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PARKINSON'S DISEASE SUBTYPES: LITERATURE REVIEW

Diachenko P. Y., Moskovko G. S.

National Pirogov Memorial Medical University, Vinnytsya (Pyrogov street 56, Vinnytsya, Ukraine, 21018)

Responsible for correspondence:
e-mail: dr.diachenko1993@gmail.com

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Annotation. Parkinson's disease, like most neurodegenerative diseases, is clinically heterogeneous with a broad spectrum of motor and non-motor features. A number of studies have proposed and described subtypes of Parkinson's disease based on the characteristics of symptoms, which can be grouped. Subtyping makes possible optimization of the research of Parkinson's disease etiology, pathogenesis, prognosis and response to treatment, as subtypes should reflect the main pathomorphological and pathophysiological differences between patients. This review considered subtypes of Parkinson's disease identified so far, grouped common concepts and understanding of the relationship between subtypes and disease progression. A systematic review of articles in PubMed between 2009 and 2020 was performed using the following search terms: "Parkinson's disease subtypes", "Parkinson's disease phenotypes" for the time period of last 10 years (2009-2020). In this review article the most commonly identified subtypes of Parkinson's disease and their distinguishing features were discussed. As a result, 12 articles were identified, among them, 3 were data driven (cluster analysis). The classification based on the motor features of the disease, suggested by Jankovic et al. in 1990, remains the most popular to this day (tremor-dominant, akinetic-rigid or so called postural instability with gait impairment and mixed), but it is not very reliable, because patients tend to switch subtypes as the disease progresses. Cluster data analysis studies lack reproducibility and the method itself is too complex to be routinely used in clinical practice. In addition, it is yet not clear, if we are dealing with subtypes or just different stages of the disease. Thus, it was detected that the existing methods of Parkinson's disease subtyping by cluster data analysis and classification into motor subtypes cannot be considered fully correct and generally accepted, because the disease is not static and patients can change the subtype (especially in the early stages of the disease), although motor phenotypes utilization remains the most prevalent today. It is obvious, that subtyping requires inclusion of other features (genetic, molecular, neuroimaging) into analysis of the disease, in addition to clinical manifestations.

Keywords: Parkinson's disease, Parkinson's disease phenotypes, Parkinson's disease subtypes, Parkinson's disease prognosis.

Introduction

A lot of different systems of grouping and classification of Parkinson's disease have been proposed and the question raises about which ones are the most useful and what their implications for further research are. They can be considered as tools for improving research methods, as well as medical or non-medical treatment. These advantages can only be used if subtypes are implemented in clinical trials. Due to chronic, multifaceted, and progressive nature of Parkinson's disease, there are many possible ways for phenotypes identification. Subtyping of Parkinson's disease can be based on the presence of motor or non-motor symptoms, cognitive characteristics, on age of manifestation, rate of progression or the appearance of a symptom at a certain point of the disease (e.g., dementia) [15].

Purpose - review available modern literature data for information about description of the existing concepts of patients with Parkinson's disease division into subtypes in order to better understand the etiology, pathogenesis, directions of research for potential biomarkers, therapeutic targets and determination of more accurate disease prognosis.

Materials and methods

Relevant articles from PubMed database were analyzed. The search was performed by keywords "Parkinson's

disease subtypes", "Parkinson's disease phenotypes" for the time period of last 10 years (2009-2020). Articles describing small samples of patients (less than 100 subjects) were excluded from the review. An overview of the original research studies results and cluster data analysis studies is presented.

Results and discussion

12 suitable articles were identified. There are two main approaches to derive subtype classifications: empirical classification, based on clinical observation of Parkinson's disease heterogeneity, and cluster data analysis classification, where relationships between variables are used to find connected groups without a priori hypothesis which variable should belong to a certain subtype. To validate subtypes identified by clustered data analysis, reproducibility must be demonstrated on independent cohorts, and if valid, new clusters will have characteristics similar to the primary distribution [14].

