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Frailty syndrome and its features in Parkinson's diseas

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ABSTRACT

Frailty syndrome is common in older adults around the world, and its emergence is associated with an increase in life expectancy. The lecture shows the multifactorial nature of the syndrome: changes in physical health, social and psychological factors, gender characteristics, and age. The classic diagnosis of the syndrome consists in assessing physical weakness according to the Fried phenotype. The modern view of the problem complements the diagnosis with indices of weakness to characterize multifactorial development and the use of digital wearable technologies for long-term health monitoring.

The lecture provides a detailed justification of the effect of comorbidity on the development of frailty syndrome. Frailty syndrome is difficult to diagnose in Parkinson's disease with possibly high prevalence. There are few studies on frailty syndrome in Parkinson's disease, probably due to the similarity of their symptoms.

The lecture identifies possible risks of frailty syndrome in Parkinson's disease: the influence of various forms of Parkinson's disease, gender, cognitive and functional disorders, polypharmacy, and levodopa doses. The role of a multidisciplinary rehabilitation team and independent physical activity in Parkinson's disease and frailty syndrome is shown.

Keywords: frailty syndrome, diagnosis, comorbidity, Parkinson's disease

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Синдром старческой астении и его особенности при болезни Паркинсона

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РЕЗЮМЕ

Синдром старческой астении распространен во всем мире, и его появление связано с увеличением продолжительности жизни. В лекции показаны мультифакторность формирования синдрома: изменения физического здоровья, социальные и психологические факторы, а также гендерные особенности и влияние возраста. Классическая диагностика синдрома состоит в оценке физической слабости по фенотипу Фрайд. Современный взгляд на проблему дополняет диагностику индексами слабости для характеристики мульти-

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факторности развития и применением цифровых носимых технологий для длительного мониторирования функциональных показателей пациента.

Дано развернутое обоснование влияния коморбидности на развитие старческой астении. Особенностью синдрома старческой астении при болезни Паркинсона является трудность его диагностики при возможно высокой распространенности. Исследования старческой астении при болезни Паркинсона малочисленны, вероятно, из-за схожести симптомов болезни и синдрома.

Определены возможные риски возникновения старческой астении при болезни Паркинсона: влияние различных форм болезни Паркинсона, пола, когнитивных и функциональных нарушений, полипрагмазии, дозы леводопы. Показана роль комплексной мультидисциплинарной реабилитации и самостоятельной физической активности при сочетании болезни Паркинсона и синдрома старческой астении.

Ключевые слова: синдром старческой астении, диагностика, коморбидность, болезнь Паркинсона

Конфликт интересов. Автор декларирует отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

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INTRODUCTION

Worldwide, the pace of population aging is fast and much faster than it used to be in the past. For example, in China in 2021, the elderly population comprised 14.2%, being the largest in the world in absolute terms. By 2050, the elderly population in China will increase to 395 million people, which will exceed the current population of the United States by 1.2 times. At the same time, the total fertility rate (the number of births per 1 woman during the reproductive period) was 6:1 in 1955 and 1:3 in 2020 [1].

The demographic change associated with population aging has a comprehensive impact on the life of society, since in addition to physiological changes during aging, which can reduce functional and adaptive capabilities to varying degrees, an elderly person often has a number of diseases with concomitant drug therapy, unfavorable lifestyle features, and social conditions [1–4]. These factors contribute to an increase in the healthcare burden, disability, inability to self-care, and the need for social care. Frailty syndrome can be attributed to an extreme combination of factors.

The syndrome is characterized by a progressive decrease in strength, strength endurance, functional reserve, increased vulnerability of the body to stress factors, dependence on other people during daily activity, and adverse outcomes [2]. The situation is complicated by the fact that a decrease in the birth rate and an increase in the elderly population lead to a decrease in the number of middle-aged working people and an increase in working elderly people, including those with concomitant diseases and a decline in the functional status [5]. Taking all this into account, the leaders of many countries cannot but plan to increase the retirement age in order to maintain economic stability. In this regard, a new term “the expected duration of a healthy working life” has appeared [5].

In order to find a consensus, the UN General Assembly declared 2021–2030 the Decade of Healthy Aging. During this decade, various activities are planned to improve the lives of older people today and in the future. These include early detection and therapy of frailty syndrome, as well as preventive measures among the elderly and youth and creation of a model of healthy aging [1].

The aim of this lecture was to bring to the attention of the medical community frailty syndrome, its manifestations, and the difficulty of diagnosing the syndrome in Parkinson’s disease.

