THE NEW ARMENIAN MEDICAL JOURNAL
Volume19 (2025), Issue 3 p.4-16

DOI: https://doi.org/10.56936/18290825-3.19v.2025-4

THE ROLE OF ALIPHATIC POLYAMINES AND α-SYNUCLEIN IN THE FORMATION OF PERIPHERAL MECHANISMS INVOLVED IN THE PARKINSON'S DISEASE INDUCTION

Avagyan A.S.[1*], Muradyan A.A.[2], Makletsova M.G.[3], Poleshchuk V.V.[4], Zilfyan A.V.[1]

[1] Scientific Research Center, Yerevan State Medical University after M. Heratsi, Yerevan, Armenia
[2] Department of Urology and Andrology, Yerevan State Medical Universit, Yerevan, Armenia
[3] Department of Biology and General Pathology, Don State Technical University, Rostov-on-Don, Russia
[4] Laboratory of Neurochemistry, Scientific center of neurology and neuroscience, Moscow, Russia

Received 11.08.2024; Accepted for printing 15.05.2025

Abstract

Currently, aspects of the pathogenesis of Parkinson's disease associated with a disorder of aliphatic polyamine metabolism not only in neurons and gliocytes of the brain, but also in parenchymatous and stromal cells of peripheral internal organs are being widely developed.

In the development of the pathological process according to the "brain-first" subtype, the leading role in Parkinson's disease should be given to central mechanisms, in which aliphatic polyamines produced in the central nervous system directly participate in the induction of neurodegenerative disorders. Enhanced synthesis of aliphatic polyamines in dopaminergic neurons is accompanied by aggregation and fibrillation of α-synuclein in situ, which participates in the formation of Lewy bodies. A similar polyamine-dependent mechanism of α-synuclein aggregation at the level of neurons and glial cells of the brain has long been considered established.

When the pathological process unfolds according to the "body-first" subtype, peripheral mechanisms are more interested in the pathogenesis of Parkinson's disease, in which, in our opinion, an important role is given to the increased synthesis of aliphatic polyamines in a number of peripheral organs, primarily in their peripheral nerve endings. In the same nerve structures, aggregation of α-synuclein occurs, which retrogrades through the blood-brain barrier, causing a symptom complex in dopaminergic neurons that is pathognomonic for Parkinson's disease.

Our own studies on the determination of aliphatic polyamines in the blood plasma of patients suffering from Parkinson's disease were carried out by us taking into account the clinical characteristics of the degrees of disability and gradation by stage. Thus, it was found that the highest levels of all three polyamines were observed at the first stage of disability. A sharp decrease in the level of all three polyamines occurred at the fourth stage. In our opinion, the levels of polyamines in the peripheral blood quite adequately reflect the processes of formation of peripheral mechanisms interested in the induction of Parkinson's disease, especially in the early stages of the disease.

Keywords: *Parkinson's disease, pathogenesis, brain-first, body-first, α-synucleins, aliphatic polyamines.*

Cite This Article as:

Avagyan A.S., Muradyan A.A., Makletsova M.G., Poleshchuk B.B., Zilfyan A.V. (2025). The role of aliphatic polyamines and α-synuclein in the formation of peripheral mechanisms involved in the Parkinson's disease induction; The New Armenian Medical Journal, vol.19 (3), 4-16; https://doi.org/10.56936/18290825-3.19v.2025-4

Address for Correspondence:

Stepan A. Avagyan
Scientific Research Center
Yerevan State Medical University
2 Koryun Street, Yerevan 0025, Armenia
Tel.: (+374 93) 58-91-79
E-mail: namj.ysmu@gmail.com

OFFICIAL PUBLICATION OF THE YEREVAN STATE MEDICAL UNIVERSITY

Introduction

In recent years, the level of alpha-synuclein in body fluids and tissues has been investigated by several researchers as an informative diagnostic and prognostic marker of Parkinson's disease severity.

However, a comparison of literature sources in this area reveals that different authors have obtained diametrically opposite results, regardless of the type of biological samples used to determine alpha-synuclein levels [*Foulds P. et al., 2013*].

Highly inconclusive results were obtained by several authors [*Foulds et al., 2013; Koehler N et al., 2015; Chang C-W et al., 2020*] when assessing plasma alpha-synuclein levels, taking into account different motor subtypes and the potential relationship between alpha-synuclein concentration and the severity of motor symptoms.

GBA-associated Parkinson's disease is associated with mutations in the GBA gene, which encodes the enzyme glucocerebrosidase (GCase). Based on clinical and genetic studies conducted in patients with Parkinson's disease (58 individuals with a sequenced GBA gene, compared with 38 healthy volunteers), the authors conclude that the level of alpha-synuclein in blood plasma is not an informative marker of the disease [*Malec-Litwinowicz M. et al., 2018*]. Similar conclusions have been reached by other researchers studying the pathogenesis of Parkinson's disease, who argue that neither plasma-derived alpha-synuclein nor alpha-synuclein detected in cerebrospinal fluid serve as reliable biomarkers of the disease [*Park M. et al., 2011; Kasuga K. et al., 2012; Malek N. et al., 2014*]. At the same time, the authors note that alpha-synuclein in the tissues of the enteric and peripheral nervous systems may serve as a "surrogate" marker of brain synucleinopathies.

In addition to the topographic characteristics of alpha-synuclein localization, considerable attention in Parkinson's disease and other synucleinopathies should be given to identifying its structural features, such as truncation, phosphorylation, and aggregation, accompanied by the formation of oligomeric structures [*Kasuga K et al., 2012*]. This view is also supported by *Pchelina S. (2011)*. It still remains to be determined which alpha-synuclein aggregates possess neurotoxic properties. In this particular context, the focus is on "modified" forms of alpha-synuclein in the blood, with identification of its oligomeric species associated with aggregation and fibrillation [Vrijsen S, et al.,].

Somewhat optimistic (in our opinion) is the conclusion that the concentrations of alpha-synuclein in biological fluids, tissues and biopsies, with the aim of their correction in BP, allow us to assume the presence of alpha-synuclein as an early diagnostic biomarker [*Atik A. et al., 2016*].

There is evidence indicating that patients with Parkinson's disease exhibit higher levels of alpha-synuclein in plasma and serum compared to the control group, i.e., healthy individuals. Particularly, a significant correlation has been observed between alpha-synuclein levels and disease stage in patients at Hoehn and Yahr stages 1–3 ($r = 0.40$, $p = 0.025$), which suggests that serum alpha-synuclein levels are "moderately" correlated with the severity of motor symptoms in patients at the early stages of the disease [*Chang C-W et al., 2020*].

In the study by *Malec-Litwinowicz M. et al. (2018)*, encouraging results were obtained for alpha-synuclein level determination at various stages of both progressive and non-progressive forms of Parkinson's disease, supporting its consideration as a potential diagnostic marker. The protein concentration was determined using the enzyme-linked immunosorbent assay (ELISA) method, following the product protocol for the Human α-Synuclein ELISA Kit (Catalog No. KHB0061, 96 tests; Invitrogen, Thermo Fisher Scientific).

Accordingly, we considered it appropriate to present the relevant data from the cited study in the form of an informative table 1 for the readers' consideration [*Malec-Litwinowicz M, et al., 2018*].

Parkinson's disease is one of the most common neurodegenerative chronic systemic multifactorial diseases.

Table 1.

The comparison of plasma alfa-synucleine level at different stages of the Parkinson disease

Groups of the Parkinson disease	Median (ng/ml)	plasma ASN (ng/ml)		Mean (ng/ml)	SD
		Lower quartile	Upper quartile		
Non-advanced	4.69	3.05	6.56	4.93	2.35
Advance	3.13	2.20	5.41	3.65	1.70
Control group	3.73	2.75	4.86	3.90	1.56

Notes: ASN – alpha-synuclein, SD – Standard Deviation, PD - Parkinson's disease.

OFFICIAL PUBLICATION OF THE YEREVAN STATE MEDICAL UNIVERSITY

It affects more than six million people worldwide, with the disease being most pronounced in individuals over the age of sixty. However, the initial symptoms of Parkinson's disease can emerge much earlier, following the degeneration of 50-60% of dopaminergic neurons located in the substantia nigra and corpus striatum. The symptoms become particularly evident at the relatively late stages of the pathological process, when 70-80% of dopaminergic neurons are affected [*Ehringer H, Hornykiewicz O, 1960; Bernheimer H et al., 1973; Albin P et al., 1998; Maruyama W et al., 2001; Reader T et al., 2001; Lev N et al., 2003; Khaindrava V et al., 2010*].

