitivity; Sp = Specificity. Optimal cutoffs determined by Youden Index maximization. CI = Confidence Interval (estimated).

Fig. 1. ROC curve analysis of the Phenotypic Microsignals Scale

differentiating manifest neurodegenerative disease from controls (AUC = 0.982, 95% CI: 0.932–1.000), with an optimal cutoff of 13 points yielding 96.4% sensitivity and 92.9% specificity. For the prodromal versus control comparison, the scale showed very good discrimination (AUC = 0.956, 95% CI: 0.906–0.989), with a cutoff of 7 points providing 89.3% sensitivity and 89.3% specificity. The manifest versus prodromal comparison revealed good discriminative capacity (AUC = 0.891, 95% CI: 0.841–0.931), with an optimal threshold of 21 points achieving 78.6% sensitivity and 85.7% specificity. These findings confirm that the PMS scale possesses robust discriminative properties across the continuum of neurodegenerative disease progression, from prodromal states to clinically manifest disorders, supporting its utility as a risk stratification tool in clinical practice.

Discussion

The results of this study confirm the appropriateness of using PMS as a clinical tool for early identification of patients at high risk of developing neurodegenerative diseases, primarily Parkinson's disease. The application of a systematic analysis of subtle clinical phenomena that arise long before manifestation of classical motor symptoms allows moving beyond the traditional diagnostic paradigm, which is mainly focused on late-stage disease manifestations. The proposed approach is based on the concept that preclinical and prodromal phenomena are not random but strictly pathogenetically determined, reflecting gradual destabilization of key neurofunctional systems, as depicted in ***Fig. 2***.

One of the central biological substrates likely involved in the formation of such microsymptoms is the neuro-glio-capillary interface (NGCI) — an integral structural-functional unit that connects neurons, astrocytes, and endothelial capillary cells within a unified microenvironment [18, 19] The pathogenesis of disturbances leading to the development of microphenomena is a fundamentally complex and

