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PARKINSON'S DISEASE RISK FACTORS. REVIEW

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Abstract

Introduction. Parkinson's disease (PD), in recent decades, remains a pressing problem in the modern world. The disease refers to the pathology of the extrapyramidal system, where the deep parts of the brain, the so-called basal ganglia, are affected. During a medical examination, at first glance, movement disorders are striking, and the patient himself or his relatives make complaints related to movement disorders. However, the disease, by the time the complaints were made, takes its beginning 5-10 years ago with non-motor manifestations, such as sleep disturbances, apathy, increased fatigue, and constipation. According to genetic studies, 10 to 15% of cases are caused by mutations in genes. The etiology of the disease is still unclear, but it is considered a consequence of the associated effects of genetic and environmental factors.

Aim: This review evaluates relevant information on the risk factors for Parkinson's disease.

Search Strategy. A literature review was conducted with the help of bibliographic databases Pubmed, Web of Science, and Scopus with the search keywords: Parkinson's disease, epidemiology, etiology, risk factors, gender, age. The depth of the search covered 10 years, from 2011 to 2021. Forty-three articles have been selected as analytical material and have undergone a critical evaluation process. In several cases, there is a reference to an earlier publication with historical and scientific value. The literature search included only English-language publications.

Results and Conclusions. In summary, after analyzing 43 articles, it was concluded that PD is a complex neurodegenerative disease resulting from the interaction of genetic and external factors, which, as a consequence, affect numerous fundamental cellular processes of the body. Therefore, environmental influences can contribute to the development of PD, which emphasizes the importance of identifying risk factors for the disease. Understanding the mechanisms of pathogenesis will enable the identification of new therapeutic targets, which will subsequently help in the development of new combined, possibly individualized treatments.

Keywords: Parkinson's disease, risk factors, epidemiology, etiology, gender, age.

Резюме

ФАКТОРЫ РИСКА БОЛЕЗНИ ПАРКИНСОНА. ОБЗОР ЛИТЕРАТУРЫ.

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Введение. Болезнь Паркинсона (БП), в последние десятилетия остается актуальной проблемой современного мира. Заболевание относится к патологии экстрапирамидной системы, где идет поражение глубоких отделов головного мозга, так называемых базальных ганглий. При медицинском осмотре на первый взгляд бросаются двигательные расстройства, да и сам пациент, или его родственники предъявляют жалобы, связанные с нарушением движений. Однако, заболевание, к моменту предъявления жалоб, началось еще 5–10 лет назад с немоторных проявлений, таких как нарушение сна, апатия, повышенная утомляемость, запоры. По данным генетических исследований, от 10 до 15% случаев обусловлено мутациями в генах. Этиология болезни пока точно не ясна, однако считается следствием ассоциированного влияния генетических факторов и факторов окружающей среды.

Цель: В этом обзоре анализируется актуальная информация о факторах риска болезни Паркинсона.

Стратегия поиска. Обзор литературы был проведен с использованием библиографической базы данных Pubmed, Web of Science, Scopus с поисковым запросом ключевых слов: болезнь Паркинсона, эпидемиология, этиология, факторы риска, пол, возраст. Глубина поиска составила 10 лет, с 2011 по 2021 г. Выбраны 43 статьи в качестве аналитического материала, которые прошли критический процесс оценки. В некоторых случаях есть ссылка на более раннюю публикацию, имеющие историческую и научную ценность. Поиск литературы включал публикации только на английском языке.

Результаты и выводы. В итоге, проанализировав 43 статьи, было выявлено, что БП – это сложное нейродегенеративное заболевание, возникающее в результате взаимодействия генетических и внешних факторов, которые, в свою очередь, влияют на многочисленные фундаментальные клеточные процессы организма. То есть, влияние окружающей среды может способствовать развитию БП, что подчеркивает важность выявления факторов риска заболевания. Понимание механизмов патогенеза позволит определить новые терапевтические мишени, которые в последующем помогут в разработке новых комбинированных, возможно индивидуальных методов лечения.

Ключевые слова: болезнь Паркинсона, факторы риска, этиология, этиология, пол, возраст.

Түйіндеме

**ПАРКИНСОН АУРУЫНЫҢ ҚАУІП ФАКТОРЛАРЫ.
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Кіріспе. Паркинсон ауруы соңғы онжылдықтарда қазіргі әлемде өзекті мәселе. Ауру экстрапирамидальдық жүйенің патологиясына жатады, яғни мидың терең бөліктері зардап шегеді, базальды ганглия деп аталады. Физикалық тексеру кезінде, бір қарағанда, қозғалыстың бұзылуы көзге түседі, ал науқас адам өзі немесе оның туыстары қозғалыс бұзылыстарына байланысты шағымдар жасайды. Алайда, осы шағымдар түскен кезден 5-10 жыл бұрын ұйқының бұзылуы, апатия, шаршаудың жоғарылауы және іш қату сияқты моторлы емес көріністерден бастау алады. Генетикалық зерттеулерге сәйкес, ауру жағдайларың 10-15 пайызы гендердегі мутациялардан туындайды. Аурудың этиологиясы әлі күнге дейін түсініксіз, бірақ бұл генетикалық және сыртқы факторларының орта ілеспе әсерінің салдары деп саналады.