The clinical manifestations of Parkinson's disease include bradykinesia, muscle rigidity, gait disturbances, movement insufficiency and limitations, and akinesia [*Fahn S, 2003*].

There is some uncertainty regarding the Parkinson's disease staging, as it is often associated with the scales used by neurologists to assess the severity and characteristics of the disease. In this regard, a review article by several leading Russian researchers [*Katunina E et al., 2023 a, b*] provides valuable data. The authors present analytical information on the potential central and peripheral mechanisms of Parkinson's disease development, taking into account the Unified Parkinson's Disease Rating Scale system.

Currently, several scales are being considered to determine topical and clinical criteria that are pathognomonic for Parkinson's disease, with the aim of finding out the potential mechanisms underlying the induction of neurodegenerative disorders of the central nervous system in case of this disease [*Perlmutter J et al., 2009*]. Two scales are particularly informative: the Webster scale from Columbia University and the Schwab and England and Northwestern University disability scale. A combined approach using both scales, based on the combination of their clinical and cognitive features, is also being tested, such as the UPDRS and the New York University scale. However, the UPDRS scale has gained the greatest recognition, as it attempts to characterize the disease based on both its earliest and latest manifestations, incorporating instrumental diagnostic tools and clinical and morphological findings underlying neurodegenerative disorders in the central nervous system [*Martínez-Martín P et al., 1994; van Hilten et al., 1994; Goetz G et al., 2004; 2007; 2020*]. Thus, the UPDRS scale consists of four subscales. Subscale 1 focuses on thinking, behavior, and mood. Notably, even at an early stage of the disease, Lewy bodies begin to be detected in the olfactory bulbs and lower parts of the brainstem [*Braak H et al., 2003; Pinter B et al., 2015*].

Clinically, this is manifested by olfactory dysfunction and dyspeptic disorders of the gastrointestinal tract.

Subscale 2 addresses thinking, behavior, and mood. The pathological process extends to the overlying structures of the brainstem, leading to behavioral disorders during the sleep phase, with rapid eye movement, as well as anxiety-depressive disorders and cognitive dysfunction.

Subscale 3 includes criteria that assess clinical manifestations pathognomonic for Parkinson's disease. The substantia nigra and corpus striatum become involved in the neurodegenerative process, resulting in the development of motor symptoms such as bradykinesia, tremor, and muscle rigidity [*Katunina E et al., 2023*].

Subscale 4 reflects the spread of neurodegenerative disorders to other parts of the brain, including the limbic system and cortex, which results in a broader range of neurological manifestations. This subscale also includes the symptom complex related to therapeutic complications associated with Parkinson's disease.

It should be especially noted that the indices of subscales 1, 2, and 4 are, to some extent, preclinical in nature, as they are based on reports from patients and caregivers. In contrast, the indices in subscale 3 are based on clinical and laboratory studies that specifically characterize the symptoms of Parkinson's disease [*Perlmutter J, 2009*]. The indices in subscales 1, 2, and 4 are also partly subjective, as they cannot be considered obligatory stages in the progressive development of the disease, which ultimately leads to the formation of symptoms characteristic of Parkinson's disease –the occurrence of neurodegenerative disorders in certain brain regions. This mainly refers to the formation of Lewy bodies, containing aggregated α-synuclein, and an elevated level of aliphatic polyamines in synapse formations localized in the dopaminergic neurons of the substantia nigra and corpus striatum.

OFFICIAL PUBLICATION OF THE YEREVAN STATE MEDICAL UNIVERSITY

While studying the progressive pathological process associated with the step-by-step development of Parkinson's disease, the most acceptable approach, in our opinion, is the clinical assessment of the disease by the degrees of disability in patients, as proposed 58 years ago [*Hoehn M, Yahr M, 1967*]. The authors outline five stages based on the principle of clinical disability:

Stage I: Patients experience unilateral damage with minimal functional disorders.

Stage II: Patients show bilateral or median damage, without balance or coordination disorders.

Stage III: The first sign of impaired righting reflexes (unsteadiness when turning or when pushed from a standing position with the legs pressed together and the eyes closed) is noted in patients. Disability at this stage is mild to moderate.

Stage IV: The disease has progressed to a severe disabling stage. The patient is incapacitated but can still walk and stand without assistance.

Stage V: Patients are confined to a bed or wheelchair.

According to *Stockholm M et al., and Lionnet A et al.*, Parkinson's disease may involve two subtypes based on the mechanisms underlying the pathological process in the neurons of the brain. These subtypes can be conditionally classified as central and peripheral, with corresponding designations: brain-first and body-first [*Stockholm M et al., 2016, Lionnet A, et al., 2018*].

The central mechanism involved in the onset of neurodegenerative disorders in Parkinson's disease (brain-first subtype) has been studied relatively well.

Thus, neurodegenerative disorders localized primarily in the substantia nigra and corpus striatum, both in familial and sporadic forms of Parkinson's disease, are progressive. This progression is marked by the accumulation of aggregated forms of α-synuclein in dopaminergic neurons, which leads to the death of large groups of neurons [*Polymeropoulos M et al., 1997; Kruger R et al., 1998; Singleton A et al., 2003; Chartier-Harlin M et al., 2004; Farrer M et al., 2004; 2006; Ibáñez P et al., 2004; 2009; Yu F et al., 2005; Yu S et al., 2004, 2007; Yu L et al., 2012*]. It should be noted that even intermediate forms of α-synuclein, such as oligomers, exhibit pronounced neurotoxicity [*Conway K et al., 2000; Volles M et al., 2001; Ding T et al., 2002; Volles M, Lansbury P, 2002; Fredenburg R et al., 2007*].

It has long been established that aliphatic polyamines (putrescine, spermidine, and spermine) play a crucial role in neuromodulatory processes, specifically in activating neuromotor functions in various parts of the brain [*Rock D, Macdonald R, 1992, 1995; Yatin S et al., 1999; Antony T et al., 2003; Rhee H et al., 2007; Velloso N, 2008; Paik M et al., 2010*]. At the same time, over the past 25 years, numerous informative publications have highlighted the significant role of aliphatic polyamines in the pathogenesis of Parkinson's disease, particularly in relation to their hyperproduction in the relevant regions of the brain [*Gomes-Trolin C et al., 2002; Kaplan B et al., 2003; Paik M et al., 2010; Krasnoslobodtser A et al., 2012; Koehler N et al., 2015*]. It is now well-established that the development of neurodegenerative disorders in Parkinson's disease is largely due to the enhanced in situ synthesis of aliphatic polyamines, which promotes the aggregation and fibrillation of α-synuclein in dopaminergic neurons, leading to the formation of Lewy bodies [*Antony T et al., 2003; Fernandez C, 2004; Bertoncini C, 2005; Rasia R, 2005; Avagyan S, Zilfyan A, 2019; Makletsova M et al., 2022*].

The body-first subtype is characterized by the appearance of autonomic disorders at the earliest stages of neurodegenerative changes in the brain that are typical of Parkinson's disease. These disorders are clinically manifested by parasomnias (such as rapid eye movement sleep behavior disorder) and bowel dysfunction [*Knudsen K et al., 2021; Katunina E et al., 2023*]. The dynamics of the development of the peripheral mechanisms involved in Parkinson's disease are primarily reflected in the "dual hit" hypothesis proposed by *Hawkes C et al. (2007)*. According to this hypothesis, α-synuclein aggregates, which are localized at the earliest stages of Parkinson's disease in the olfactory bulb and the intestine, reach brain structures through the olfactory pathways, as well as through the parasympathetic and sympathetic pathways. In our opinion, it is also possible that peripheral aggregated α-synuclein penetrates the central nervous system through selective increased permeability of the blood-brain barrier.