Empirical identification of Parkinson's disease subtypes uses more convenient, easily measurable signs of the disease. The most common empirical forms are tremor-dominant versus non-tremor-dominant (also called postural instability and gait impairment or akinetic-rigid) and early versus late onset. Tremor-dominant, postural instability with gait impairment and mixed subgroups are

most often determined according to the method used by J. Jankovic et al. (1990), that uses the sum of UPDRS tremor elements (history of hand tremor, facial tremor at rest, arms, legs, postural and kinetic hand tremor), divided by the sum of akinetic-rigid elements of UPDRS (postural instability and gait freezing, history of falls) [9]. This ratio divides Parkinson's disease into subtypes as follows: 1.0 is classified as postural instability with gait impairment, >1.5 is classified as tremor-dominant, 1.0-1.5 is classified as mixed. The prognostic value of empirically defined subtypes (early versus late onset and akinetic-rigid versus tremor-dominant) has been demonstrated earlier in a number of studies, which imply early manifestation and tremor-dominant phenotype to be associated with slower disease progression [18].

M. Selikhova et al. (2009) made an attempt to confirm the subtype classification on the basis of the results published by Lewis et al. (2005) by analyzing data obtained from 242 patients with Parkinson's disease [13, 19]. The groups were established as: early onset (25%), tremor-dominant (31%), non-tremor-dominant (bradykinetic) (36%) and rapid progression without dementia (8%). A strong association between non-tremor-dominant subgroup and cognitive impairment has been reported. The group of earlier disease onset showed longer life expectancy, longer delay in onset of falls and dementia. Patients with the tremor-dominant form did not have a significant longer life expectancy and showed no difference in the mean time to dementia and hallucinations onset. Rapid progression was associated with older age, early depression, early motor axial symptoms and, in 70% of cases, with tremulous onset. Non-tremor-dominant subgroup had broader spreading of cortical Levy bodies than other groups, greater accumulation of amyloid- β plaques and more prominent cerebral amyloid angiopathy than other subgroups. A direct relationship has been established between bradykinetic onset, decreased cognitive function, and Levy body deposition in the neocortex [19].

S. M. Van Rooden et al. (2011) collected data on motor and non-motor symptoms of 802 patients with Parkinson's disease in two different European predominant cohorts. Four subtypes of the disease were identified: cluster 1 (49%) was characterized by a generally mild severity of impairment in all clinical domains. These patients were relatively young, had an earlier age of manifestation, less duration of administration and dose of dopaminergic drugs. Cluster 2 subtype (13%) was characterized by severe motor complications, moderate sleep problems and depressive symptoms. These patients had a longer duration of the disease, longer administration and greater dose of dopaminergic drugs than patients of other subtypes. Patients of this subtype were relatively young and had the youngest age of manifestation; the proportion of women was relatively large. Cluster 3 was characterized by impairment of non-dopaminergic domains (axial motor features, cognitive decline, depression, psychotic

symptoms, excessive daytime sleepiness and autonomic dysfunction) without severe motor complications, while cluster 4 was severely affected in all domains. The subtypes mostly had similar average duration of the disease [22].

D. J. Burn et al. (2012) examined 513 patients with Parkinson's disease. Taking into account motor symptoms, they indicated increased anxiety in patients with early onset of the disease and motor fluctuations. In contrast, the onset of depression was strongly associated with axial motor symptoms (postural instability with falls and stiffness) [2].

T. Herman et al. (2014) divided the cohort of patients with Parkinson's disease into a subtype of predominant postural instability with gait impairment (N=62) and a tremor-dominant subtype (N=42), but marked two additional subgroups of patients with the most prominent features of each subtype (N=31 and N=32 respectively) [7]. An interesting and unpredictable finding was that the number of steps per day did not differ between the groups. Only the subgroup with pure postural instability and gait impairment had reduced gait speed (in single and double task conditions), shorter steps, increased step length variability and decreased regularity of steps. The authors also noted an overlap between groups in many objective gait features and the predominance of mixed subtypes over pure [7].