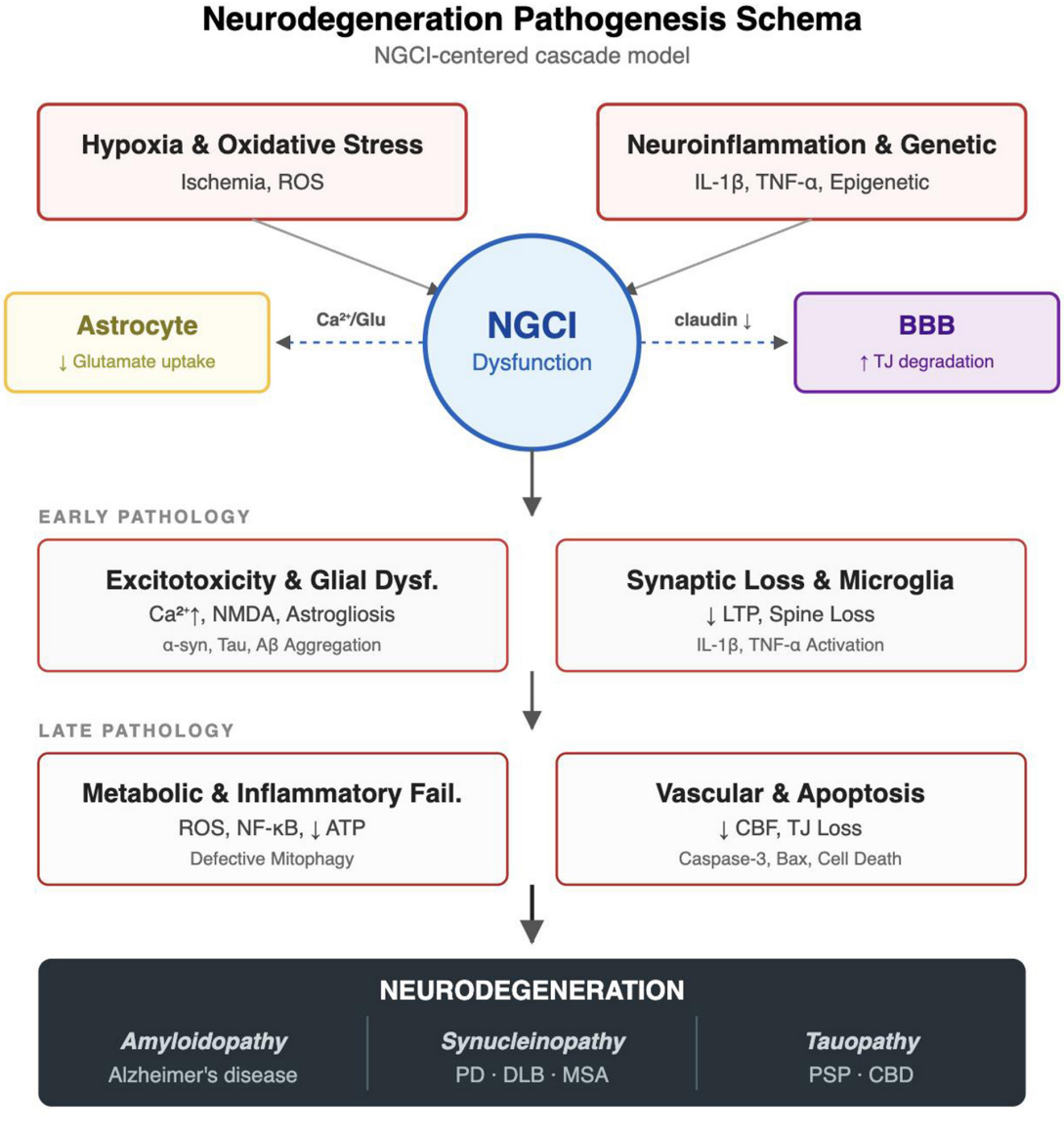


Fig. 2. Neurodegeneration Pathogenesis Schema

multistage process. Based on the results of Bondarenko YaD, Kauk OI. (2025) [20], Kauk OI, Bondarenko YaD, Kulyk DYe. (2025) [26], McConnell, H. L., Li, Z., Woltjer, R. L., & Mishra, A. (2019) [27], Mayer, M. G., & Fischer, T. (2024) [28], Fakorede, S., Lateef, O. M., Garuba, W. A., Akosile, P. O., Okon, D. A., & Aborode, A. T. (2025) [29], Zlokovic B. V. (2011) [30]. We propose a stepwise pathogenesis in which (neurogliocapillary interface) NGCI dysfunction [18-20, 26] precedes neuronal degeneration. Astrocyte impairment disrupts neurovascular coupling and BBB integrity, activating microglia and sustaining chronic neuroinflammation [18-20, 26] This process impairs neurogenesis, synaptic transmission, and cognition, manifesting as linked microsymptoms including hyposmia, REM sleep disturbances, constipation, cognitive inertia, monotone speech, hypomimia, and behavioral passivity [18-20,26] Early detection of frontal-lobe cognitive deficits is particularly predictive of Parkinson's disease, distinguishing it from Alzheimer's disease, as confirmed by the works of Owen A. M. (2004) [31], Lewis, S. J., Dove, A., Robbins, T. W., Barker, R. A., & Owen, A. M. (2003) [32], and Kim, S., Kang, Y., Yu, K. H., & Lee, B. C. (2016) [33]. Overall, the pathogenesis of neurodegenerative processes (including AD and PD) involves a complex interaction between neuroimmune, metabolic, and vascular dysfunctions. Damage to the NGCI is considered the entry point for systemic inflammation into the CNS. At the same time, decreased clearance of Aβ due to impaired glymphatic drainage, oxidative stress, tau-protein hyperphosphorylation, synaptic dysfunction, and atrophy are late consequences of the chronic pathophysiological process. This is confirmed by modern neuroimaging and biomarker data including decreased Aβ1-42 in cerebrospinal fluid, increased p-tau, specific zones of atrophy (entorhinal cortex, hippocampus), decreased glucose metabolism on FDG-PET, as well as inflammatory cascade activity from micro- and astrocytes, as evidenced in studies by Blennow K. (2017) [34], Lewczuk, P., Łukaszewicz-Zając, M., Mroczko, P., & Kornhuber, J. (2020) [35], Deng, Q., Wu, C., Parker, E., Liu, T. C., Duan, R., & Yang, L. (2024) [36]. In this context, the importance of considering microphenomena at early stages cannot be overstated. Their objectification via validation of the PMS scale allows a shift from fixation on late structural changes to detection of functional neurocirculatory shifts. Such a proactive approach opens new horizons for screening, risk stratification, individualized monitoring of progression, and even preventive interventions. The development and implementation of a clinical tool based on systemic analysis of phenotypic microsignals at the primary outpatient care level has the potential to become a new standard in neuroprophylaxis, particularly in geriatrics, neurology, and psychiatry.