OFFICIAL PUBLICATION OF THE YEREVAN STATE MEDICAL UNIVERSITY

Currently, the possible mechanisms involved in the aggregation and fibrillation of α-synuclein in the peripheral nerve structures of the gastrointestinal tract remain highly controversial. In Parkinson's disease, in addition to the increased aliphatic polyamine content in neurons and glial cells of the brain, high levels of all three aliphatic polyamines – putrescine, spermidine, and spermine, are also observed in the plasma and erythrocytes of peripheral blood [*Shin E et al., 2000; Gomez-Trolin C et al., 2002; Kaplan B et al., 2003; Krasnoslobodtsev A et al., 2012; Koehler N et al., 2015; Avagyan S et al., 2019*].

In our opinion, the high levels of aliphatic polyamines in peripheral blood may result from the disruption of intracellular mechanisms governing their balanced synthesis in somatic cells, caused by various provoking factors, including infectious and non-infectious diseases. It is possible that neuronal and mesenchymal cells located in the peripheral nerve endings of the gastrointestinal tract, vagus nerve, intramural nervous apparatus of the heart, and other areas, also act as potential sources of increased synthesis of aliphatic polyamines under certain extreme conditions.

According to the currently debated "dual hit" hypothesis [*Hawkes C et al., 2007*], under certain conditions, α-synuclein produced in peripheral nerve structures undergoes aggregation. In Parkinson's disease, aggregated α-synuclein penetrates the blood-brain barrier and/or retrogradely through perineural pathways into the brain, leading to the development of neurodegenerative disorders in specific central nervous system structures, such as the corpus striatum, substantia nigra, and locus coeruleus.

It can be assumed with a high degree of certainty that a possible source of such aggregation of α-synuclein in situ are the high concentrations of aliphatic polyamines produced both in somatic cells of internal organs and in submucosal structures of the stomach and intestinal tract by nerve and glial cells of peripheral nerve endings. It is also possible that, under certain extreme conditions, peripheral mechanisms associated with increased level of aliphatic polyamines in somatic cells of internal organs, including those localized in peripheral nerve endings, may contribute to the broader spectrum of neurodegenerative disorders in the central nervous system in Parkinson's disease. In such case, it is possible that, by entering the peripheral bloodstream and lymph, aliphatic polyamines could penetrate the brain as a result of selective increase of the permeability of the blood-brain barrier.

If we adhere to the currently widely discussed hypothesis of two subtypes of possible development of the pathogenesis of Parkinson's disease – body-first and brain-first, the above-described retrograde pathway of α-synuclein penetration into the brain is realized according to the body-first mechanism [*Stockholm M et al., 2016; Lionnet A et al., 2018*].

The Head of the Laboratory of immunoenzymatic researches at the Scientific Research Center of YSMU, Avagyan S.A., during his business trip to the Scientific Center of Neurology (RF, Moscow), along with the co-authors of this publication and employees of the Laboratory of Neurochemistry at the same center, conducted chromatographic studies back in 2017 to investigate shifts in the content of aliphatic polyamines (putrescine, spermidine,

TABLE 2.

Aliphatic polyamines levels in blood plasma of patients with Parkinson's disease at different stages (according to *Hoehn, Yahr, 1967*)

Indicators	Donors (n=21)	Stages of development of Parkinson's disease			
		First (n=27)	Second (n=23)	Third (n=20)	Fourth (n=10)
Putrescine (*μg/ml*)	189.3±20.7	471.4±50.9 p<0.0005	223.6±33.6 0.1<p<0.25	296.4±29.6 0.0005<p<0.005	83.5±14.9 0.0005<p<0.005
Spermidine (*μg/ml*)	279.7±30.3	813.6±90.9 p<0.0005	213.8±35.8 0.05<p<0.1	57.3±18.2 p<0.0005	63.9±10.8 p<0.0005
Spermine (*μg/ml*)	90.5±13.5	603.6±60.7 p<0.0005	212.5±30.6 0.0005<p<0.005	320.0±40.5 p<0.0005	40.4±8.9 0.0005<p<0.01

***Note**: p value in relation to the indicators of each stage of the biochemical parameter of blood corresponds to the indicators of donors (control group).*

OFFICIAL PUBLICATION OF THE YEREVAN STATE MEDICAL UNIVERSITY

and spermine) in the blood plasma of patients suffering from Parkinson's disease. The patient cohort was divided into stages (from I to V) based on their disability levels [*Hoehn M, Yahr M, 1967*].

The results of the chromatographic studies on the content of polyamines in the blood of patients suffering from Parkinson's disease are presented in the table 2.

As can be seen from the table, the highest values of all three aliphatic polyamines were determined in patients with the first degree of disability. Specifically, the level of putrescine in the blood plasma exceeded the control level by 2.5 times, spermidine by 2.9 times, and spermine by 6.7 times. In patients at the second stage of disability, the values for putrescine and spermidine were within the control range, while the spermine level remained elevated, exceeding the control by 2.35 times. In patients classified as stage III disability, the putrescine content remained high compared to the control, the spermine level increased by 3.5 times, and the spermidine level, conversely, decreased by nearly five times compared to the control. The fourth stage of disability was characterized by a sharp decrease in the content of all three aliphatic polyamines in the blood plasma in Parkinson's disease compared to the control level: putrescine by 2.8 times, spermidine by 4.4 times, and spermine by 2.25 times [*Makletsova M 2017; Makletsova M et al., 2019*].

The dynamics of shifts in the content of aliphatic polyamines (putrescine, spermidine, and spermine) in the blood of patients at different stages of Parkinson's disease development are shown in the figure.

We tried to analyze the chromatographic study

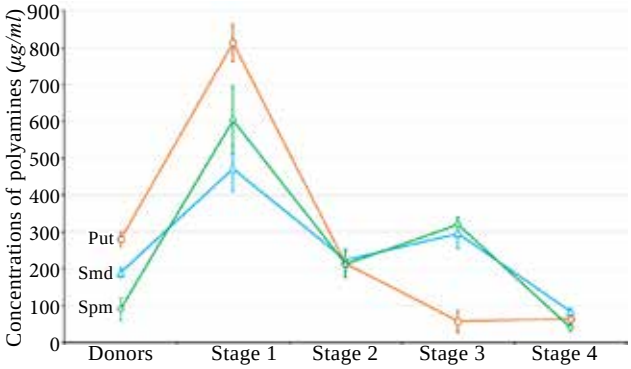

Figure. *The level of polyamines (putrescine, spermidine, spermine) in blood of patients with Parkinson's disease at their stage gradation*

results of the content of aliphatic polyamines in the blood plasma of patients suffering from Parkinson's disease, adhering to the distribution of the disease by degrees of disability. This interpretation takes into account the early symptoms of the disease and its conditional gradation into brain-first and body-first subtypes.

Thus, high levels of all three aliphatic polyamines in blood plasma at the first stage of disability, as well as high levels of putrescine and spermine at the third stage, can be considered as additional, yet informative criteria, indicating the important role of peripheral aliphatic polyamines in the induction of aggregation and fibrillation of α-synucleins localized in peripheral nerve endings. Subsequently, it is possible that denatured α-synucleins are able to penetrate the brain retrogradely (perineurally, or due to increased permeability of the blood-brain barrier), leading to the development of a symptom complex characteristic of Parkinson's disease. In this case, it is not excluded that the early manifestations of Parkinson's disease also follow the "body-first" subtype.

Hyperproduction of aliphatic polyamines in internal organs, particularly in their neuritis, with a subsequent increase in their content in the blood, should be considered a degree of risk for developing peripheral neurodegenerative disorders, which significantly exacerbate the course of Parkinson's disease. At the fourth stage of disability, where very low concentrations of all three aliphatic polyamines are found in the blood of patients, this stage, in our opinion, most objectively reflects the full spectrum of neurodegenerative disorders in the brain, which are primarily realized according to the "brain-first" subtype.

It should be especially noted that, even at the early stages of the disease, central polyamine-dependent mechanisms involved in the aggregation and fibrillation of α-synucleins in dopaminergic neurons of the brain may already be active.

In the induction mechanism of neurodegenerative disorders in the central nervous system, according to the "body-first" subtype, aspects related to the role of infection are currently the subject of special discussion, particularly considering the taxonomic potentials and features of the persistence of resident opportunistic and pathogenic microorganisms in the gastrointestinal tract. In this regard, information on

OFFICIAL PUBLICATION OF THE YEREVAN STATE MEDICAL UNIVERSITY

the role of Helicobacter pylori (H. pylori) in the pathogenesis of Parkinson's disease, as presented in several informative publications over the last 20 years, deserves particular attention [*Necchi V et al., 2007; Hildebrandt E, McGee D, 2009; Dobbs R et al., 2012; Mulak A, Bonar B, 2015; Noto J, Peek R, 2017; McGee D et al., 2018*].