S. M. Fereshtehnejad et al. (2015) identified three subtypes of Parkinson's disease on a cohort of 113 patients: predominantly motor with slow progression, diffuse (malignant) and intermediate. Despite the similar age and duration of the disease, patients with diffuse (malignant) phenotype were more likely to have mild cognitive impairment, orthostatic hypotension, and sleep behavior with rapid eye movement at baseline, and they demonstrated more rapid cognitive impairment and progression of motor and non-motor symptoms on follow-up. By increasing the sample size to 421 patients and adding new selection criteria, S. M. Fereshtehnejad et al. (2017) did not change the classification (223 were classified as predominantly motor subtype, 146 - to intermediate and 52 - to diffuse malignant), but noted that patients with diffuse malignant subtype had more pronounced dopaminergic deficiency, liquor profile similar to Alzheimer's disease, greater atrophy in specific areas of the brain and faster progression [5, 6].

M. Lawton et al. (2015, 2018) examined 769 patients and determined three most important factors, such as features of psychological well-being, non-tremor motor features and cognitive features. Five cluster models were identified, respectively, which defined the groups, which were characterized by: 1. mild impairment of motor and non-motor sphere (25.4%), 2. poor posture and cognitive abilities (23.3%), 3. severe tremor (20.8%), 4. poor psychological well-being, sleep disorders with rapid eye movement (18.9%) and 5. severe motor and non-motor disease with poor psychological well-being (11.7%). Subsequently, authors conducted another cluster analysis,

increasing the analyzed sample to 2545 people with Parkinson's disease. The number of subtypes has been reduced to three by combining a cluster of poor psychological well-being, sleep disorders with rapid eye movement and a cluster of severe motor and non-motor illnesses with poor psychological well-being. It was also noted that postural hypotension and worsening of cognitive status predicted faster progression of motor symptoms [11, 12].

T. Simuni et al. (2016) observed a sample of 320 patients with Parkinson's disease to study the stability of subtypes as the disease progresses. Patients were classified into subtypes during the 1st year of observation and included into the analysis. At the beginning 228 (71%) participants were classified as a tremor-dominant form, 56 (18%) as postural instability with gait impairment, and 36 (11%) as an intermediate form. After a year of observation and re-evaluation, 215 (67%) were re-classified as tremor-dominant; 68 (21%) as postural instability with gait impairment, 37 patients (12%) as an intermediate form. Taking into account migration from one subgroup to another, 82% remained tremor-dominant, 10% developed postural instability with gait impairment and 8% became intermediate. For the initially postural instability and gait impairment 61% remained unchanged, 29% switched to the tremor-dominant form and 10% to the mixed form. For the initially classified intermediate subtype 36% remained intermediate, 33% became tremor-dominant and 31% moved into the subgroup of postural instability with gait impairment. Thus, 39% of subjects with the initial subtype of postural instability with gait impairment versus 18% of the tremor-dominant subtype changed the subtype during the first year of follow-up. In order to investigate the effect of dopaminergic therapy, same analysis was repeated in the subgroups of subjects during the "Off" state versus the "On" state. The effect of drugs did not affect the classification. There was no difference in the subgroup of subjects who changed subtype compared to stable patients by any demographic characteristics, age of onset, duration of illness, or most affected domain. The authors doubt the appropriateness of the existing system of subtyping Parkinson's disease due to the above-described changes in the subtype during disease progression [20].

J. Mu et al. (2017) conducted a cluster analysis on a cohort of patients with Parkinson's disease (N=951). The authors identified four main clusters: mild, non-motor predominant, motor predominant and severe. In addition, six new smaller subgroups were identified from the clustering of symptoms, each of which was characterized by clinically significant non-motor symptoms. Cluster S1 is similar to a mild subtype. S2-S6, while increasing in the severity of motor symptoms, were expressed by specific non-motor symptoms, thus supporting the clinical concept of non-motor symptoms based subtyping. The main components of the S2 cluster included restless legs syndrome, swallowing disorders, pain. Cluster S3 was characterized by impaired urination. Cluster S4 was

characterized by symptoms of mood swings/apathy. Clusters S5 and S6 are of particular clinical interest because they are non-motor symptoms predominant, that overshadows motor symptoms with an emphasis on cognitive impairment in S5 and autonomic (cardiovascular and gastrointestinal) symptoms in S6. The clusters, discovered in this study, provide statistical evidence of the increasingly important role of non-motor symptoms in the heterogeneity of Parkinson's disease [16].