EPIDEMIOLOGY AND PATHOGENESIS OF FRAILTY SYNDROME

The prevalence of frailty syndrome is high worldwide [3]. It ranges from 4 to 59% among the elderly. The syndrome is widespread in the elderly population not only in high-income countries with longer life expectancy, but also in low-income countries, for example, in Brazil and Vietnam [1–4, 6]. Social and economic inequality leads to different incidence of the syndrome. Even in one country, the incidence may vary. For example, the syndrome

occurs in European countries more often in the south than in the north, in accordance with the geographical grade of the prevalence of concomitant pathology [7].

Most often, the cycle of frailty syndrome formation includes poor nutrition in terms of quality and / or quantity, a progressive decrease in muscle mass (sarcopenia), and decreased strength, mobility and activity of daily living. Age-related type 2 muscle fiber atrophy responsible for exercise training is the main reason for a decrease in physical capabilities. However, not every elderly person of the same age is diagnosed with frailty.

Frailty syndrome is a multifactorial syndrome that includes various factors: physical, psychological, and social. The interaction between these factors determines the severity of the syndrome. Concomitant diseases, such as deforming arthrosis, Parkinson's disease, diabetes mellitus, and others contribute to its emergence [8, 9]. Frailty syndrome is provoked by both diseases and lifestyle features. Social isolation, living in a nursing home, taking medications without considering side effects, polypharmacy, and a sedentary lifestyle accelerate the development of the syndrome [10, 11].

Women are more likely to suffer from frailty syndrome [12]. Despite their long life expectancy, unlike men of the same age, they sometimes have several diseases, but not critical. This dissonance is designated as the male – female health survival paradox. Men are more likely to suffer from life-threatening diseases, such as coronary heart disease and stroke. In addition, men are more likely to suffer from type 2 diabetes mellitus, non-specific lung diseases, chronic obstructive bronchitis, peptic ulcer, and Parkinson's disease. Women of the same age are more likely to have non-fatal diseases that are associated with a worse quality of life: migraine, musculoskeletal pathology, autoimmune diseases [7, 13]. Cancer prevails in men until old age, and in women from the age of 75.

The frequency of frailty increases with the age of an elderly person [10]. Since the life expectancy of men is shorter than that of women, the frequency of the syndrome increases as women get older.

DIAGNOSIS AND CLINICAL VARIANTS OF FRAILTY SYNDROME

An experienced doctor with knowledge of the syndrome intuitively understands that a patient has frailty syndrome. Patients move slowly and get tired very quickly. They complain that they cannot perform basic household chores. Currently, there is no unanimous opinion on the diagnosis of the syndrome. Doctors use different assessment scales. Assessment of the criteria that are pre-defined for the Fried frailty phenotype is most commonly used to diagnose weakness [2, 14].

The Fried frailty phenotype includes the following criteria: weight loss of more than 5 kg per year, hand grip strength, fatigue in the last month (the physician either asks a patient about their symptoms or uses questionnaires to assess them), slow gait speed (less than 4 meters in 5 seconds), and daily physical activity [2]. A patient is considered frail if at least three criteria are positive and pre-frail if one or two criteria are positive [15]. The Fried criteria are criticized because they evaluate only physical weakness.

The new concept of frailty syndrome interprets the syndrome as a multiple domain consisting of biological, social, psychological, and functional disorders [15]. Therefore, in addition to evaluating the Fried frailty phenotype, physicians use other scales. For example, the Rockwood Clinical Frailty Scale includes 7 points. The EFS scale (Edmonton Frail Scale) consists of 9 components. Ten additional cognitive components have been added to the FI-CGA (Frailty Index Comprehensive Geriatric Assessment). The Tilburg Frailty Indicator aims at assessing physical, psychological, and social condition of an elderly person. The scales include questions about education, nutrition, medications taken, episodes of falling and identify disorders of cognitive status, bladder function, etc. [15, 16].

In addition to scales, modern instrumental diagnosis is used, including digital wearable technologies separately or in combination with platforms, and video cameras. It is especially important to diagnose daily activity, including walking, climbing stairs, washing, dressing, eating, going to bed [16, 17]. Daily activity can be combined with a task that involves a cognitive component. Inertial sensors of wearable technologies on the waist and lower extremities based on the operation of an accelerometer or gyroscope are used to describe gait. Additional inertial sensors on the waist help diagnose balance disorders [16–19].