Epidemiological studies have been especially informative, showing that individuals with Parkinson's disease have a threefold increased risk of H. pylori seropositivity compared to controls [*Charlett A et al., 1999; Dobbs R et al., 2000; Weller C et al., 2005; Nielsen H et al., 2012; Çamcı G, Oğuz S. S, 2016; Shen X et al., 2017; Huang H et al., 2018*].

There is an opinion suggesting that several toxic substances, which are products of H. pylori synthesis, are "interested" in the induction of neurodegenerative disorders in the brain in Parkinson's disease, such as tetrahydropyridine [*Altschuler E, 1996*], vacuolating toxin [*Weller C et al., 2005*], and cholesterol glucosides [*Bjorkhem J et al., 2013*]. Furthermore, the aggregation of α-synuclein in dopaminergic neurons is also facilitated by neurotoxic factors produced by immunocompetent cells in situ, as a result of their penetration through the blood-brain barrier into brain tissue [*Dobbs R et al., 2000; 2016; Noto J, Peck R, 2007; Mulak A, Bonar B, 2015; Avagyan S et al., 2019*].

Possible peripheral mechanisms contributing to the induction of neurodegenerative disorders involving α-synuclein produced in various regions of the gastrointestinal tract have been extensively analyzed and summarized in the form of a hypothesis [*Mulak A, Bonar B, 2015*]. The proposed hypothesis suggests the existence of a brain-gastrointestinal tract-microbiota axis in Parkinson's disease, which progresses through the following chronological stages:

1. Dysbiosis associated with disruption of intestinal bacterial homeostasis.
2. Synthesis and aggregation of α-synuclein in the neurites of the gastrointestinal tract's nervous tissue, followed by the production of autoantibodies against aggregated α-synuclein by immunocompetent cells.
3. α-synuclein that enters the brain from the periphery primarily accumulates in glial cells.
4. Due to the established association between glial cells and neurons, α-synuclein begins to accumulate within the cytoplasm of neurons, leading to the formation of Lewy bodies.
5. The accumulation of α-synuclein in dopaminergic neurons of the brain, initiating the development of neurodegenerative processes in dopaminergic neurons.

The abovementioned hypothesis primarily relies on literature data concerning the mechanisms of peripheral synthesis and aggregation of α-synuclein in neurites localized in the gastrointestinal tract, specifically in the context of H. pylori infection. However, the role of resident opportunistic microorganisms persisting in the intestinal tract has not been sufficiently studied. Only a few studies explore the role of Escherichia coli in the targeted synthesis of antibodies to α-synuclein by immunocompetent cells.

Thus, a single intraperitoneal injection of bacterial endotoxin (commercial preparation of lipopolysaccharides from Escherichia coli) significantly increased the number of immunocompetent cells (macrophages and lymphocytes) expressing high levels of α-synuclein in the lymph nodes. Stimulation of immunocompetent cells with Escherichia coli endotoxin, following prior administration of specific stimulated macrophages to animals, resulted in the activation of humoral immune responses that selectively promoted the synthesis of antibodies against α-synuclein [*Sergeeva T, Sergeev V, 2011*].

In our opinion, the perineural and/or hematogenous pathways of α-synuclein entry from the periphery into the brain in Parkinson's disease are highly questionable, as α-synucleins, during their perineural migration or entry into the bloodstream may be exposed to various hematogenic factors, including phagocytosis, which likely prevents their entry into the brain. Conversely, we propose that in Parkinson's disease, particularly in the context of intestinal dysbiosis, the autoimmune mechanism leading to dopaminergic neuron damage through the penetration of autoantibodies to α-synuclein into the brain seems more plausible. This hypothesis appears reasonable, as it is supported by informative experimental data indicating that autoantibodies to α-synuclein, produced in immunogenic organs, are toxic and induce selective death of dopaminergic neurons in the substantia nigra [*Huber V et al., 2006*]. Moreover, it is likely that dysbiosis in the intestinal tract, particularly

OFFICIAL PUBLICATION OF THE YEREVAN STATE MEDICAL UNIVERSITY

with the activation of resident gram-negative microflora, influences the morphofunctional state of the brain [*Avagyan S et al., 2019*]. We further suggest that in Parkinson's disease, bacterial translocation processes may be activated, leading to the migration of opportunistic microorganisms (primarily E. coli) from the intestine. These microorganisms, along with their metabolic by-products (including putrescine and endotoxins) may then spread hematogenously to new ecological niches in the host, potentially allowing their entry into the central nervous system.

According to the "body-first" subtype, the induction of peripheral mechanisms underlying the early manifestations of Parkinson's disease should also consider the role of dysbiosis, which selectively promotes the aggregation of α-synuclein in gastrointestinal tract neurites, as well as the production of biologically active factors that exert a neurotoxic effect on dopaminergic neurons localized in specific brain areas.

Conclusion

Currently, the mechanisms underlying the development of Parkinson's disease are the subject of extensive discussion, with both central and peripheral mechanisms being of significant interest. In the case of peripheral mechanisms, the "dual hit" hypothesis proposed by Hawkes C et al. (2007) highlights the critical role of α-synucleins, which are produced in the peripheral nerve endings of various internal organs. These α-synucleins, upon aggregation, retrogradely spread from the periphery to the central nervous system, leading to neurodegenerative processes in dopaminergic neurons, primarily in the corpus striatum, substantia nigra, and locus coeruleus.

In our view, one potential cause of α-synuclein aggregation and fibrillation in the periphery is the increased synthesis of aliphatic polyamines (putrescine, spermidine, and spermine) in somatic cells of internal organs.

When analyzing the results obtained from studying the shifts in the levels of three aliphatic polyamines in blood plasma in Parkinson's disease (table 2), it is important, in our opinion, to take into account following point. High levels of all three polyamines at the first stage of disability reflect their equal involvement in the formation of the peripheral mechanisms of the disease. In patients with the second and third stages of disability, the role of each of the three polyamines in the development of peripheral mechanisms, according to the "body-first" subtype, was far from straightforward.

Thus, elevated spermine levels, in the context of normalized putrescine and spermidine levels, suggest that only spermine is involved in the development of peripheral mechanisms in the induction of Parkinson's disease. Similarly, high levels of putrescine and spermine at the third stage, with a significant decrease in spermidine content, indicate that only two polyamines – putrescine and spermine, are involved in the formation of peripheral mechanisms. In our opinion, each of the three aliphatic polyamines, even individually, has the potential to trigger the "body-first" subtype, as all three polyamines (putrescine, spermidine, spermine) can induce the aggregation of α-synuclein in peripheral nerve endings.

The hypothesis we proposed is supported by a foundational study on the aggregation potential of the three aliphatic polyamines, carried out by a team of leading researchers [*Antony T et al., 2003*].

The authors showed that aliphatic polyamines, whether combined or used individually, promote the aggregation and fibrillation of α-synuclein, a key protein component of Lewy bodies linked to Parkinson's disease.

Using scanning electron microscopy to identify the substrate, aggregated particles – protofibrils and small fibrils, were detected.

Upon completion of the transient phase, α-synuclein forms long fibrils with minimal morphological variations. In the presence of each of the three polyamines, the fibrils begin to form extensive network-like structures, ultimately leading to the thickening of aggregates. In the absence of aliphatic polyamines, the fibrils remain more isolated, showing no signs of adhesion to one another or the formation of aggregates.

Therefore, polyamine-dependent processes that lead to the hyperproduction of aliphatic polyamines in peripheral internal organs are of significant interest in understanding one of the potential mechanisms of Parkinson's disease induction. High concentrations of these polyamines could be considered a contributing factor to the aggregation

OFFICIAL PUBLICATION OF THE YEREVAN STATE MEDICAL UNIVERSITY

of α-synucleins localized in peripheral nerve terminals. This mechanism likely plays a role when the peripheral nervous system is engaged early in the pathological process, consistent with the "body-first" subtype.