D. Aleksowski et al. (2018) observed a sample of 254 patients with Parkinson's disease during 4 years. After division into subtypes, the number of patients who had postural instability with gait impairment and tremor-dominant form was 36 people against 144. Patients of the postural instability with gait impairment subgroup initially had more severe motor symptoms, but faster progression was observed only in three non-motor elements of MDS-UPDRS: cognitive impairment, hallucinations with psychosis, and dopamine dysregulation syndrome. The authors support the idea about instability of classification into subgroups at the beginning of the disease (more than 60% of patients who were initially assigned to the subgroup with postural instability and gait change changed the subtype during subsequent visits, which did not happen in the tremor-dominant subgroup) [1].

X. Huang et al. (2019) observed 132 patients with early Parkinson's disease, which were included into analysis after a comprehensive examination of motor and non-motor symptoms. The division into subtypes was: 50% tremor-dominant, 35.6% postural instability with gait impairment and 14.5% as mixed. Postural instability with gait impairment subtype was characterized by significantly more serious sleep problems, fatigue and urination disorders, which were identified as the most important factors influencing the quality of life, regardless of relation to motor subtype [8].

T. Konno et al. (2018) analyzed 1003 patients, 694 of them were observed again after a few years. Data were collected on motor and non-motor symptoms during the first and last visit. Based on the most pronounced symptoms at the first visit, patients were classified into four subtypes: tremor-dominant, akinetic-rigid, gait impairment and mixed. Tremor-dominant was the most common subtype (44%), followed by akinetic-rigid (29%), mixed (18%) and gait disorders (9%). Rapid progression was observed in the subtype of gait impairment more often compared to akinetic-rigid. Hallucinations occurred in the akinetic-rigid form and mixed more often during the last visit in comparison with tremor-dominant form [10].

E. De Pablo-Fernández et al. (2019) identified the following subtypes of the disease: motor predominant, diffuse malignant with non-motor symptoms predominance and mixed. Several conclusions have been drawn about the mechanisms underlying the clinical and pathological variability of Parkinson's disease. Younger patients with a predominance of motor symptoms had a slow course of

the disease and neuropathological progression before they reached the terminal stages of the disease. The duration of the disease directly correlated with severity of clinical and pathological progression in this subgroup. Additional factors may contribute to the faster spread of Lewy bodies in all parts of the brain in diffuse malignant subtype. For example, other age-related pathologies and comorbidities hasten the progression of the clinical picture in elderly patients with a more complex course of the disease [3].

R. Erro et al. (2019) studied the stability of the Parkinson's disease classification in a cohort of 103 patients for 4 years. The classification was performed by motor function: tremor-dominant subtype against postural instability with gait disorders and tremor-dominant subtype against akinetic-rigid. Approximately half of the cohort changed subtype within the first 2 years, regardless of the classification scheme. A lower level of shifts was observed in the period from 2 to 4 years of observation. The authors question feasibility of dividing Parkinson's disease into subtypes in the early stages of the disease [4].