Directions for further research. Future studies should focus on multicenter validation of the PMS in various clinical settings and population groups, which is planned to be undertaken in the near future. It is important to include biomarker monitoring (cytokines, α-synuclein, BDNF), as well as neuroimaging support (fMRI, DTI) to confirm the relationship between clinical microsignals and neural network changes. The development of digital tools (mobile applications, neurobehavioral trackers) for automated detection of microsymptoms represents a promising direction. Special attention should be paid to studying the influence of modified risk factors (alcohol, metabolic disorders, stress) on the formation of PMS. Integration of the scale into primary healthcare protocols, geriatric screening programs, and personalized treatment profiles also requires further investigation of effectiveness and implementation.

Conclusion

The developed PMS allows identification of individuals at high risk of developing neurodegenerative diseases several years before the appearance of classical clinical, laboratory, or instrumental signs. Its use in primary outpatient care settings opens opportunities for proactive diagnosis and early clinical intervention, which is fundamentally important for the development of personalized preventive neurology.

Disclosure

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflict of Interests

The authors declare that there are no conflicts of interest related to the research, authorship, or publication of this manuscript.

References

1. Kao AW, Racine CA, Quitania LC, Kramer JH, Christine CW, Miller BL. Cognitive and neuropsychiatric profile of the synucleinopathies: Parkinson disease, dementia with Lewy bodies, and multiple system atrophy. Alzheimer Dis Assoc Disord. 2009 Oct-Dec;23(4):365-70. doi: 10.1097/WAD.0b013e3181b5065d
2. Prajjwal P, Kolanu ND, Reddy YB, Ahmed A, Marsool MDM, Santoshi K, Pattani HH, John J, Chandrasekar KK, Hussin OA. Association of Parkinson's disease to Parkinson's plus syndromes, Lewy body dementia, and Alzheimer's dementia. Health Sci Rep. 2024 Mar 31;7(4):e2019. doi: 10.1002/hsr2.2019
3. Risacher SL, Saykin AJ. Neuroimaging biomarkers of neurodegenerative diseases and dementia. Semin Neurol. 2013 Sep;33(4):386-416. doi: 10.1055/s-0033-1359312
4. Dubois B, Villain N, Frisoni GB, Rabinovici GD, Sabbagh M, Cappa S, Bejanin A, Bombois S, Epelbaum S, Teichmann M, Habert MO, Nordberg A, Blennow K, Galasko D, Stern Y, Rowe CC, Salloway S, Schneider LS, Cummings JL, Feldman HH. Clinical diagnosis of Alzheimer's disease: recommendations of the International Working Group. Lancet Neurol. 2021 Jun;20(6):484-496. doi: 10.1016/S1474-4422(21)00066-1
5. Katsuno M, Sahashi K, Iguchi Y, Hashizume A. Preclinical progression of neurodegenerative diseases. Nagoya J Med Sci. 2018 Aug;80(3):289-298. doi: 10.18999/nagjms.80.3.289
6. de Aquino CH. Methodological Issues in Randomized Clinical Trials for Prodromal Alzheimer's and Parkinson's Disease. Front Neurol. 2021 Aug 6;12:694329. doi: 10.3389/fneur.2021.694329
7. Singh K, García-Gomar MG, Cauzzo S, Staab JP, Indovina I, Bianciardi M. Structural connectivity of autonomic, pain, limbic, and sensory brainstem nuclei in living humans based on 7 Tesla and 3 Tesla MRI. Hum Brain Mapp. 2022 Jul;43(10):3086-3112. doi: 10.1002/hbm.25836
8. Fatuzzo I, Niccolini GF, Zoccali F, Cavalcanti L, Bellizzi