In cases where high levels of aliphatic polyamines (putrescine, spermidine, and spermine) are observed in the peripheral blood (plasma, serum, and erythrocytes), these should, in our opinion, be considered informative criteria for assessing the risk of developing Parkinson's disease. Additionally, under certain extreme conditions, where there is a significant increase in the levels of aliphatic polyamines in the peripheral blood, these polyamines may be capable of penetrating the brain through the blood-brain barrier, thereby potentially triggering processes in specific areas of the brain that promote the aggregation and fibrillation of α-synucleins in dopaminergic neurons.

The study of the pathogenetic aspects of Parkinson's disease should also be approached from a new perspective, focusing on the induction of the peripheral pathological process. This process, characterized by the aggregation and fibrillation of α-synuclein in the nerve fibers of the gastrointestinal tract, may involve infectious agents, persisting in situ, including conditionally pathogenic and pathogenic microorganisms.

REFERENCES

1. *Albin RL, Young AB, Penney JB (1998).* The functional anatomy of basal ganglia disorders. Trends Neurosci. 12: 366-375
2. *Altschuler E (1996).* Gastric Helicobacter pylori infection as a cause of idiopathic Parkinson's disease and non-arteric anterior optic ischemic neuropathy. 47(5): 413-414 DOI: 10.1016/s0306-9877(96)90223-6
3. *Antony T, Hoyer W, Cherny D, Heim G, Jovin TM, Subramaniam V (2003).* Cellular polyamines promote the aggregation of alpha-synuclein. J Biol Chem. 278: 3235-3240
4. *Atik A., Stewart T., Zhang, J. . (2016).* Alpha-Synuclein as a Biomarker for Parkinson's Disease. Brain Pathology, 26(3), 410–418. doi:10.1111/bpa.12370
5. *Avagyan SA, Zilfyan AV (2019).* Polyamines and synucleines in the diagnosis and phatogenesis neurological and oncological diseases. Yerevan, Armenia. 185p
6. *Avagyan SA, Zilfyan AV, Ghazaryan HV (2019).* Possible role of resident conditional pathogenic microorganisms and helicobacter pylori in the genesis of Parkinson's disease. New Armenian Medical Journal. 13(1): 97p
7. *Bernheimer H, Birkmayer W, Hornykiewicz O., et al., (1973).* Brain dopamine and the syndromes of Parkinson and Huntington. Clinical, morphological and neurochemical correlations. J Neurol Sci. 20: 415-455
8. *Bertoncini CW, Jung YS, Fernandez CO, Hoyer W, Griesinger C., et al., (2005).* Release of long-range tertiary interactions potentiates aggregation of natively unstructured alpha-synuclein. Proc Natl Acad Sci. USA. 102: 1430-1435 DOI: 10.1073/pnas.0407146102
9. *Björkhem I, Lövgren-Sandblom A, Leoni V, Meaney S, Brodin L., et al., (2013).* Oxysterols and Parkinson's disease: Evidence that levels of 24S-hydroxycholesterol in cerebrospinal fluid correlates with the duration of the disease. Neuroscience Letters. 555: 102-105 DOI: 10.1016/j.neulet.2013.09.003
10. *Braak H, Sastre M, Bohl JR., et al., (2007).* Parkinson's disease: lesions in dorsal horn layer I, involvement of parasympathetic and sympathetic pre- and postganglionic neurons. Acta Neuropathol. 113: 421-429 DOI: 10.1007/s00401-007-0193-x
11. *Çamcı G, Oğuz S (2016).* Association between Parkinson's Disease and Helicobacter Pylori. J Clin Neurol. 12(2): 147-150 DOI: 10.3988/jcn.2016.12.2.147
12. *Chang C-W, Yang S-Y, Yang C-C, Chang C-W and Wu Y-R (2020)* Plasma and Serum Alpha-Synuclein as a Biomarker of Diagnosis in Patients With Parkinson's Disease. Front. Neurol. 10:1388. doi: 10.3389/fneur.2019.01388
13. *Charlett A, Dobbs RJ, Dobbs SM, Weller C, Brady P, Peterson DW (1999).* Parkinsonism: siblings share Helicobacter pylori seropositivity and facets of syndrome. Acta Neurol Scand. 99: 26-35 DOI: 10.1111/j.1600-0404.1999.tb00654.x

OFFICIAL PUBLICATION OF THE YEREVAN STATE MEDICAL UNIVERSITY

14. *Chartier-Harlin MC, Kachergus J, Roumier C, Mouroux V, Douay X., et al., (2004).* Alpha-synuclein locus duplication as a cause of familial Parkinson's disease. Lancet. 364: 1167-1169

15. *Conway KA, Lee SJ, Rochet JC, Ding TT, Williamson RE, Lansbury PT Jr (2000).* Acceleration of oligomerization, not fibrillization, is a shared property of both alpha-synuclein mutations linked to early-onset Parkinson's disease: implications for pathogenesis and therapy. Proc Natl Acad Sci. USA. 97: 571-576 DOI: 10.1073/pnas.97.2.571

16. *Ding TT, Lee SJ, Rochet JC, Lansbury PT (2002).* Annular α-Synuclein Protofibrils Are Produced When Spherical Protofibrils Are Incubated in Solution or Bound to Brain-Derived. Biochemistry. 41(32): 10209-10217 DOI: 10.1021/bi020139h

17. *Dobbs RJ, Charlett A, Dobbs SM., et al., (2012).* Leukocyte-subset counts in idiopathic parkinsonism provide clues to a pathogenic pathway involving small intestinal bacterial overgrowth. A surveillance study. Gut Pathog. 4: 12 DOI: 10.1186/1757-4749-4-12

18. *Dobbs SM, Dobbs RJ, Weller C, Charlett A (2000).* Link between Helicobacter pylori infection and idiopathic parkinsonism. 55(2): 93-98 DOI: 10.1054/mehy.2000.1110

19. *Dobbs SM, Dobbs RJ, Weller C., et al., (2016).* Peripheral aetiopathogenic drivers and mediators of Parkinson's disease and co-morbidities: role of gastrointestinal microbiota. J. Neurovirol. 22: 22-32 DOI: 10.1007/s13365-015-0357-8

20. *Ehringer H, Hornykiewicz O (1960).* Distribution of noradrenaline and dopamine (3-hydroxytyramine) in the human brain and their behavior in diseases of the extrapyramidal system. Klin Wochenschr: 38: 1236-1239

21. *Fahn S (2003).* Description of Parkinson's disease as a clinical syndrome. Ann N Y Acad Sci. 991: 1-14 DOI: 10.1111/j.1749-6632.2003.tb07458.x. PMID: 12846969

22. *Farrer M, Kachergus J, Forno L, Lincoln S, Wang DS., et al., (2004).* Comparison of kindreds with parkinsonism and alpha-synuclein genomic multiplications. Ann Neurol. 55(2): 174-179

23. *Farrer MJ (2006).* Genetics of Parkinson disease: paradigm shifts and future prospects. Nat Rev Genet. 7: 306-318 DOI: 10.1038/nrg1831

24. *Fernandez CO, Hoyer W, Zweckstetter M, Jares-Erijman EA, Subramaniam V., et al., (2004).* NMR of α-synuclein–polyamine complexes elucidate the mechanism and kinetics of induced aggregation. 23(10): 2039-2046 DOI: 10.1038/sj.emboj.7600211

25. *Foulds P. G.; Diggle P.; Mitchell J., Parker A.; Hasegawa, M., Masuda-Suzukake M., Mann David M. A., Allsop D. (2013).* A longitudinal study on α-synuclein in blood plasma as a biomarker for Parkinson's disease. Scientific Reports, 3(), –. doi:10.1038/srep02540

26. *Fredenburg RA, Rospigliosi C, Meray RK, Kessler JC, Lashuel HA., et al., (2007).* The Impact of the E46K Mutation on the Properties of α-Synuclein in Its Monomeric and Oligomeric States. Biochemistry. 46(24): 7107-7118 DOI: 10.1021/bi7000246

27. *Goetz CG, Fahn S, Martinez-Martin P, Poewe W, Sampaio C., et al., (2007).* Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS): Process, format, and clinimetric testing plan. 22(1): 41-47 DOI: 10.1002/mds.21198

28. *Goetz CG, Stebbins GT (2004).* Assuring interrater reliability for the UPDRS motor section: Utility of the UPDRS teaching tape. Movement Disorders. 19(2): 1453-1456