Мақсаты: Бұл шолуда Паркинсон ауруының қауіп факторлары туралы тиісті ақпарат бағаланады.

Іздеу стратегиясы. Әдебиеттерді іздеу PubMed, Web of Science және Scopus библиографиялық дерекқорлары арқылы жүргізілді. Іздеу үшін «Паркинсон ауруы», «эпидемиология», «этиология», «қауіп факторлары», «жыныс», «жасы» деген түйінді сөздерді қолданды. Іздеу тереңдігі 10 жыл (2011–2021). Қырық үш мақала аналитикалық материал ретінде таңдалды және сыни бағалау процесінен өтті. Бірнеше жағдайда тарихи және ғылыми құндылығы бар бұрынғы басылымға сілтеме бар. Әдебиетті іздеу тек ағылшын тіліндегі басылымдарды қамтыды.

Нәтижелер мен қорытындылар. Нәтижесінде, 43 мақала талданды. Паркинсон ауруы генетикалық және сыртқы факторлардың өзара әрекеттесуінен туындайтын күрделі нейродегенеративті ауру екендігі анықталды. Бұл өз кезегінде дененің көптеген негізгі жасушалық процестеріне әсер етеді. Яғни, қоршаған ортаның әсері Паркинсон ауруының дамуына ықпал етуі мүмкін, бұл аурудың қауіп факторларын анықтаудың маңыздылығын көрсетеді. Патогенез механизмдерін түсіну жаңа терапевтік мақсаттарды анықтауға мүмкіндік береді, бұл кейіннен жаңа біріктірілген, мүмкін жеке емдеу әдістерін жасауға көмектеседі.

Түйінді сөздер: Паркинсон ауруы, қауіп факторлары, эпидемиология, этиология, жынысы, жасы.

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Introduction

Parkinson's disease (PD), in recent decades, remains a pressing problem in the modern world. The disease refers to the pathology of the extrapyramidal system, where the deep parts of the brain, the so-called basal ganglia, are affected. During a medical examination, at first glance, movement disorders are striking, and the patient himself or his relatives make complaints related to movement disorders. However, the disease, by the time the complaints were made, takes its beginning 5-10 years ago with non-motor manifestations, such as sleep disturbances, apathy, increased fatigue, and constipation. According to genetic studies, 10 to 15% of cases are caused by mutations in genes. The etiology of the disease is still unclear, but it is considered a consequence of the associated effects of genetic and environmental factors.

Parkinson's disease (PD) is the second most common degenerative disease of the brain, after Alzheimer's disease. The first description of the disease can be found in

the work of James Parkinson, which was published in 1817 entitled "Essays on Shaking Palsy". The main symptoms of PD are related to motor disorders and include resting tremor, bradykinesia - slowness of movement, muscle stiffness, and postural instability. Non-motor manifestations include disorders such as anxiety and depression, and autonomic nervous system disorders such as arterial hypotension and constipation, paresthesia, sense of smell, and seborrheic dermatitis are also observed. The cognitive function decreases as the disease progresses. [27,5] The worldwide increase in the incidence of the disease has been attributed to increased life expectancy, but external factors may also play a role. Difficulties exist in diagnosing the disease, especially in the early stages, because the diagnosis of Parkinson's disease is made primarily on the basis of the clinical manifestations and course of the disease. There are epidemiological observations that suggest that exposure to pesticides, exhaust fumes, and prolonged consumption of well water are risk factors for

Parkinson's disease. [21]. Both patients with a history of Parkinson's disease and those without a family history have a risk for Parkinson's disease. However, exposure to environmental factors may be important in triggering the disease in a genetically predisposed person [39].

Aim: to conduct a literature review of English-language articles on risk factors for Parkinson's disease.

Search strategy. A literature review was conducted with the help of bibliographic databases Pubmed, Web of Science, and Scopus with the search keywords: Parkinson's disease, risk factors, epidemiology, etiology, gender, age. The depth of the search covered 10 years, from 2011 to 2021. Forty-four articles have been selected as analytical material and have undergone a critical evaluation process. In several cases, there is a reference to an earlier publication with historical and scientific value. Inclusion criteria considered: reports of randomized and cohort studies conducted on large populations, meta-analyses and systematic reviews, and original studies in English. The literature search included only English-language publications.

Results and Discussion.

