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To search for targets of therapy that changes the course of Parkinson's disease

Abstract. ***Background.*** *Parkinson's disease (PD) is a multisystem disease that requires a more comprehensive approach to its study and treatment. The purpose was to give clinical and laboratory characteristics of PD patients, in whom the onset of motor symptoms of the disease is associated with the action of precipitating factors and provide a theoretical justification for the underlying and/or associated electrophysiological phenomena.* ***Materials and methods.*** *Two hundred and seven patients with PD were examined. Questionnaire analysis and laboratory research were performed.* ***Results.*** *Among patients with a rapidly progressive type of PD, pain during the survey was registered in 49 (42.2 %) cases, and stress in 73 (62.3 %). In cases of a slowly progressive course, 14 (15.4 %) individuals experienced pain syndromes, and 53 (58.2 %) patients — stress. Statistically significant differences between patients with rapidly and slowly progressive PD courses were noted in the number of cases of herpetic diseases, inflammatory diseases of the oral cavity. The results of laboratory tests also showed statistically significant differences between these groups in the blood serum level of IL1β and cortisol, the level of IL1β in the cerebrospinal fluid, and the albumin coefficient. The patients with a rapidly progressive type of disease presented with a greater number of precipitating factors for PD development. In patients with rapidly progressive PD, the number of precipitating factors and the serum level of antibodies to α-synuclein ($r = -0.18$), IL10 ($r = 0.31$), and cortisol ($r = 0.18$) correlated. Some objective characteristics of non-motor PD symptoms statistically significantly correlated with a level of laboratory biomarkers in blood serum (Montreal Cognitive Assessment value with cortisol level ($r = -0.4$); Pittsburgh Sleep Quality Index value with antibodies to α-synuclein ($r = 0.31$); Epworth Sleepiness Scale value with IL10 level ($r = -0.21$)). Significant acute psychological stresses and pain syndromes may change the pattern of propagation of depolarization waves in the nervous system with the formation of "autowave penumbra". Possible clinical criteria for the effectiveness of therapy that change the course of PD are presented.* ***Conclusions.*** *Pain syndromes and acute significant psychological stresses not only contribute to the onset of motor symptoms of PD but also lead to the rapid progression of the disease. The effect of precipitating factors may manifest itself not only in clinical, morphological, and laboratory changes but also in changes in the excitability of nerve cells. The electrophysiological penumbra ("autowave penumbra") can be considered a possible target for the action of a therapy method that modifies the course of PD.*

Keywords: *Parkinson's disease; precipitating factors; stress; pain syndrome; autowave penumbra; depolarization wave; therapy criteria*

Introduction

Several authors suggest Parkinson's disease (PD) as a multi-system disease, the description of which should be approached more comprehensively than the currently accepted classical neurodegenerative approach, focused on symptomatic, replacement therapy of neurotransmitter deficiency [1]. It is believed that the aggregation of α-synuclein has a central role in the occurrence and progression of PD, but other processes are also involved: abnormal protein clearance, mitochondrial dysfunction and neuroinflammation [2]. However, the relationship between these factors remains unclear [2]. At the same time, patients with newly developed PD wonder if it is possible to slow down or even stop the progression of the disease [3]. It is considered dubious that all patients with PD will benefit from the same treatment that changes the course of the disease [3]. Studies have shown that the classic motor symptoms of PD in patients begin to manifest after the 50% loss of all dopaminergic neurons and

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75–80% of striatum dopamine [4, 5]. Therefore, the study of non-neurodegenerative mechanisms of PD development (including factors leading to accelerated excessive degeneration of neurons in the substantia nigra) is an important task for the development of approaches to therapy that changes its course. Our studies have shown that the impact of significant psychological stress, pain syndromes contributes to the manifestation of motor symptoms of PD [6], which is probably due to the last straw effect: an increase in previously asymptomatic dopamine deficiency in the striatonigral system, followed by a violation of the synaptic transmission of a nerve impulse (action potential). Experimental studies show that exposure to acute and chronic stress modulates the threshold for the occurrence of cortical spreading depression in mice [7]. At the same time, the pathophysiology underlying the symptoms of pain has not yet been clearly defined, but it is already well known that chronic pain conditions are associated with a decrease in the internal supraspinal function of pain modulation, which often manifest itself in a decrease in motor excitability of the cortex [8–10]. Also, in addition to the degeneration of dopaminergic neurons in the compact part of the substantia nigra [11] and the loss of neurons in the ventral tegmental area [12], PD is associated with increased excitability of the cerebral cortex, mainly arising from a decrease in inhibition, which can be partially reduced by dopaminergic therapy [13, 14]. It is known that an imbalance of excitation/inhibition can lead to pathological changes in the excitability of the cerebral cortex and the development of neurological diseases [15, 16].