The area of the stabilogram of an elderly person obtained during monitoring is interrelated with the criteria of the Fried frailty phenotype. For diagnosis, built-in sensors are used in objects surrounding an elderly person in the form of an eChair (electronic chair), ePOD (electronic carpet) and others, combining diagnostic capabilities of wearable technology

with other parameters of the Internet of Things. The characteristic of gait includes an increase in the time of the standing phase on two legs, as this compensates for the lack of balance during movement, an irregular pattern, and a decrease in gait speed. The Stand up and Walk test is evaluated using inertial sensors and 3D anatomical motion data [17–20]. Parameters obtained during long-term monitoring undergo machine learning in the form of big data and form a phenotype model that includes kinetic parameters. Balance and gait parameters in combination with the history of falls and vector machine learning with the formation of a frailty index model are used to assess falls [19, 20].

Gait speed is the main indicator in the frailty index, all other data are integrated with this parameter. There is currently no accurate predictive model of frailty syndrome. Exergame technology is the future of digital medicine. It is an interactive gaming platform that is a diagnostic and training site for investigating the presence and reversibility of frailty syndrome [16].

Despite the fact that the main age-related changes in body composition occur in power muscle fibers, the syndrome affects various tissues and systems: nervous, endocrine, immune and musculoskeletal [17]. The connection between cognitive impairment and physical frailty is widely known. However, comorbidity does not imply the concept of cognitive frailty in the form of dementia. Cognitive frailty is defined as the simultaneous presence of frailty syndrome based on the Fried frailty phenotype and cognitive impairment without dementia [15, 21–25].

Cognitive frailty is divided into two subtypes: reversible and potentially reversible. Reversible cognitive frailty includes an incomplete Fried phenotype – pre-frailty and subjective cognitive impairment and / or positive biomarkers. Potentially reversible frailty is more severe cognitive frailty, including mild cognitive impairment and the Fried phenotype in which all the criteria are positive. The next stage of development involves the adverse effects of cognitive frailty: falls, disability, Alzheimer's disease, non-Alzheimer's dementia, and death. The prevalence of cognitive frailty is 10.7–22.0% in clinical studies and 1.0–4.4% in population-based studies. Understanding the physiological relationship between cognitive impairment and physical frailty will help guide the development of geriatrics and neurology to create a model for the treatment of two pathological conditions [21].

In cognitive frailty, multimorbidity is observed due to chronic inflammation with changes in immune markers, the endocrine system, and oxidative stress, which negatively affect the nervous system and muscle tissue. For example, the lack of interleukin 10 (IL-10) increases the expression of the inflammatory mediator, nuclear factor NF-kV, reduces muscle metabolism, and negatively affects information processing speed. Lack of growth hormone leads to a combined decrease in brain mass and muscle mass. Elderly women, who are often diagnosed with frailty syndrome, have low ghrelin levels, which results in decreased muscle strength, endurance, and impaired memory and information processing speed [21].

Frailty syndrome can be associated with orthostatic hypotension. Orthostatic hypotension occurs in 30% of people over 65 years of age [26]. The frequency of orthostatic hypotension in the elderly population depends on comorbidity. The pathology is most often observed in Parkinson's disease, multiple system atrophy, dementia with Lewy bodies. Orthostatic hypotension is associated with falls, heart failure, stroke, decreased quality of life, and an increased risk of death [27]. Physical frailty and orthostatic hypotension increase the likelihood of adverse effects. The homeostasis of maintaining blood pressure includes the integrated activity of the nervous system, heart, blood vessels, and muscles. Age-related changes in these organs and systems lead to a decrease in baroreflex, hypoperfusion of the brain, retina and muscles, dizziness, and loss of consciousness [26, 27].

Frailty syndrome may be accompanied by pain syndrome [28]. Chronic pain occurs in 66% of the elderly and is three times more common in women than in men. The most common complaint among the elderly is lower back pain (33% of people over 65 years of age). The cause of the pain can also be deforming osteoarthritis, which occurs in 12% of the world's elderly population, or rheumatoid polyarthritis occurring in 1–2%. Pain syndrome accompanies malignant neoplasms, neurodegenerative diseases, diabetes mellitus, kidney and liver diseases [28].

Depression lowers pain tolerance, while neuroinflammation is considered as a common pathogenetic step in the development of depression and pain. Patients suffering from depression complain of a variety of common pains. The severity of frailty syndrome is aggravated in such cases [28]. Conversely, physical frailty is a predictor of depression. In 30.3% of patients with frailty syndrome without depression, the disease is subsequently diagnosed. Long–term

depression is a heavy burden for the patient and society due to its chronic course and relapses. The peculiarity of depression in the elderly is mood disorders of various etiology, combined with high comorbidity, cognitive impairment, and physical suffering.