In the 1980s, the first studies were carried out revealing that exposure to the rural environment at an early age, as well as exposure to well water, was associated with the development of Parkinson's disease later in life. [18].

Autopsy examinations have shown that the clinical diagnosis of PD is not confirmed at autopsy in a significant proportion of patients. Increased knowledge of genetic and environmental risk factors for PD is most likely to elucidate the cause of this disease in the near future. [38]

The primary mechanism of PD is related to the degeneration of dopaminergic neurons in the substantia nigra, resulting in a loss of dopamine in the striatum. Symptoms do not develop until approximately 50-60% of the substantia nigra neurons are lost and approximately 80-85% of the dopamine content of the corpus striatum is depleted [40]. Around 10% of PD cases involve positive family history, that is, arising from genetic mutations in α -synuclein, LRRK2, DJ-1, PINK1, etc. The majority of PD cases are idiopathic, which means they do not have a clear etiology. PD is characterized by a progressive accumulation of insoluble inclusions known as Lewy bodies, predominantly composed of α -synuclein and membrane components. In addition, impaired regulation of cellular proteostasis and mitochondrial function, impaired autophagy, oxidative stress, and neuroinflammation may underlie the disease, which are probably interdependent, however, whether they are the cause or consequence of neurodegeneration remains to be studied. [2]. PD is diagnosed in about 1% of people over 65 years of age, sometimes with an early onset of about 40 years of age, and rarely PD occurs as early as age 18 years. The prevalence of the disease has increased 2-5-fold over the past 30 years [37]. A group of scientists from Canada conducted a systematic review of 47 studies. A meta-analysis of worldwide data reported an increase in the prevalence of PD with age, as shown in Table 1 [26].

Approximately 7 to 10 million people worldwide have Parkinson's disease. [41]. However, due to the overall aging of the population, the number of PD patients is expected to double by 2030.

PD is usually more common among males than females, with a female-to-male ratio of about 1:1.5. Possible explanations for this difference include more frequent occupational exposures in men, the neuroprotective effects of estrogen in women, and an X-linked genetic factor. [12].

Table 1.

Prevalence of PD with age (per 100).

Age group	All included studies
40-49	41
50-59	107
55-64	173
60-69	428
65-74	425
70-79	1089
80+	1903

According to the United Nations studies (2015), the number of elderly people in the world has increased by 48% since 2000 and is expected to increase further by 56% (2015-2030). It follows that the number of patients with PD in the coming years will increase both globally and in Kazakhstan. The growth of morbidity and prevalence of PD leads to a high level of incapacity, deterioration of the quality of life of patients, and disability, and also puts the burden of responsibility and strain on the relatives of the patient, which leads to medical and socially significant problems.

Speaking of PD risk factors such as aging, heredity, the influence of environmental factors, and the presence of concomitant diseases; the role of gender as an equally important factor in the development of PD has been widely discussed recently. PD affects men twice as often as women [35], but women have a higher mortality rate and more rapid progression of the disease [11]. According to a meta-analysis, the incidence ratio in men and women before 60 years of age is nearly similar, but men have a steep rise in incidence starting at age 60 and older. [14]. At the same time, the prevalence of PD in men over 60, both with and without dementia, is increasing. [30]. A growing amount of experimental and clinical findings confirm the idea that PD occurs differently in both genders. To understand the differences more fully in the mechanism of disease development, and to find out what underlies these differences, scientists and clinicians around the world are continuing research efforts. Regarding motor disorders, in women, tremor is the most frequent first sign of the disease, [7] as well as an increased tendency to postural instability; and dyskinesias associated with levodopa ingestion are more frequent [10]. Camptocormia, an involuntary pronounced forward tilt of the torso, is a common feature in the advanced stages of PD in male patients [24].

One of the risk factors for PD that can be corrected is physical activity. Several studies have convincing evidence for an inverse association between regular physical activity and the onset of Parkinson's disease [32,29]. This meta-analysis confirms the inverse relationship between physical activity and risk of Parkinson's disease. Physical exercise has been associated with neuroprotective effects in the nigrostriatal dopaminergic system. [42]. A shortcoming of these studies is that they all assessed physical activity

using a self-reported questionnaire completed by patients or their caregivers.

Cigarette smoking is probably the most studied modifiable risk factor for Parkinson's disease. Case-control studies, as well as prospective cohort studies, confirm a decreased risk of Parkinson's disease among smokers, ex-smokers, and passive smokers. [31, 23] Cigarette smoke contains many chemicals besides nicotine, yet nicotine appears to have neuroprotective effects. The pathway is not fully studied, but nicotine blocks monoamine oxidase-B (MAO-B), which is an enzyme that metabolizes dopamine. Moreover, the protective factor of nicotine works for prolonged smoking, meaning, throughout life [33]. Of course, we should mention the ethical debate about the point of view: do these positive effects compensate for the detrimental effects of nicotine on health in general?