The purpose was to give clinical and laboratory characteristics of PD patients, in whom the onset of motor symptoms of the disease is associated with the action of precipitating factors (acute psychological stress, pain syndromes) and provide a theoretical justification for the underlying and/or associated electrophysiological phenomena.

Materials and methods

The study was approved by the independent ethics committees of the State Educational Institution "Belorussian Medical Academy of Postgraduate Education" and healthcare institution "5th City Clinical Hospital". The basic group (BG) included 207 patients with PD (men and women ratio was 1 : 1.13; mean age 65 [58, 70] years). In BG, 116 (56 %) patients had a rapidly progressive course of the disease with a change in PD stages up to 5 years after the onset of PD motor symptoms. In 91 (44 %) patients, a slow rate was noted with a change in the stages of the disease after 5 or more years. The anamnestic data on the precipitating factors for the development of motor symptoms of PD were collected using an independently developed questionnaire [6]. The control group (CG) consisted of 34 patients (men and women ratio was 1 : 1.3; mean age 62 [57, 66] years). The differences in age and sex between BG and CG were not statistically significant ($p > 0.05$), which indicates the clinical homogeneity of the formed groups by the age-sex principle.

Physical and neurological examination of patients of BG and CG was supplemented by obtaining objective information using the following scales: Montreal Cognitive Assessment (MOCA), Hamilton Rating Scale for Depression, Non-Motor Symptoms Questionnaire, Pittsburgh Sleep Quality Index (PSQI), and Epworth Sleepiness Scale (ESS). The levels of cytokines (IL10 and IL1β), antibodies to α-synuclein, and cortisol were determined in blood serum and cerebrospinal fluid (CSF) using appropriate enzyme-linked immunosorbent assay kits.

When processing the data obtained, nonparametric methods of biomedical statistics were used. The results are presented in the form of median, 25th and 75th percentiles (Me, Q25-Q75). Kruskal-Wallis test (H test) was used to assess the differences between three or more samples at the same time in terms of the level of the required trait. The Mann-Whitney test (U test) was used to compare the two groups. The relationship of quantitative and/or ordinal features was assessed using the Spearman's rank correlation with the determination of the rank correlation coefficient (R). The strength of the correlation was assessed depending on the value of the coefficient R: $|R| \leq 0.25$ — weak correlation; $0.25 < |R| < 0.75$ — moderate correlation; $|R| \geq 0.75$ — strong correlation.

Results and discussion

The results of the anamnestic data analysis demonstrated that 126 (60.9 %) patients with PD in the period from 1 day to 4 years before the development of motor symptoms of the disease experienced severe acute psychological stressful situations. Twenty-two (17.5 %) patients reported several different separate stresses. In 80 (63.5 %) patients, the effect of stress took place against the background of other factors: herpes viral infections, pain syndrome, inflammatory diseases of the ENT (ear, throat, nose) organs. Forty-six (36.5 %) patients noted only psychological stress in their history before the development of PD motor symptoms. Eighty-one (39.1 %) patients did not notice the action of acute stressful situations before the development of PD motor symptoms. Sixty-three (30.4 %) patients reported cases of pain syndromes in the past, before the development of PD motor symptoms. During the survey, 49 (42.2 %) individuals with a rapidly progressive type of PD experienced pain, and 73 (62.3 %) patients — stress. In cases of a slowly progressive course, 14 (15.4 %) patients presented with pain syndromes, and 53 (58.2 %) — stress. The difference between the cases of the onset of motor symptoms of rapidly and slowly progressive forms of PD against the background of the previous pain syndrome was statistically significant ($p < 0.05$) but did not follow the stress ($p > 0.05$).

Statistically significant differences between patients with rapidly and slowly progressive PD courses were also noted in the number of cases of herpetic diseases (50 (43.1 %) cases with a rapidly progressive course and 15 (16.53 %) with a slowly progressive course), inflammatory diseases of the oral cavity (12 (10.3 %) cases with a rapidly progressive course and 2 (2.3 %) with a slowly progressive course). The results of laboratory tests also showed statistically significant ($p < 0.05$) differences between these groups in the serum level of IL1β and cortisol, the level of IL1β in the CSF, and the albumin coefficient (laboratory marker of blood-brain barrier permeability). The study of the levels of

albumin coefficient, IL1β, and cortisol may be informative for determining the likelihood of a rapidly progressive form of PD in a patient.

