Neuroinflammatory penumbra in Parkinson’s disease

Abstract. To date, the etiology and pathogenesis of Parkinson’s disease (PD) are not fully understood. In this publication, we present a critical review of the available international data on the involvement of inflammation processes in the etiopathogenesis of the disease in the context of our research results. The data obtained by us during modeling of parkinsonian syndrome of neuroinflammatory origin (lipopolysaccharide endotoxin was used) in laboratory rats (basic group, n = 21; control group, n = 7) indicate that intranasal administration of lipopolysaccharide in all three studied doses (1, 10 and 100 μg/kg/ml) seven days after the end of the experiment (21 injections) causes the same moderate morphological degenerative and inflammatory changes in the histostructure of the substantia nigra, extending to the striatum area (p > 0.05). This fact can be best explained by the all-or-none law. The staged, sequential transition of primary reversible (neuroinflammatory) pathomorphological changes to secondary irreversible (neurodegenerative) ones in PD, as well as secondary activation of microglia during neuronal degeneration, allows proposing the term “neuroinflammatory penumbra”, which will best help understand the pathogenesis of the disease and the development of therapies that change the course of Parkinson’s disease. Our data on the use of mesenchymal multipotent stromal cells in rats with neurotoxic (rotenone) parkinsonian syndrome (n = 10) and in PD individuals (n = 10) demonstrate a decrease in motor impairment, overall improvement of patients and an effect on laboratory parameters compared with control groups. We associate the early positive effect, observed already in the first week after the administration of mesenchymal multipotent stromal cells, with their paracrine action, including on the neuroinflammatory penumbra.

Keywords: Parkinson’s disease; penumbra; multipotent stromal cells; review

Parkinson’s disease (PD) is one of the most common ones in neurological practice, which are traditionally attributed to the group of conformational pathology of the brain (substantia nigra pars compacta) [1]. It has been more than 200 years since the first scientific description of this disease by the English doctor James Parkinson in 1817. Unfortunately, the exact etiology of the disease is not fully known until now. It is believed that mutations of some molecules, such as α-synuclein, parkin and ubiquitin C-terminal hydrolase L1 [2], correlate with early onset of PD and familial cases of PD, which represent only a very small part of the incidence, while most cases of disease (sporadic PD) are most likely associated with environmental toxins, mitochondrial dysfunction and oxidative stress [3]. Among the various factors that can provoke the degeneration of dopaminergic neurons of the substantia nigra and the clinical manifestation of PD, data on the possible involvement of inflammation in the brain (neuroinflammation) aroused great scientific and practical interest. Thus, postmortem studies of the brain of patients with PD indicate an increase in activated microglia and high levels of inflammatory factors (interleukin (IL) 1β, tumor necrosis factor α, nitric oxide, etc.) in the nigrostriatal system [4]. Numerous examples of microglial activation and high levels of inflammatory factors were found in the brains of animals with a PD model [5, 6]. So, can an infectious, viral or bacterial agent provoke the development of PD? In 2019, a team of European authors published an article in the journal “Frontiers in Neurology” entitled “Infectious
etologies of parkinsonism: pathomechanisms and clinical implications” [7] at the end of which the accumulated data in recent years indicated the role of infectious etiology in the development of parkinsonism and Parkinson’s disease, but the authors caution against the conclusion that all cases of PD are associated with increased inflammatory reactions and underlying chronic infection. The authors suggest that further researches are needed to study the involvement and degree of involvement of pathogens and inflammatory cytokines in the etiopathogenesis of PD. For our experimental work in this direction, we decided to use a bacterial lipopolysaccharide (LPS). The choice was due to the fact that LPS is an integral part of the cell membrane of all Gram-negative bacteria and its introduction to experimental animals when modeling parkinsonian syndrome causes inflammation in the brain and induces neurodegeneration of dopaminergic neurons [8–10]. Qing He et al. [11] confirmed the activation of microglia and the release of tumor necrosis factor α and IL-1β in the substantia nigra in mice after intranasal administration of LPS. The absence of a direct effect of LPS on neurons makes it an excellent tool for studying inflammation-mediated dopaminergic neurodegeneration, along with neurotoxic models of parkinsonism (rotenone, paraquat, etc.). Our data [12, 13] obtained by comparing the results of repeated laboratory studies of dopamine and homovanillic acid levels in the blood serum and cerebrospinal fluid of experimental animals (rats) on days 7 and 21 from the beginning of modeling parkinsonian syndrome of neuroinflammatory (LPS was used, n = 6) and neurotoxic (rotenone was used, n = 20) origin showed progressive neurotransmitter deficiency in animals of both groups, which indicates the validity of the neuroinflammatory and neurotoxic models of parkinsonism used to study the pathogenesis of PD [14, 15].