29. *Goetz CG, Stebbins GT, Luo S (2020).* Movement Disorder Society–Unified Parkinson's Disease Rating Scale Use in the Covid-19 Era Mov Disord. 35(6): 911 DOI: 10.1002/mds.28094

30. *Gomes-Trolin C, Nygren I, Aquilonius SM, Askmark H (2002).* Increased red blood cell polyamines in ALS and Parkinson's disease. Exp Neurol. 177(2): 515-520 DOI: 10.1006/exnr.2002.7952

31. *Hawkes CH, Tredici KD, Braak H (2007).* Parkinson's disease: a dual-hit hypothesis, Neuropathology and Applied Neurobiology. 33(6): 599-721 DOI: 10.1111/j.1365-2990.2007.00874.x

32. *Hildebrandt E, McGee DJ (2009).* Helicobacter pylori lipopolysaccharide modification, Lewis antigen expression, and gastric colonization are cholesterol-dependent. BMC Microbiol. 9: 258 DOI: 10.1186/1471-2180-9-258

OFFICIAL PUBLICATION OF THE YEREVAN STATE MEDICAL UNIVERSITY

33. *Hoehn MM, Yahr MD (1967).* Parkinsonism: onset, progression, and mortality. Neurology. 17(5): 427-427 DOI: 10.1212/WNL.17.5.427

34. *Huang HK, Wang JH, Lei WYi, Chen CL, Chang CYa, Liou LiS (2018).* Helicobacter pylori infection is associated with an increased risk of Parkinson's disease: A population-based retrospective cohort study. Parkinsonism & Related Disorders. 47: 26-31 DOI: 10.1016/j.parkreldis.2018.11.331

35. *Huber VC, Mondal T, Factor SA., et al., (2006).* Serum antibodies from Parkinson's disease patients react with neuronal membrane proteins from a mouse dopaminergic cell line and affect its dopamine expression. J Neuroinflammation. 3(1): DOI: 10.1186/1742-2094-3-1

36. *Ibáñez P, Bonnet AM, Debarges B, Lohmann E, Tison F., et al., (2004).* Causal relation between alpha-synuclein gene duplication and familial Parkinson's disease. Lancet. 364(9440): 1169-1171 DOI: 10.1016/S0140-6736(04)17104-3

37. *Ibáñez P, Lesage S, Janin S., et al., (2009).* Alpha-synuclein gene rearrangements in dominantly inherited parkinsonism: frequency, phenotype, and mechanisms. Arch. Neurol. 66: 102-108

38. *Kaplan B, Ratner V, Haas E (2003).* α-Synuclein: Its Biological Function and Role in Neurodegenerative Diseases. Journal of Molecular Neuroscience. 20: 83-92 DOI: 10.1385/JMN:20:2:83

39. *Katunina EA, Blokhin V, Nodel MR, Pavlova EN, Kalinkin AL., et al., (2023a).* Searching for Biomarkers in the Blood of Patients at Risk of Developing Parkinson's Disease at the Prodromal Stage. International Journal of Molecular Sciences. 24(3): 1842 DOI: 10.3390/ijms24031842

40. *Kasuga, Kensaku; Nishizawa, Masatoyo; Ikeuchi, Takeshi. (2012).* -Synuclein as CSF and Blood Biomarker of Dementia with Lewy Bodies. International Journal of Alzheimer's Disease, 2012(), 1–9. doi:10.1155/2012/437025

41. *Katunina EA, Zalyalova ZA, Pokhabov DV, Ivanova MZ, Semenova AM (2023b).* [Parkinson's disease. Focus on early stages] [Published in Russian]. Neurology, Neuropsychiatry, Psychosomatics (Nevrologiya, neiropsikhiatriya, psikhosomatika). 15(3): 95-103 DOI: 10.14412/2074-2711-2023-3-95-103

42. *Khaindrava VG, Kozina EA, Kucheryanu VG, Kryzhanovsky GN, Kudrin VS., et al., (2010).* Modeling of preclinical and early clinical stages of Parkinson's disease. Journal of Neurology and Psychiatry. 7: 41-47

43. *Knudsen K, Fedorova TD, Horsager J., et al., (2021).* Asymmetric Dopaminergic Dysfunction in Brain-First versus Body-First Parkinson's Disease Subtypes. Journal of Parkinson's Disease. 11(4): 1677-1687 DOI: 10.3233/JPD-212761

44. *Koehler NK, Stransky E, Meyer M, Gaertner S, Shing M, Schnaidt M., et al., (2015).* Alpha-synuclein levels in blood plasma decline with healthy aging. PLoS One. 10(4): e0123444 DOI: 10.1371/journal.pone.0123444

45. *Krasnoslobodtsev AV, Peng J, Asiago JM, Hindupur J, Rochet JC., et al., (2012).* Effect of Spermidine on Misfolding and Interactions of Alpha-Synuclein. PLoS ONE. 7(5): e38099 DOI: 10. Koehler 1371/journal.pone.0038099

46. *Kruger R, Kuhn W, Muller T, Woitalla D, Graeber M, Kosel S., et al., (1998).* Ala30Pro mutation in the gene encoding alpha-synuclein in Parkinson's disease. Nat Genet. 18: 106-108

47. *Lev N, Melamed E, Offen D (2003).* Apoptosis and Parkinson's disease. Prog Neuropsychopharmacol Biol Psychiat. 27: 245-250

48. *Lionnet A, Leclair-Visonneau L, Neunlist M., et al., (2018).* Does Parkinson's disease start in the gut? Acta Neuropathol. 135: 1-12 DOI: 10.1007/s00401-017-1777-8

49. *Makletsova MG, Rikhireva GT, Kirichenko EY., et al., (2022).* The Role of Polyamines in the Mechanisms of Cognitive Impairment. Neurochem J. 16: 283-294 DOI: 10.1134/S1819712422030059

50. *Makletsova MG, Syatkin SP, Poleshchuk VV, Urazgildeeva GR, Chigaleychik LA, Sungrapova CY, SIllarioshkin SN (2019),* Polyamines in Parkinson's Disease: Their Role in Oxidative Stress Induction and Protein Aggregation, 2019, Journal of Neurology Research 9(1-2):1-7 DOI:10.14740/jnr509

51. *Makletsova MG, Poleshchuk BB, Zilfyan AV, Avagyan SA. (2017).* Level of spermine in blood pasma in patients with Parkinson's

OFFICIAL PUBLICATION OF THE YEREVAN STATE MEDICAL UNIVERSITY

disease. NAMJ. 2017;11:33

52. *Malek, N.; Swallow, D.; Grosset, K. A.; Anichtchik, O.; Spillantini, M.; Grosset, D. G.. (2014).* Alpha-synuclein in peripheral tissues and body fluids as a biomarker for Parkinson's disease - a systematic review. Acta Neurologica Scandinavica, 130(2), 59–72. doi:10.1111/ane.12247 https://doi.org/10.1134/S1819712422030059

53. *Martínez-Martín P, Gil-Nagel A, Morlán Gracia L, Balseiro Gómez J, Martínez-Sarriés J, Bermejo F (1994).* Unified Parkinson's disease rating scale characteristics and structure. Movement Disorders. 9(1): 76-83 DOI: 10.1002/mds.870090112

54. *Maruyama W, Akao Y, Youdim MB., et al., (2001).* Transfection-enforced Bcl-2 overexpression and an anti-Parkinson drug, rasagiline, prevent nuclear accumulation of glyceraldehyde-3-phosphate dehydrogenase induced by an endogenous dopaminergic neurotoxin, N-methyl(R)salsolinol. J Neurochem. 78: 727-735

55. *McGee DJ, Lu HH, Disbrow EA (2018).* Stomaching the possibility of the pathogenic role of Helicobacter pylori in Parkinson's disease. J Parkinson's Dis. 8: 367-374 PMID: 29966206 DOI: 10.3233/JPD-181327.