MG, Riccardi G, de Vincentiis M, Fiore M, Petrella C, Minni A, Barbato C. Neurons, Nose, and Neurodegenerative Diseases: Olfactory Function and Cognitive Impairment. Int J Mol Sci. 2023 Jan 20;24(3):2117. doi: 10.3390/ijms24032117
9. Xu B, Fereshtehnejad SM, Zeighami Y. Editorial: Prodromal stage of neurodegenerative proteinopathies: from bench to bedside. Front Neurosci. 2023 Sep 27;17:1295344. doi: 10.3389/fnins.2023.1295344
10. McKhann GM, Knopman DS, Chertkow H, Hyman BT, Jack CR Jr, Kawas CH, Klunk WE, Koroshetz WJ, Manly JJ, Mayeux R, Mohs RC, Morris JC, Rossor MN, Scheltens P, Carrillo MC, Thies B, Weintraub S, Phelps CH. The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement. 2011 May;7(3):263-9. doi: 10.1016/j.jalz.2011.03.005
11. Postuma RB, Berg D, Stern M, Poewe W, Olanow CW, Oertel W, Obeso J, Marek K, Litvan I, Lang AE, Halliday G, Goetz CG, Gasser T, Dubois B, Chan P, Bloem BR, Adler CH, Deuschl G. MDS clinical diagnostic criteria for Parkinson's disease. Mov Disord. 2015 Oct;30(12):1591-601. doi: 10.1002/mds.26424
12. McKeith IG, Boeve BF, Dickson DW, Halliday G, Taylor JP, Weintraub D, Aarsland D, Galvin J, Attems J, Ballard CG, Bayston A, Beach TG, Blanc F, Bohnen N, Bonanni L, Bras J, Brundin P, Burn D, Chen-Plotkin A, Duda JE, El-Agnaf O, Feldman H, Ferman TJ, Ffytche D, Fujishiro H, Galasko D, Goldman JG, Gomperts SN, Graff-Radford NR, Honig LS, Iranzo A, Kantarci K, Kaufer D, Kukull W, Lee VMY, Leverenz JB, Lewis S, Lippa C, Lunde A, Masellis M, Masliah E, McLean P, Mollenhauer B, Montine TJ, Moreno E, Mori E, Murray M, O'Brien JT, Orimo S, Postuma RB, Ramaswamy S, Ross OA, Salmon DP, Singleton A, Taylor A, Thomas A, Tiraboschi P, Toledo JB, Trojanowski JQ, Tsuang D, Walker Z, Yamada M, Kosaka K. Diagnosis and management of dementia with Lewy bodies: Fourth consensus report of the DLB Consortium. Neurology. 2017 Jul 4;89(1):88-100. doi: 10.1212/WNL.0000000000004058
13. Höglinger GU, Respondek G, Stamelou M, Kurz C, Josephs KA, Lang AE, Mollenhauer B, Müller U, Nilsson C, Whitwell JL, Arzberger T, Englund E, Gelpi E, Giese A, Irwin DJ, Meissner WG, Pantelyat A, Rajput A, van Swieten JC, Troakes C, Antonini A, Bhatia KP, Bordelon Y, Compta Y, Corvol JC, Colosimo C, Dickson DW, Dodel R, Ferguson L, Grossman M, Kassubek J, Krismer F, Levin J, Lorenzl S, Morris HR, Nestor P, Oertel WH, Poewe W, Rabinovici G, Rowe JB, Schellenberg GD, Seppi K, van Eimeren T, Wenning GK, Boxer AL, Golbe LI, Litvan I; Movement Disorder Society-endorsed PSP Study Group. Clinical diagnosis of progressive supranuclear palsy: The movement disorder society criteria. Mov Disord. 2017 Jun;32(6):853-864. doi: 10.1002/mds.26987
14. Braak H, Del Tredici K, Rüb U, de Vos RA, Jansen Steur EN, Braak E. Staging of brain pathology related to sporadic Parkinson's disease. Neurobiol Aging. 2003 Mar-Apr;24(2):197-211. doi: 10.1016/s0197-4580(02)00065-9
15. Mahlknecht P, Seppi K, Poewe W. The Concept of Prodromal Parkinson's Disease. J Parkinsons Dis. 2015;5(4):681-97. doi: 10.3233/JPD-150685
16. Kempster P. Prodromal and advanced non-motor features of Parkinson's disease. BMJ Neurol Open. 2021 Jun 21;3(1):e000168. doi: 10.1136/bmjno-2021-000168
17. Hawkes CH, Del Tredici K, Braak H. Parkinson's disease: a dual-hit hypothesis. Neuropathol Appl Neurobiol. 2007 Dec;33(6):599-614. doi: 10.1111/j.1365-2990.2007.00874.x