According to literature data, frailty occurs in 6.8% of elderly patients with depression; in nursing homes the disease combination was noted more often – from 10.7 to 40% [29, 30]. The severity of frailty syndrome negatively correlates with the remission duration of depression [29]. On the other hand, severe syndrome affects the frequency of remissions and increases the risk of depression: 75% of patients with severe depression have frailty syndrome [29]. The pathophysiological mechanisms of the syndrome in depression are diverse, including low-grade inflammation, deficiency and qualitative eating disorders, especially vitamin D deficiency, low physical activity, sarcopenia, and age-related hormonal changes. Additional factors include the number of psychoactive medications taken, lack of education, loneliness, lack of socialization, and lack of Internet access at home [2]. The relationship between psychosocial factors and the occurrence of physical frailty in depression requires further study [30]. Apathy, lack of hygiene, low physical activity, and poor nutrition affect the development of depression in frailty syndrome.

Despite the general development mechanisms, the concept of physical frailty in mental distress did not go any further, since the diagnostic signs of the two pathologies overlap, even though initially no criteria in the Fried phenotype are associated with depression. Obviously, while treating patients with a combination of physical frailty and depression, it is difficult to determine cause-and-effect relationships in order to identify the primary pathology. However, there is a positive aspect in such cases, as treatment of one pathology makes the manifestations of the other less pronounced [30].

The literature presents data on the genetic predisposition to the development of frailty syndrome [31]. However, studies have not found a link between changes in candidate genes encoding IL-6, tumor necrosis factor (TNF), insulin-like growth factor-1 (IGF-1) and the onset of the syndrome, which is due to the fact that frailty syndrome is a multifactorial disease that depends on lifestyle, genetic and epigenetic factors. Epigenetic mechanisms include chromatin remodeling during aging. The genes at the 9p21-23 locus are susceptible to this process, which may be the cause of the syndrome [32].

PARADOXES OF FRAILTY SYNDROME IN PARKINSON'S DISEASE

Parkinson's disease is a neurodegenerative disease that is not the result of aging, but the risk of its occurrence increases with age. Old age contributes to the progression of the disease and a decrease in response to levodopa, a drug used to treat Parkinson's disease. The incidence of frailty syndrome in people with Parkinson's disease is high, according to the literature, from 32.6 to 55.3% [33].

Nevertheless, scientists try not to include patients with Parkinson's disease in scientific studies on the syndrome, since the clinical symptoms of the pathologies are similar. This is the paradox of diagnosing frailty syndrome in Parkinson's disease [14, 34]. Often, the concomitant syndrome is misinterpreted as aggravation of the underlying pathology [14, 34]. Usually, female patients who have got Parkinson's disease and are frail are older than men and have greater disturbances in the everyday life activity [13, 33, 35]. Women suffer from the syndrome twice more often than men, and the severity of the syndrome depends on the stage of Parkinson's disease: frailty syndrome is more common at the advanced stage of the disease [33, 35, 36].

Low physical activity and severe Parkinson's disease contribute to the emergence of frailty syndrome. These factors have got direct and indirect effects, with the latter being associated with changes in behavior, and quantity and quality of medications taken [33, 34, 37]. For example, manifestations of kinesiophobia could lead to low everyday life activity, since patients believe that any movement leads to a fall, injury, and increased pain. Patients with Parkinson's disease have high frequency of behavioral changes in the form of kinesiophobia [37]. Restriction of physical activity contributes to a poor physical condition, functional disability, and depression.

However, there is an opposite opinion about physical activity in Parkinson's disease: patients are more actively involved in physical education programs, with better commitment, regardless of all the Fried physical frailty criteria being positive [13]. In patients without Parkinson's disease, low physical activity leads to the development of frailty syndrome. Patients with Parkinson's disease have greater self-reported physical activity and are less susceptible to frailty syndrome [13].

The development of frailty syndrome is influenced not only by the duration, but also by the type of

Parkinson's disease. The syndrome is most often found in patients with predominance of postural instability and walking disorders than in those with tremor [33]. Although another paradox of the syndrome in Parkinson's disease is that tremor reduces protein synthesis in muscles. Thus, tremor may be a trigger for sarcopenia, the main age-related change leading to the onset of physical frailty [34, 36].