56. *Mulak A, Bonaz B (2015).* Brain-gut-microbiota axis in Parkinson's disease. World J Gastroenterol. 21(37): 10609-10620 DOI: 10.3748/wjg.v21.i37.10609, PMID: 26457021, PMCID: PMC4588083

57. *Necchi V, Candusso ME, Tava F, Luinetti O, Ventura U., et al., (2007).* Intracellular, Intercellular, and Stromal Invasion of Gastric Mucosa, Preneoplastic Lesions, and Cancer by Helicobacter pylori. 132(3): 1009-1023 DOI: 10.1053/j.gastro.2007.01.049

58. *Nielsen HH, Qiu J, Friis S, Wermuth L, Ritz B (2012).* Treatment for Helicobacter pylori infection and risk of Parkinson's disease in Denmark. Eur J Neurol. 19(6): 864-869 DOI: 10.1111/j.1468-1331.2011.03643.x, PMID: 22248366, PMCID: PMC3330170

59. *Noto JM, Peek RM Jr (2017).* The gastric microbiome, its interaction with Helicobacter pylori, and its potential role in the progression to stomach cancer. PLoS Pathog. 13(10): e1006573 DOI: 10.1371/journal.ppat.1006573

60. *Park M.G.; Cheon, S-M; Bae H-R; Kim S-Ho; Kim J. W. (2011).* Elevated Levels of α-Synuclein Oligomer in the Cerebrospinal Fluid of Drug-Naïve Patients with Parkinson's Disease. Journal of Clinical Neurology, 7(4), 215–. doi:10.3988/jcn.2011.7.4.215

61. *Pchelina S.N. (2011).* Alpha-synuclein as a biomarker of Parkinson's disease // Annals of Clinical and Experimental Neurology. - 2011. - Vol. 5. - N. 4. - P. 46-51. doi: 10.17816/psaic289

62. *Perlmutter JS (2009).* Assessment of Parkinson disease manifestations. Curr Protoc Neurosci. Chapter 10: Unit 10.1 DOI: 10.1002/0471142301.ns1001s49 PMID: 19802812 PMCID: PMC2897716

63. *Pinter B, Diem-Zangerl A, Wenning GK, Scherfler C, Oberaigner W., et al., (2015).* Mortality in Parkinson's disease: A 38-year follow-up study. Movement Disorders. 32(1): 266-269 DOI: 10.1002/mds.26060

64. *Polymeropoulos MH, Lavedan C, Leroy E, Ide SE, Dehejia A., et al., (1997).* Mutation in the alpha-synuclein gene identified in families with Parkinson's disease. Science. 276: 2045-2047

65. *Rasia RM, Bertoncini CW, Marsh D, Hoyer W, Cherny D., et al., (2005).* Structural characterization of copper(II) binding to α-synuclein: Insights into the bioinorganic chemistry of Parkinson's disease. PNAS. 102(12): 4294-4299

66. *Reader TA, Hebert C, Ase AR, Le Marec N (2001).* Distribution of serotonin, its metabolites and 5-HT transporters in the neostriatum of Lurcher and weaver mutant mice. Neurochem Int. 39: 169-177

67. *Rhee HJ, Kim EJ, Lee JK (2007).* Physiological polyamines: simple primordial stress molecules. J Cell Mol Med. 11: 685-703

68. *Rock DM, MacDonald RL (1992).* Spermine and related polyamines produce a voltage-dependent reduction of N-methyl-D-aspartate receptor single-channel conductance. Mol Pharmacol. 42(1): 157-164

69. *Rock DM, Macdonald RL (1995).* Polyamine regulation of N-methyl-D-aspartate receptor channels. Annu Rev Pharmacol Toxicol. 35: 463-482

70. *Sergeeva TN, Sergeev VG (2011).* Administration of LPS-Stimulated Autologous Macrophages Induces α-Synuclein Aggregation

OFFICIAL PUBLICATION OF THE YEREVAN STATE MEDICAL UNIVERSITY

in Dopaminergic Neurons of Rat Brain. Bull Exp Biol Med. 150: 406-408 DOI: 10.1007/s10517-011-1153-y

71. *Shen X, Yang H, Wu Y, Zhang D, Jiang H (2017).* Association of Helicobacter pylori infection with Parkinson's diseases: A meta-analysis. Helicobacter. e12398 DOI: 10.1111/hel.12398
72. *Shin EC, Cho SE, Lee DK., et al. (2000).* Expression Patterns of α-Synuclein in Human Hematopoietic Cells and in Drosophila at Different Developmental Stages. Mol Cells. 10: 65-70 DOI: 10.1007/s10059-000-0065-x
73. *Singleton AB, Farrer M, Johnson J, Singleton A, Hague S., et al., (2003).* alpha-Synuclein locus triplication causes Parkinson's disease. Science. 302: 841
74. *Stockholm MG, Danielsen EH, Hamilton-Dutoit SJ, Borghammer P (2016).* Pathological α-synuclein in gastrointestinal tissues from prodromal Parkinson disease patients Annals of Neurology. 79(6): 940-949 DOI: 10.1002/ana.24685
75. *van Hilten JJ, van der Zwan AD, Zwinderman AH, Roos RA (1994).* Rating impairment and disability in Parkinson's disease: Evaluation of the unified Parkinson's disease rating scale. 9(1): 84-88 DOI: 10.1002/mds.870090113
76. *Velloso NA, Dalmolin GD, Fonini G., et al., (2008).* Spermine attenuates behavioral and biochemical alterations induced by quinolinic acid in the striatum of rats. Brain Res. 1198: 107-114
77. *Volles MJ, Lansbury PT (2002).* Jr: Vesicle permeabilization by protofibrillar alpha-synuclein is sensitive to Parkinson's disease linked mutations and occurs by a pore-like mechanism. Biochemistry. 41: 4595-4602
78. *Volles MJ, Lee SJ, Rochet JC, Shtilerman MD, Ding TT., et al., (2001).* Vesicle permeabilization by protofibrillar alpha-synuclein: implications for the pathogenesis and treatment of Parkinson's disease. Biochemistry. 40: 7812-7819 DOI: 10.1021/bi0102398
79. Vrijsen S, Houdou M, Cascalho A, Eggermont J, Vangheluwe P. (2023). Polyamines in Parkinson's Disease: Balancing Between Neurotoxicity and Neuroprotection. Annu Rev Biochem. 2023 Jun 20;92:435-464. doi: 10.1146/annurev-biochem-071322-021330. Epub 2023 May 4. PMID: 37018845
80. *Weller C, Charlett A, Oxlade NL, Dobbs SM, Dobbs RJ, Peterson DW, Bjarnason IT (2005)* Role of chronic infec-tion and inflammation in the gastrointestinal tract in the etiology and pathogenesis of idiopathic parkinsonism. Part 3: Predicted probability and gradients of severity of idio-pathic parkinsonism based on H. pylori antibody profile. Helicobacter. 10: 288-297
81. *Weller C, Oxlade N, Dobbs SM, Dobbs RJ, Charlett A, Bjarnason IT (2005).* Role of inflammation in gastrointestinal tract in aetiology and pathogenesis of idiopathic parkinsonism. FEMS Immunol Med Microbiol. 44(2): 129-135
82. *Yatin SM, Yatin M, Varadarajan S, Ain KB, Butterfield DA (2001).* Role of spermine in amyloid beta-peptide-associated free radical-induced neurotoxicity. J Neurosci Res. 63(5): 395-401
83. *Yu F, Xu H, Zhuo M, Sun L, Dong A, Liu X (2005).* Impairment of redox state and dopamine level induced by alpha-synuclein aggregation and the prevention effect of hsp70. Biochemical and Biophysical Research Communications. 331(1): 278-284
84. *Yu L, Cui J, Padakanti PK, Engel L, Bagchi DP., et al., (2012).* Synthesis and in vitro evaluation of alpha-synuclein ligands. Bioorg Med Chem. 20: 4625-4634
85. *Yu S, Li X, Liu G, Han J, Zhang C., et al., (2007).* Extensive nuclear localization of alpha-synuclein in normal rat brain neurons revealed by a novel monoclonal antibody. Neuroscience. 145: 539-555
86. *Yu S, Zuo X, Li Y, Zhang C, Zhou M., et al., (2004).* Inhibition of tyrosine hydroxylase expression in alpha-synuclein-transfected dopaminergic neuronal cells. Neurosci Lett., 367: 34-39

OFFICIAL PUBLICATION OF THE YEREVAN STATE MEDICAL UNIVERSITY

THE NEW ARMENIAN MEDICAL JOURNAL
Volume19 (2025). Issue 3

CONTENTS

4. *Avagyan A.S., Muradyan A.A., Makletsova M.G., Poleshchuk B.B., Zilfyan A.V.*
THE ROLE OF ALIPHATIC POLYAMINES AND A-SYNUCLEIN IN THE FORMATION OF PERIPHERAL MECHANISMS INVOLVED IN THE PARKINSON'S DISEASE INDUCTION