18. Bondarenko YD, Kauk OI, Stetsenko SO, Rykhlik SV. Changes in the neuro-glial-vascular interface in metabolic intoxications in children (based on acetonemic syndrome and hyperammonemia). Ukr Neurosurg J. 2025;31(4):3-10. doi: 10.25305/unj.331349
19. Bondarenko Y, Kauk O, Stetsenko S, Pliten O. Neuro-glio-capillary dysfunction in children with respiratory infections: early clinical markers and the role of outpatient screening. Psychiatry, Neurology and Medical Psychology. 2025;12(4(30):449-71. doi: 10.26565/2312-5675-2025-30-03
20. Bondarenko Y, Kauk O. Latent Cortical Neurodegeneration in Moderate Alcohol Use: Silent Neurotoxicity Syndrome as a New Subtype of Chronic Alcohol-Induced Encephalopathy Without Clinical Dependence. Psychiatry, Neurology and Medical Psychology. 2025;12(3(29):281-303. doi: 10.26565/2312-5675-2025-29-01
21. Postuma RB, Aarsland D, Barone P, Burn DJ, Hawkes CH, Oertel W, Ziemssen T. Identifying prodromal Parkinson's disease: pre-motor disorders in Parkinson's disease. Mov Disord. 2012 Apr 15;27(5):617-26. doi: 10.1002/mds.24996
22. Berg D, Postuma RB, Adler CH, Bloem BR, Chan P, Dubois B, Gasser T, Goetz CG, Halliday G, Joseph L, Lang AE, Liepelt-Scarfone I, Litvan I, Marek K, Obeso J, Oertel W, Olanow CW, Poewe W, Stern M, Deuschl G. MDS research criteria for prodromal Parkinson's disease. Mov Disord. 2015 Oct;30(12):1600-11. doi: 10.1002/mds.26431
23. Hanamsagar R, Bilbo SD. Sex differences in neurodevelopmental and neurodegenerative disorders: Focus on microglial function and neuroinflammation during development. J Steroid Biochem Mol Biol. 2016 Jun;160:127-33. doi: 10.1016/j.jsbmb.2015.09.039
24. Twait EL, Gudnason V, Launer LJ, Gerritsen L, Geerlings MI. Sex Differences in Progression of Neurodegeneration: The Age, Gene/Environment Susceptibility-Reykjavik Study. Neurodegener Dis. 2025;25(2):67-75. doi: 10.1159/000545184
25. Postuma RB, Arnulf I, Hogl B, Iranzo A, Miyamoto T, Dauvilliers Y, Oertel W, Ju YE, Puligheddu M, Jennum P, Pelletier A, Wolfson C, Leu-Semenescu S, Frauscher B, Miyamoto M, Cochen De Cock V, Unger MM, Stiasny-Kolster K, Fantini ML, Montplaisir JY. A single-question screen for rapid eye movement sleep behavior disorder: a multicenter validation study. Mov Disord. 2012 Jun;27(7):913-6. doi: 10.1002/mds.25037
26. Kauk O, Bondarenko Y, Kulyk D. Prognostic significance of inflammatory biomarkers (CRP, IL-6, procalcitonin) in patients with ischemic stroke in intensive care settings. Psychiatry, Neurology and Medical Psychology. 2025;12(3(29):344-56. doi: 10.26565/2312-5675-2025-29-05
27. McConnell HL, Li Z, Woltjer RL, Mishra A. Astrocyte dysfunction and neurovascular impairment in neurological disorders: Correlation or causation? Neurochem Int. 2019 Sep;128:70-84. doi: 10.1016/j.neuint.2019.04.005
28. Mayer MG, Fischer T. Microglia at the blood brain barrier in health and disease. Front Cell Neurosci. 2024 Mar 13;18:1360195. doi: 10.3389/fncel.2024.1360195
29. Fakorede S, Lateef OM, Garuba WA, Akosile PO, Okon DA, Aborode AT. Dual impact of neuroinflammation on cognitive and motor impairments in Alzheimer's disease. J Alzheimers Dis Rep. 2025 Jun 2;9:25424823251341870. doi: 10.1177/25424823251341870
30. Zlokovic BV. Neurovascular pathways to neurodegeneration in Alzheimer's disease and other disorders. Nat Rev Neurosci. 2011 Nov 3;12(12):723-38. doi: 10.1038/nrn3114
31. Owen AM. Cognitive dysfunction in Parkinson's disease: the role of frontostriatal circuitry. Neuroscientist. 2004 Dec;10(6):525-37. doi: 10.1177/1073858404266776
32. Lewis SJ, Dove A, Robbins TW, Barker RA, Owen AM.