While discussing the classification of Parkinson's disease, it is worth paying attention to genetic biomarkers. During the study of the genetics of Parkinson's disease, it was found that the genotype can determine the subtype of the disease. For example, patients with the LRRK2 mutation have asymmetric tremor, a slight reduction in the risk of dementia, and hyposmia. Patients with the parkin mutation have a subtype with a normal sense of smell and a low incidence of dementia, as well as a more severe dystonia and hyperreflexia. It should be noted that patients with the parkin gene mutation are not determined by presence of synuclein on pathomorphological examination, which questions the presence of true Parkinson's disease in these patients. Humans with the SNCA mutation have a poor prognosis, i.e. reduced response to levodopa, a higher risk of dementia, mental, pyramidal disorders, and rapid progression. A new endophenotype of Parkinson's disease with the rs356182 GG genotype near SNCA was also identified, which reduced SNCA expression in the cerebellum, resulting in a tremor-dominant phenotype with a slower rate of progression. There are also clear links between GBA gene mutations and traits that determine diffuse malignant subtype features with a threefold increase in the risk of developing dementia. Genetic-based classification does not necessarily have to be considered as separate subtypes, but rather as single markers of disease progression. However, given that by default penetrant genetic mutation is the cause of Parkinson's disease in selected person, the genetic association contributes to the understanding of the intersection between clinical and pathophysiological features [6, 17].

The classification of Parkinson's disease using cluster analysis has the disadvantage that only 2 studies have demonstrated cluster reproducibility in well-characterized cohorts so far [13, 21, 22]. Also, data is quite limited on longitudinal monitoring, as the disease progresses [15].

Motor subtypes (tremor-dominant and akinetic-rigid or postural instability with gait impairment) may be not exactly different subtypes of Parkinson's disease, but stages as well. Patients, who present with tremor-dominant symptoms, usually become akinetic-rigid during progression of the disease and suffer from all complications of long-term disease. The practical significance of the evidence presented is that clinicians should be careful to inform patients that the presence of tremor portends a milder disease [15].

The existence of "indeterminate", or "mixed" subtype requires inclusion of other features (genetic, molecular, neuroimaging) into analysis of the disease, in addition to clinical manifestations, which should more accurately explain the heterogeneity of the disease.

Table 1. Parkinson's disease subtypes, identified by review of literature data (2009-2019).

Studies	Identified subtypes
van Rooden S. M., Colas, F, Martinez-Martin P., Visser M., Verbaan D., Marinus J., Chaudhuri R. K., Kok J. N, van Hilten J. J. Clinical subtypes of Parkinson's disease. <i>Mov. Disord.</i> , 2011*	1. Mild impairment of all clinical domains 2. Severe motor complications 3. Impairment of non-dopaminergic domains 4. All domains severely affected
Selikhova M., Williams D. R., Kempster P. A., Holton J. L., Revesz T., Lees A.J. A clinico-pathological study of subtypes in Parkinson's disease. <i>Brain</i> , 2009	1. Early onset 2. Tremor-dominant 3. Non-tremor-dominant 4. Rapid progression without dementia
Fereshtehnejad S. M., Romenets S. R., Anang J. B., Latreille V., Gagnon J. F., Postuma R. B. New Clinical Subtypes of Parkinson Disease and Their Longitudinal Progression: A Prospective Cohort Comparison With Other Phenotypes. <i>JAMA Neurol.</i> , 2015	1. Motor-predominant with slow progression 2. Diffuse (malignant) 3. Intermediate
Lawton M., Ben-Shlomo Y., May M. T., Baig F., Barber T. R., Klein J. C. Developing and validating Parkinson's disease subtypes and their motor and cognitive progression. <i>J. Neurol. Neurosurg. Psychiatry</i> , 2018*	1. Mild impairment of motor and non-motor sphere 2. Severe tremor 3. Severe motor and non-motor disease with poor psychological well-being
Mu J., Chaudhuri K. R., Bielza C, de Pedro-Cuesta J., Larra?aga P., Martinez-Martin P. Parkinson's Disease Subtypes Identified from Cluster Analysis of Motor and Non-motor Symptoms. <i>Front Aging Neurosci.</i> , 2017*	1. Mild 2. Non-motor predominant 3. Motor predominant 4. Severe
Konno T., Deutschlander A., Heckman M. G., Ossi M., Vargas E. R. Comparison of clinical features among Parkinson's disease subtypes: A large retrospective study in a single center. <i>J. Neurol. Sci.</i> , 2018	1. Tremor-dominant 2. Akinetic-rigid 3. Gait impairment 4. Mixed
De Pablo-Fernandez E., Lees A. J., Holton J. L., Warner T. T. Prognosis and Neuropathologic Correlation of Clinical Subtypes of Parkinson Disease. <i>JAMA Neurol.</i> , 2019	1. Motor predominant 2. Diffuse malignant with non-motor symptoms predominance 3. Mixed

Continuation of table 1.