Analysis of the data obtained showed a greater number of precipitating factors for the development of PD in patients with a rapidly progressive type of disease. So, the precipitating factors in the anamnesis were absent in 21 (18.1 %) cases; 1 factor was revealed in 30 (25.9 %) cases, 2 factors — in 28 (24.1 %) cases, 3 factors — in 26 (22.4 %) cases, 4 factors — in 11 (9.5 %) cases. In patients with a slowly progressive course, the precipitating factors in the anamnesis were absent in 25 (27.5 %) cases; 1 factor was determined in 37 (40.7 %) cases, 2 factors — in 22 (24.2 %) cases, 3 factors — in 6 (6.6 %) cases, 4 factors — in 1 (1.1 %) case. The differences between the groups were statistically significant ($p < 0.05$). In patients with rapidly progressive PD, a correlation was found between the number of precipitating factors and the serum level of antibodies to α-synuclein ($r = -0.18$), IL10 ($r = 0.31$), and cortisol ($r = 0.18$).

Some objective characteristics of non-motor PD symptoms statistically significantly correlated with a level of laboratory parameters: MOCA value with cortisol level ($r = -0.4$) in blood serum; PSQI value with antibodies to α-synuclein ($r = 0.31$) in blood serum; ESS value with serum IL10 level ($r = -0.21$). In the group of rapidly progressive course of PD, only the difference in serum IL10 level among patients with no history of precipitating factors and 4 factors was statistically significant (Z adjusted −2.91; $p = 0.004$).

The data obtained suggest that pain syndromes and acute psychological stresses can contribute not only to the onset of motor symptoms of PD but also to the rapid progression of the disease. Precipitating factors can be considered predictors of the rapid progression of PD. Several studies confirm the multifaceted effect of these factors on the body. Thus, in a series of animal experiments, Rocío M. de Pablos et al. have shown that chronic stress increases the activation of microglia and the death of dopaminergic neurons after the previous induction of the inflammatory process in the ventral part of the midbrain [17]. Smith A.D. et al. [18] demonstrated that stress causes excessive neuronal death in some areas of the brain and increases the extracellular availability of dopamine, glucocorticosteroids, and glutamate in the striatum. At pains, neuroimmune interactions are bidirectional [19–22]. Thus, immune cells secrete cytokines, lipids, and growth factors that impact the peripheral nociceptors and neurons of the central nervous system, increasing pain sensitivity, and nociceptors actively release neuropeptides from their peripheral nerve endings that modulate the activity of innate and adaptive immune cells.

In our opinion, the study of the effect of stress and pain should not be limited only to cellular, immune, and hormonal studies but should also include electrophysiological phenomena which affect the intercellular transmission of the action potential. We name it as an electrophysiological target of therapy that changes the course of PD. Such electrophysiological phenomena as striatal spreading depolarization [23], spreading depression or spreading depolarization [24], cortical spreading depression [25] are actively studied in a number of neurological diseases [26], especially in elderly people [27, 28].

The language of description of the biophysical properties of the action potential (its conduction in different tissues (active media)) was formed in biophysics by the 80s of the XX century. We refer interested readers to the fundamental work on this topic [29]. As an example of using the language of biophysics to describe a possible target for therapy that changes the course of PD, we propose to call pathological variants of depolarization waves an "autowave penumbra". In our opinion, not only ischemic stroke, subarachnoid hemorrhage, migraine, and brain injury but also inflammatory (infectious and non-infectious) diseases of the nervous system, including significant stress and pain syndromes, can change the pattern of propagation of depolarization waves in the nervous system with the formation of pathological electrophysiological, autowave modes. This "autowave penumbra" will also manifest as a change in immune responses (activation of cytokines, for example), excessive neurodegeneration (activation of neuronal apoptosis, for example), etc. that will eventually form the level of neuronal and dopamine deficiency in the striatonigral system sufficient for the clinical manifestation of PD. The prospects of studying the "autowave penumbra" are confirmed not only by the fact that some authors consider the similarity of the occurrence and propagation of depression waves in different animals as a property of the nervous system that has developed to control complex behavior that requires energy-consuming, fast information processing in a tightly regulated extracellular environment [30], which supports a systematic approach to understanding the electrophysiological basis of human neuropathology associated with migraine, stroke, and traumatic brain injury [30]. The prospects are also confirmed by the discovery of the connection of several electrophysiological phenomena with some clinical symptoms of amyotrophic lateral sclerosis (a fatal neurodegenerative disease) [31] and PD [23].

From our point of view, the study of electrophysiological phenomena in PD, as well as their connection with immune, morphological and other changes, is a very promising direction for the development of methods for controlling the onset and progression of the disease. However, even now we can talk about the need to develop preventive measures to control precipitating factors (pain, stress, etc.). We consider the use of anti-epileptic drugs to be scientifically justified.