The hypothesis of the effect of pesticides and other chemicals on the progression of PD was suggested by the discovery of the neurotoxic effect of the metabolite 1-methyl, -4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), which converts in the body to a proparkinsonian molecule with a structure similar to the herbicide paraquat. [3]. Among agricultural workers, working days longer than 397 days, a relationship between the risk of disease and exposure to pesticides, which are known to affect the mitochondrial complex and/or cause oxidative stress, has been found [36]. The most epidemiological data point to the effect of two pesticides on the development of PD, these are paraquat and rotenone. [20]. Studies conducted in Turkey confirmed the hypothesis about the influence of environmental factors such as well water, pesticides, and ionizing radiation in early and adolescence on the development of PD in old age. Levels of heavy metals and anions were higher in well water than in the urban water network in Iğdır province. [6]. Scientists from Greece, by conducting a systematic review and meta-analysis to examine the association between air pollution exposure and PD, found a weak connection between air pollution, mainly from motor vehicles, and PD [17].

There is scientific evidence on the likelihood of developing PD in patients with type 2 diabetes mellitus. Environmental hazards, genetic predisposition, and lifestyle factors cause mitochondrial and endoplasmic reticulum dysfunction, and inflammation, which leads to the development of neurodegenerative diseases (such as PD) and/or diabetes [43]. PD and type 2 diabetes have a common pathogenesis of development, such as neuroinflammatory processes and oxidative stress. It has been proven in experimental models that insulin can control dopaminergic activity, and prolonged hyperglycemia causes dopaminergic dysfunction. [25] Controlled randomized trials of medications used in the treatment of diabetes mellitus are also ongoing, particularly pioglitazone and exenatide, which have positive effects on mitochondrial dysfunction in both diseases. [4].

A number of scientists have conducted experiments on the effect of dairy product consumption on the risk of PD, where they found a positive relation between PD and daily consumption of dairy products, especially milk. [19]. Especially, the present study supports the hypothesis that high milk intake increases the risk of developing PD in women [28]. Another cohort study found a positive

association between milk consumption and the development of Parkinson's disease, especially in men [8].

Additionally, when analyzing the composition of dairy products, pesticides that are known to be the cause of PD were found. [16]. According to the Honolulu-Asia Aging Study, where data on milk consumption and the smoking factor were collected from 1965 to 1968 among 449 men aged 45-68 years, and post-mortem studies were conducted in 1992. It was found that non-smoking patients who consumed milk daily had a low density of neurons in the substantia nigra of the brain [1]. It is important to note the effect of caffeine: large epidemiological studies have shown that caffeine consumption is an inverse predictor of PD [34, 9]. Caffeine intake was associated with a reduction in the increase in motor and non-motor disability over 4 years of follow-up in de novo PD, highlighting the usefulness of using adenosine A2A antagonists in the early stages of PD [22]. This meta-analysis shows that caffeine is associated with a low risk of developing PD in healthy people and slowing the progression of motor symptoms in patients with PD [15].

Another prospective study of plasma urate level showed that men with higher urate concentrations had a lower risk of developing PD, suggesting that urate may be a protective factor in PD or may slow disease progression in the preclinical stage. [13].

Conclusion.

In summary, after analyzing 43 articles, it was concluded that PD is a complex neurodegenerative disease resulting from the interaction of genetic and external factors, which, as a consequence, affect numerous fundamental cellular processes of the body. However, the etiology of PD is largely unclear, but the environment has been associated with PD. So it is very important to determine the risk factors which can lead to PD.

Over the past 10 years, quite a large number of studies, including prolonged studies, have been conducted to identify various risk factors for PD, including modifiable factors. Large-scale discoveries have fundamentally changed our understanding of PD and its determinant. The influence of external agents on genetically determined patients contributes significantly to the occurrence of PD. According to research, the disease occurs worldwide, in almost all ethnic groups, to varying degrees. Therefore, knowing and studying the risk factors for the disease will help to better understand what underlies the pathology and establish a causal relationship. These perceptions of PD epidemiology will allow in the future to identify the risk group among the population even in the prodromal period, to develop a strategy for disease prevention, and to optimize treatment, including rehabilitation.

Therefore, environmental influences can contribute to the development of PD, which emphasizes the importance of identifying risk factors for the disease. Understanding the mechanisms of pathogenesis will enable the identification of new therapeutic targets, which will subsequently help in the development of new combined, possibly individualized treatments.

Authors' contribution. *This work had carried out as part of a PhD Dissertation on "Clinical and demographic analysis of Parkinson's disease in the South region of Kazakhstan".*

All authors were equally involved in the search and analysis of the literature and writing the sections of the article.

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The authors state that this manuscript is original, has not been published before, and is not currently being considered for publication elsewhere.

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