17. *Shuliatnikova O.A., Karakulova Y.V., Batog E.I., Rogoznikov G.I.*
STUDY OF THE COMORBID ASSOCIATION OF INFLAMMATORY PERIODONTAL DISEASES AND PATHOLOGY OF THE NERVOUS SYSTEM

23. *Bari Md.N., Anwar Md., Ansari Md.R., Osman. E.H.A., Alfaki, M.A., Mohammad I.*
A COMPLICATED SITUATION OF DIAGNOSIS OF BIOMARKERS IN ALCOHOLIC LIVER CIRHOSIS INJURY BY ROUSSEL UCLAF CAUSALITY ASSESSMENT METHOD

30. *Gavanji S., Bakhtari A., Baghshahi H., Hamami Chamgordani Z., Gavanji J., Sinaei J., Hassani D.*
COMPARING THE ANTI-CANDIDA ALBICANS EFFECT OF ZINGIBER OFFICINALE WITH COMMON ANTIFUNGAL DRUGS

37. *Masnavi E., Hasanzadeh S.*
FREQUENCY OF AMINOGLYCOSIDES RESISTANCE GENES (ANT(4')-IA, APH(3')-IIIA, AAC-(6')-IE-/APH]2) IN STAPHYLOCOCCUS AUREUS ISOLATED FROM SURGICAL AND RESPIRATORY SITE INFECTIONS

44. *Shahsafi M., Madrnia M., Mohajerani H.R., Akbari M.*
EVALUATION OF THE ANTIBACTERIAL ACTIVITY OF CYNARA SCOLYMUS EXTRACT AND ITS WOUND HEALING POTENCY AGAINST MULTIDRUG-RESISTANT *ACINETOBACTER* BAUMANNII, *In vitro* AND *In Vivo* STUDY

57. *Kanannejad Z., Hosseini S.F., Karimpour F., Taylor W.R, Gevorgian L., Ghatee M. A.*
EXPLORING CLIMATIC AND GEOGRAPHICAL DRIVERS OF HEPATITIS B VIRUS SPREAD IN KOHGILUYEH AND BOYER-AHMAD PROVINCE, IRAN

67. *Sametzadeh M., Roghani M., Askarpour S., Shayestezadeh B., Hanafi M.G.*
NON-ENHANCED CT FINDINGS IN PATIENTS SUSPECTED OF ACUTE APPENDICITIS WITH NON-DIAGNOSTIC ULTRASONOGRAPHY

75. *Zharfan A.S., Airlangga P.S., Santoso K.H., Fitriati M.*
PERIOPERATIVE MANAGEMENT OF CESAREAN SECTION IN A PATIENT WITH SEVERE SCOLIOSIS: A CASE REPORT

82. *Mohammadi Arani F., Shirmohammadi M., Tavakol Z., Karami M., Raeisi Shahraki H., Khaledifar A.*
EFFECTIVENESS OF COGNITIVE BEHAVIORAL THERAPY ON SEXUAL SELF-EFFICACY IN REPRODUCTIVE-AGED WOMEN WITH CARDIOVASCULAR DISEASE (A RANDOMIZED CLINICAL TRIAL STUDY)

91. *Maghakyan S.A., Aghajanova E.M., Khachaturyan S.R., Hrantyan A.M., Melkonyan N.R., Aleksanyan A.Y., Barseghyan E.S., Muradyan A.A.*
ASSOCIATION OF PRIMARY HYPERPARATHYROIDISM AND PAPILLARY THYROID CARCINOMA IN A PATIENT WITH BROWN TUMOR AND PARKINSONISM: CASE REPORT

97. *Martirosyan D. A., Muradyan A. A.*
COVID-19 ASSOCIATED INCRUSTING CYSTITIS: A CASE REPORT

102. *Faghihrad H.R., Sheikhbagheri B., Roknabadi M., Shapouri R.*
HERBAL OINTMENT BLEND AND ANTIBACTERIAL ACTIVITY

108. *Fanarjyan R.V., Zakaryan A.V., Kalashyan M.V., Zakaryan A.N.*
ACUTE INTRATUMORAL HEMORRHAGE IN A MENINGOTHELIAL MENINGIOMA: A CASE REPORT OF EMERGENCY RESECTION

112. *Mkrtchyan R.A., Ghardyan G.K., Abrahamyan L.R., Karalyan N.Yu., Abrahamyan S.H., Abrahamyan R.A.*
SIRENOMELIA: A UNIQUE CONGENITAL ANOMALY (CLINICAL CASE)

OFFICIAL PUBLICATION OF THE YEREVAN STATE MEDICAL UNIVERSITY

THE NEW ARMENIAN MEDICAL JOURNAL

Volume19 (2025). Issue 3

The Journal is founded by
Yerevan State Medical
University after M. Heratsi.

Rector of YSMU

Armen A. Muradyan

Address for correspondence:

Yerevan State Medical University
2 Koryun Street, Yerevan 0025,
Republic of Armenia

Phones:

(+37410) 582532 YSMU
(+37493 588697 Editor-in-Chief
Fax: (+37410) 582532
E-mail:namj.ysmu@gmail.com, ysmiu@mail.ru
URL:http//www.ysmu.am

Our journal is registered in the databases of Scopus, EBSCO and Thomson Reuters (in the registration process)

SCOPUS *EBSCO*
REUTERS

Copy editor: Kristina D Matevosyan

LLC Print in "Monoprint" LLC

Director: Armen Armenakyan
Andraniks St., 96/8 Bulding
Yerevan, 0064, Armenia
Phone: (+37491) 40 25 86
E-mail: monoprint1@mail.ru

Editor-in-Chief

Arto V. **Zilfyan** (Yerevan, Armenia)

Deputy Editors

Hovhannes M. **Manvelyan** (Yerevan, Armenia)
Hamayak S. **Sisakyan** (Yerevan, Armenia)

Executive Secretary

Stepan **A. Avagyan** (Yerevan, Armenia)

Editorial Board

Armen A. **Muradyan** (Yerevan, Armenia)
Drastamat N. **Khudaverdyan** (Yerevan, Armenia)
Suren A. **Stepanyan** (Yerevan, Armenia)

Foregin Members of the Editorial Board

Carsten N. **GUTT** (Memmingen, Germay)
Muhammad **MIFTAHUSSURUR** (Indonesia)
Alexander **WOODMAN** (Dharhan, Saudi Arabia)

Coordinating Editor (for this number)

Hesam Adin **Atashi** (Tehran, Iran)

Editorial Advisory Council

Mahdi **Esmaeilzadeh** (Mashhad, Iran)
Ara S. **Babloyan** (Yerevan, Armenia)
Ines **Banjari** (**Osijek, Croatia**)
Mariam R **Movsisyan** (Gymri, Armenia) Azat A. **Engibaryan** (Yerevan, Armenia) Ruben V. **Fanarjyan** (Yerevan, Armenia) Gerasimos **Filippatos** (Athens, Greece) Gabriele **Fragasso** (Milan, Italy)
Samvel G. **Galstyan** (Yerevan, Armenia)
Arthur A. **Grigorian** (Macon, Georgia, USA)
Armen Dz. **Hambardzumyan** (Yerevan, Armenia)
Seyran P. **Kocharyan** (Yerevan, Armenia)
Aleksandr S. **Malayan** (Yerevan, Armenia)
Mikhail Z. **Narimanyan** (Yerevan, Armenia)
Yumei **Niu** (Harbin, China)
Linda F. **Noble-Haeusslein** (San Francisco, USA)
Arthur K. **Shukuryan** (Yerevan, Armenia)
Levon M. **Mkrtchyan** (Yerevan, Armenia)
Gevorg N. **Tamamyan** (Yerevan, Armenia)
Hakob V. **Topchyan** (Yerevan, Armenia)
Alexander **Tsiskaridze** (Tbilisi, Georgia)
Konstantin B. **Yenkoya**n (Yerevan, Armenia)
Peijun **Wang** (Harbin, Chine)

OFFICIAL PUBLICATION OF THE YEREVAN STATE MEDICAL UNIVERSITY