In this article, we do not touch on mitochondrial, antioxidant, and synuclein targets for therapy that changes the course of PD. Speaking about this promising type of preventive treatment, we must first, in our opinion, determine the primary, leading and secondary, dependent mechanisms of the pathogenesis of the disease not only in general but also in every patient and person at risk of developing PD. Some authors believe [3] that the absence of primary application points that reflect the progression of PD at the prodromal stages remains a crucial vulnerability in clinical studies at the stage when the black substance is not affected or is only very weakly affected.

Efforts should be undertaken in the methodological field to find new endpoints that are sensitive to therapy and reflect the progression of PD both inside and outside the brain. From our point of view, the possible clinical criteria for the effectiveness of therapy that changes the course of PD can be conditionally divided into A) the nearest, expected shortly after the start of the use and manifest as 1) reducing the dose of dopaminergic replacement therapy, 2) reducing the severity of motor and/or non-motor symptoms (without any changes at dopaminergic replacement therapy), as well as B) long-term criteria in the form of 1) slowing the progression of the disease (motor and non-motor symptoms development) and 2) slowing escalation of the dose of dopaminergic replacement therapy compared to patients who did not receive similar therapy. A change in the pattern of propagation of depolarization waves under the influence of therapy aimed at inhibiting the onset and/or progression of PD can also be considered a possible electrophysiological, autowave marker of the effectiveness of preventive therapy.

Conclusions

Pain syndromes and acute significant psychological stresses not only contribute to the onset of motor symptoms of PD but also lead to the rapid progression of the disease. The effect of these factors on the body may manifest itself not only in clinical, morphological, and laboratory changes but also in changes in the excitability of nerve cells. The electrophysiological penumbra ("autowave penumbra") can be considered a possible target for a therapy method that modifies the course of PD.

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Пошук цілей терапії, що змінює перебіг хвороби Паркінсона

Резюме. ***Актуальність.*** Хвороба Паркінсона (ХП) — це багатосистемне захворювання, що вимагає більш комплексного підходу до свого вивчення й лікування. ***Мета дослідження:*** дати клініко-лабораторну характеристику пацієнтів із ХП, у яких розвиток рухових симптомів пов'язаний із дією провокуючих чинників, і навести теоретичне обґрунтування електрофізіологічних явищ, що лежать в основі захворювання і/або асоціюються з ним. ***Матеріали та методи.*** Було обстежено 207 пацієнтів із ХП. Проведені анкетний аналіз, лабораторні дослідження. ***Результати.*** Серед пацієнтів із швидко прогресуючим типом ХП біль при обстеженні відзначений у 49 (42,2 %) випадках, стрес — у 73 (62,3 %). При повільно прогресуючому перебігу больові синдроми зареєстровані в 14 (15,4 %) випадках, стресові — у 53 (58,2 %) випадках. Відзначено статистично значущі відмінності між пацієнтами зі швидко й повільно прогресуючим перебігом ХП за кількістю випадків герпетичних захворювань, запальних захворювань порожнини рота. ***Результати*** лабораторних тестів також показали статистично значущі відмінності між цими групами за рівнем IL-1β і кортизолу в сироватці крові, рівнем IL-1β в спинномозковій рідині й коефіцієнтом альбуміну. Виявлено більшу кількість провокуючих чинників розвитку ХП у пацієнтів зі швидко прогресуючим перебігом захворювання. У пацієнтів зі швидко прогресуючою ХП була виявлена кореляція між кількістю провокуючих чинників і рівнем антитіл до α-синуклеїну (r = –0,18), IL-10 (r = 0,31) і кортизолу (r = 0,18) у сироватці крові. Деякі об'єктивні характеристики нерухових симптомів ХП статистично значущо корелювали з рівнем лабораторних показників у сироватці крові (значення MOCA з рівнем кортизолу (r = –0,4); значення PSQI з антитілами до α-синуклеїну (r = 0,31); значення ESS з рівнем IL-10 (r = –0,21)). Значні гострі психологічні стреси й больові синдроми можуть змінювати характер поширення хвиль деполяризації в нервовій системі з утворенням «автохвильової півтіні». Наведені можливі клінічні критерії ефективності терапії, що змінює перебіг ХП. ***Висновки.*** Больові синдроми й гострі значні психологічні стреси призводять не тільки до виникнення рухових симптомів ХП, а й до швидкого прогресування захворювання. Дія провокуючих чинників може проявлятися не тільки клінічними, морфологічними й лабораторними змінами, а й змінами збудливості нервових клітин. Електрофізіологічна (автохвильова) півтінь може розглядатися як імовірна мішень для дії терапії, що змінює перебіг ХП.

Ключові слова: хвороба Паркінсона; провокуючі фактори; стрес; больовий синдром; автохвильова півтінь; хвиля деполяризації; критерії терапії