Studies	Identified subtypes
- Rosenberg-Katz K, Herman T, Jacob Y, Giladi N, Hendler T, Hausdorff JM. Gray matter atrophy distinguishes between Parkinson disease motor subtypes. <i>Neurology</i> . 2013 - Herman T, Weiss A, Brozgov M, Giladi N, Hausdorff J. M. Gait and balance in Parkinson's disease subtypes: objective measures and classification considerations. <i>J. Neurol.</i> , 2014 - Simuni T, Caspell-Garcia C., Coffey C., Lasch S., Tanner C., Marek K. How stable are Parkinson's disease subtypes in de novo patients: Analysis of the PPMI cohort. <i>Parkinsonism Relat Disord.</i> , 2016 - Aleksovski D., Miljkovic D., Bravi D., Antonini A. Disease progression in Parkinson subtypes: the PPMI dataset. <i>Neurol. Sci.</i> , 2018 - Huang X., Ng S. Y., Chia N. S., Setiawan F., Tay K. Y., Au W. L., Tan E. K., Tan L. C. Non-motor symptoms in early Parkinson's disease with different motor subtypes and their associations with quality of life. <i>Eur. J. Neurol.</i> , 2019	1. Tremor-dominant 2. Postural instability with gait impairment 3. Intermediate
* - cluster data analysis	

The conclusions of the Parkinson's disease subtyping studies are presented in table 1.

Conclusions and prospects for further development

1. Existing methods for determining subtypes of Parkinson's disease using cluster data analysis and motor subtypes classification cannot be considered correct and generally acceptable, because the disease is not static and patients can change the subtype, especially in the early stages of the disease. Determinants specific to a particular stage of Parkinson's disease may lead to the inclusion of the same patient into different subtypes of Parkinson's disease during particular stages of the disease.

As long as motor subtypes cannot be clearly differentiated from Parkinson's disease stages, they should not be used to stratify patients in studies. Optimally, subtypes of Parkinson's disease should reflect a set of symptoms that remain stable in patients and allow them to be identified throughout the course of the disease, despite the change in the clinical picture. It is important to imply that these sets of features should include not only a set of clinical symptoms but also biological markers.

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ПІДТИПИ ХВОРОБИ ПАРКІНСОНА: ОГЛЯД ЛІТЕРАТУРИ

Дяченко П.Ю., Московко Г.С.

Анотація. Хвороба Паркінсона є клінічно неоднорідною, як і більшість нейродегенеративних захворювань, і має широкий спектр моторних та немоторних проявів. У ряді досліджень запропоновано та описано підтипи хвороби Паркінсона на основі особливостей проявів, які можливо згрупувати. Субтипизування надає змогу оптимізувати дослідження етіології, патогенезу, прогнозування та реакції на лікування хвороби Паркінсона, оскільки підтипи повинні відображати основні патоморфологічні та патофізіологічні відмінності між хворими. У статті розглянуто, які підтипи хвороби Паркінсона були визначені на даний час, узагальнено загальноприйняті поняття та розуміння зв'язку між підтипами та прогресуванням захворювання. Було проведено систематичний огляд статей бази даних PubMed між 2009 і 2020 роками, використовуючи такі пошукові терміни: "Parkinson's disease subtypes", "Parkinson's disease phenotypes" за період останніх 10 років (2009-2020). У цій оглядовій статті було обговорено найчастіше виявлені підтипи хвороби Паркінсона та їх відмінні риси. В результаті визначено 12 статей, що відповідають вищезазначеним критеріям, серед них 3 - з кластерним аналізом даних. Класифікація, заснована на рухових особливостях захворювання, запропонована Jancovic et al. в 1990 р. залишається найпопулярнішою і донині (тремор-домінантна форма, акінетико-ригідна, вона ж - постуральна нестабільність з порушенням ходи та змішана). Дослідження, що проводились за допомогою кластерного аналізу даних, не мають відтворюваності на незалежних вибірках і занадто складні, щоб їх можна було регулярно використовувати в клінічній практиці. Крім того, поки точно незрозуміло, чи ми маємо справу з підтипами чи лише з різними стадіями захворювання. Таким чином, визначено, що існуючі методи субтипизування хвороби Паркінсона за допомогою кластерного аналізу даних та класифікації на моторні підтипи не можна вважати коректними та загальноприйнятими через те, що хвороба не є статичною і пацієнти можуть, особливо на ранніх етапах захворювання, змінювати підтип, хоча на сьогодні найбільшу розповсюдженість і досі має розподіл на моторні підтипи. Очевидно, що субтипизування потребує включення інших ознак (генетичних, молекулярних, нейровізуалізаційних) в аналіз захворювання на додачу до клінічних проявів.