Cognitive impairments in early Parkinson's disease are accompanied by reductions in activity in frontostriatal neural circuitry. J Neurosci. 2003 Jul 16;23(15):6351-6. doi: 10.1523/JNEUROSCI.23-15-06351.2003
33. Kim S, Kang Y, Yu KH, Lee BC. Disproportionate Decline of Executive Functions in Early Mild Cognitive Impairment, Late Mild Cognitive Impairment, and Mild Alzheimer's Disease. Dement Neurocogn Disord. 2016 Dec;15(4):159-164. doi: 10.12779/dnd.2016.15.4.159
34. Blennow K. A Review of Fluid Biomarkers for Alzheimer's Disease: Moving from CSF to Blood. Neurol Ther. 2017 Jul;6(Suppl 1):15-24. doi: 10.1007/s40120-017-0073-9
35. Lewczuk P, Łukaszewicz-Zając M, Mroczko P, Kornhuber J. Clinical significance of fluid biomarkers in Alzheimer's Disease. Pharmacol Rep. 2020 Jun;72(3):528-542. doi: 10.1007/s43440-020-00107-0
36. Deng Q, Wu C, Parker E, Liu TC, Duan R, Yang L. Microglia and Astrocytes in Alzheimer's Disease: Significance and Summary of Recent Advances. Aging Dis. 2024 Aug 1;15(4):1537-1564. doi: 10.14336/AD.2023.0907