To date, it is known that numerous solid suspended particles (particulate matter) in the air can enter the brain through the nose, bypassing the blood–brain barrier [8]. The hypothesis of an olfactory vector of neurodegenerative diseases proposed in recent years is based on the fact that disorders in PD can be caused or catalyzed by agents that enter the brain directly through the nasal cavity [16]. To assess the applicability of this hypothesis to describe the development of PD, we, together with the staff of the Institute of Physiology of the National Academy of Sciences of the Republic of Belarus, conducted studies on the influence of chronic daily (21 days) intranasal administration of various concentrations of LPS (1, 10 or 100 μg/kg/ml, the same concentration throughout the study in each group of animals) on the formation of morphological signs of neuroinflammation and neurodegeneration in the extrapyramidal system. The experiments were carried out on male Wistar rats with a body weight of 320–350 g (basic group, n = 21; controls, n = 7) who received water for injection for 21 days (JSC “Borimed”). All manipulations with animals were carried out in accordance with the European Convention for the Protection of Vertebrate Animals [17]. Seven days after the end of the experiment (21 injections), after decapitation, the biological material (brain) was taken, followed by a morphological blinded study. A month after the start of instillation, there were no differences in the clinical characteristics of the motor activity of rats in the basic and control groups (grooming, open field test, p > 0.05). The study of histological preparations with Nissl staining (the processing of the data was aimed to determine the severity and the volume of neuron damage [18]) revealed statistically significant differences in the morphological picture of degenerative and inflammatory changes in the control group compared to the basic group rats who received LPS (p < 0.05, Mann–Whitney U test). But there were no statistically significant differences in the morphological picture between rats receiving different doses of LPS (p > 0.05, Kruskal–Wallis test). In the animals of the basic group, the morphological picture was of the same type, most of the neurons had some signs of neurodegeneration. In our opinion, morphological damage to neurons under the influence of prolonged intranasal administration of LPS occurs according to the all-or-none law: different doses of LPS exceeding the threshold value (the minimum required amount that may cause neurodegenerative changes), when ingested in the same period, will lead to neuroinflammatory and neurodegenerative changes of the same severity.

The gradual, sequential transition of reversible (neuroinflammatory) pathomorphological changes to irreversible (neurodegenerative) ones in PD allows us to propose the term “neuroinflammatory penumbra”. Initially, the definition of penumbra referred to areas of the brain that were damaged, but have not yet dead, which makes it possible to restore them with the help of appropriate treatment, i.e. it indicates the potential reversibility of pathomorphological changes existing in tissues [19]. The term “penumbra” is currently widely used in vascular neurology to define the zone of ischemic penumbra that surrounds the necrosis zone in ischemic stroke. From our point of view, the term “neuroinflammatory penumbra” allows us to better understand/reflect the pathophysiological mechanisms of various types of neurotransmitter deficiency: a) degenerative or true, associated with the death of neurons that can be compensated only with replacement therapy, and b) inflammatory or secondary, associated with a violation of the neurotransmitter function of the neuron due to an inflammatory reaction of microglia and/or still reversible neuroinflammatory damage to the neuron, which can be corrected by immunomodulatory therapy. It is worth emphasizing that the classic symptoms of PD in patients begin to appear only after the loss of 50 % of all dopaminergic neurons and 75–80 % of striatal dopamines [8]. It is possible that in some patients, neurons are in a state of neuroinflammatory penumbra and clinical improvement in these individuals can be achieved not only with replacement neurotransmitter therapy but also the use of drugs that affect the processes of neuroinflammation.
Currently, studies of drugs that modify the course of PD due to the immunomodulatory effect are being actively conducted [20]. We proposed using autologous mesenchymal multipotent stromal cells (MMSCs) to modify the course of Parkinson’s disease [21]. Different studies have shown that MMSCs, in addition to their substitution role, embedding in the nervous system, also have numerous paracrine effects on the body, particularly by influencing the immune system [22].

Studies conducted on the basis of the vivarium of the State Educational Institution “Belarusian Medical Academy of Postgraduate Education” on rats (n = 10) with neurotoxic (rotenone) parkinsonian syndrome showed regression of motor symptoms (rigidity, postural instability and ptoesis) and an increase in the level of dopamine and homovanillic acid in blood serum and spinal fluid on days 7 and 21 after intravenous single administration of allogeneic (rat) MMSCs. In patients with PD (n = 10, basic group), on the very next day after a single intravenous injection of autologous MMSCs, a statistically significant (p < 0.05) overall improvement was observed according to the Clinical Global Impression-Improvement scale and unidirectional changes in cytokines (IL-1β, IL-10) of blood serum on day 7 were recorded. These changes were not observed in the group of patients with PD who received placebo (saline solution) once intravenously (n = 13, control group). We associate the positive effect of intravenous single administration of MMSCs in laboratory animals and patients with the paracrine effect of cell therapy, particularly on the neuroinflammatory penumbra.

**Conclusions**

The results of our research and the work of foreign colleagues confirm the data on the clinical heterogeneity and etiological multifactorial nature of PD. The application and further development of the concept of neuroinflammatory penumbra are important both for a more effective search for drugs that change the course of PD and for the development of a personalized approach to the choice of therapy for other diseases of the nervous system in the future. We agree with the opinion of foreign colleagues [23] that further study of etiological factors and pathogenetic mechanisms that reveal the variability of the development and progression of PD is a high priority area of research.

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Резюме. На сьогодні етіологія і патогенез хвороби Паркінсона (ХП) до кінця не вивчені. У цій публікації ми наводимо критичний огляд доступних міжнародних даних щодо участі процесів запалення в етіопатогенезі захворювання в контексті результатів власних досліджень. Дані, отримані нами при моделюванні синдрому паркінсонізму нейрозапальна пенумбра (використовувався ендотоксин ліпополісахарид) у лабораторній моделі синдрому паркінсонізму нейрозапального генезу, свідчать про те, що інтраназальне введення ліпополісахариду до кінця не вивчені. У цій публікації ми наводимо резюме:

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