Polypharmacy is the use of more than 5 medications by patients with Parkinson's disease, including drugs that affect the central nervous system, dopaminergic therapy: carbidopa and levodopa, and dopamine receptor stimulators that increase the QT interval and interact with cytochrome P450, increasing the likelihood of frailty syndrome [33, 34]. High doses of levodopa increase the risk of motor complications in the form of dyskinesia, which further reduces physical activity of patients. A high dose of carbidopa or levodopa may trigger the syndrome, since taking drugs, while improving motor characteristics, does not affect postural stability and thus increases the risk of injury. In addition, carbidopa and levodopa increase the risk of osteoporosis and fractures [38].

The probability of the syndrome increases with additional intake of antidepressants and drugs that improve bladder function while increasing the anticholinergic load on the body [14]. Poor adherence to drug therapy and errors in drug intake are often the cause of hospitalization and delirium, which increases the likelihood of developing frailty syndrome [14].

Frailty syndrome in Parkinson's disease, like in other pathologies, is associated with aging, cognitive dysfunction, and orthostatic hypotension [15, 33, 39]. Inability to undertake purposeful activity is revealed in patients with Parkinson's disease, like in other neurodegenerative diseases. This disorder is a predictor of the development of frailty [15, 39]. It is more common in people living in social shelters, using additional care from a nurse or relative when performing necessary daily activities, and in hospital patients. Hospitalization of patients with Parkinson's disease and frailty syndrome is associated with an increase in 30-day mortality, an increase in the duration of hospitalization, and rehospitalization within a month [33, 35]. Fatigue, the most common criterion of the Fried phenotype in Parkinson's disease, is also a non-motor symptom of the disease. Fatigue reduces daily physical activity and contributes to the progression of frailty syndrome.

An additional examination of a patient with Parkinson's disease and suspected frailty syndrome includes filling out questionnaires to assess the risk of falls, screening using a cognitive scale, examining for orthostatic hypotension, and screening for fatigue and hallucinations [33, 40].

Early diagnosis and therapy of the syndrome in a patient with Parkinson's disease are necessary for successful therapy of comorbid pathology. Given the diagnostic paradox, it is very difficult to do this. However, the risk is increased in women with a functional status decline and cognitive impairment [41]. Therapy requires the interaction of a geriatrician, neurologist, physical rehabilitation doctor, and psychotherapist (psychiatrist). A multidisciplinary approach helps reduce the risk of polypharmacy and select an adequate dose of medications for Parkinson's disease, reducing its severity, as well as motor and non-motor symptoms.

Physical therapy is the leading non–drug method of treating Parkinson's disease [42]. The classic treatment of Parkinson's disease with frailty syndrome is strength training, since the rehabilitation process is primarily aimed at overcoming sarcopenia [36, 42, 43]. Another paradox is that the possibilities of strength training are limited. Strength training increases muscle rigidity, exacerbating one of the main symptoms of Parkinson's disease. The second component of physical therapy is functional training which focuses on real-life activities, adapting the patient to the disease. The patient becomes less dependent on symptoms and becomes active in everyday life. A psychotherapist adapts patients to adequate emotional tolerance of their condition, conducts depression therapy, and reduces the effect of depression on face, voice, and posture [42].

The problems of the elderly are recognized in many countries, regardless of their economic situation. In Russia, an additional payment and social services have been established for people over 80 years of age. Vietnam, a low-income country, also provides a similar payment [6]. Financial and social support is justified from an ethical point of view and is also a preventive measure, since it reduces the expenses of the state on the treatment and rehabilitation in neglected cases [44].

CONCLUSION

Despite the fact that research on frailty syndrome began 15–20 years ago, increasing attention to the problem has been paid in the last 2–3 years. It is due to the COVID-19 pandemic. The elderly population aged 65 and older was the most affected group by

COVID-19. However, during the pandemic, it turned out that some of the elderly were not affected by this infection, since they had nonspecific resistance and did not get sick even before the vaccine was developed. Another part of the elderly died of COVID-19. These elderly people suffered from frailty and comorbid diseases.

Old age is associated with a stereotype: illness, loneliness, and limited financial resources. There are also elderly people who lead an active lifestyle: working, taking care of themselves and even their family, engaged in sports and recreational activities, gardening, and personal life. A lifestyle that prevents diseases of the modern world and slows down the rate of sarcopenia and aging is of great importance in the development of frailty syndrome, although the article also considers the contribution of genetic factors [45]. Undoubtedly, early diagnosis and rehabilitation play an important role in preventing the spread of frailty syndrome.

First of all, it is necessary to familiarize practitioners with frailty syndrome and conduct a differential diagnosis so as not to attribute the symptoms of frailty syndrome to other relevant pathologies. Still, prevention is even more important, especially among young and middle-aged people, to stop early aging and the onset of diseases of the modern world [1, 46].

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