Ключові слова: хвороба Паркінсона, підтипи хвороби Паркінсона, субтипи хвороби Паркінсона, фенотипи хвороби Паркінсона, прогноз хвороби Паркінсона.

ПОДТИПИ БОЛЕЗНИ ПАРКИНСОНА: ОБЗОР ЛИТЕРАТУРЫ

Дяченко П. Ю., Московко Г. С.

Аннотация. Болезнь Паркинсона является клинически неоднородной, как и большинство нейродегенеративных заболеваний, и имеет широкий спектр моторных и немоторных проявлений. В ряде исследований предложены и описаны подтипы болезни Паркинсона на основе особенностей проявлений, которые можно сгруппировать. Субтипирование дает возможность оптимизировать исследование этиологии, патогенеза, прогнозирования и реакции на лечение болезни Паркинсона, поскольку подтипы должны отражать основные патоморфологические и патофизиологические различия между больными. В статье рассмотрено, какие подтипы болезни Паркинсона были определены в настоящее время, обобщенно общепринятые понятия и понимание связи между подтипами и прогрессированием заболевания. Был проведен систематический обзор статей базы данных PubMed между 2009 и 2020 годами, используя такие поисковые термины: "Parkinson's disease subtypes", "Parkinson's disease phenotypes" за период последних 10 лет (2009-2020). В этой обзорной статье обсуждались наиболее часто обнаруженные подтипы болезни Паркинсона и их отличительные черты. В результате определены 12 статей, соответствующие вышеуказанным критериям, среди них 3 - с кластерным анализом данных. Классификация, основанная на двигательных особенностях заболевания, предложенная Jancovic et al. в 1990 г. остается популярной и по сей день (тремор-доминантная форма, акинетико-ригидная, она же - нестабильность с нарушением походки и смешанная). Исследования, которые проводились с помощью кластерного анализа данных, не имеют воспроизводимости на независимых выборках и слишком сложны, чтобы их можно было регулярно использовать в клинической практике. Кроме того, пока точно непонятно, мы имеем дело с подтипами или только с различными стадиями заболевания. Таким образом, определено, что существующие методы субтипирования болезни Паркинсона с помощью кластерного анализа данных и классификации на моторные подтипы нельзя считать корректными и общепризнанными из-за того, что болезнь не статична и пациенты могут, особенно на ранних этапах заболевания, изменять подтип, хотя на сегодня наибольшую распространенность и до сих пор имеет деление на моторные подтипы. Очевидно, что субтипирование требует включения других признаков (генетических, молекулярных, нейровизуализационных) в анализ заболевания дополнительно к клиническим проявлениям.

Ключевые слова: болезнь Паркинсона, подтипы болезни Паркинсона, субтипа болезни Паркинсона, фенотипа болезни Паркинсона, прогноз болезни Паркинсона.