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Immunoinflammatory Aspects of Parkinson's Disease

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This review analyzes immunological impairments in Parkinson's disease (PD). We present data on neuroinflammation, with which cell degeneration in the substantia nigra of the brain is associated and in which innate and adaptive immune system cells are involved. Brain, cerebrospinal fluid, and peripheral blood cytokine levels are analyzed. The interaction between neuroinflammation and neuron dysfunction is considered. Data on immunological impairments in people with PD and animals with models of this disease are presented. The characteristics of models of PD are discussed. Data on impairments to the blood–brain barrier are presented, along with evidence for the occurrence of autoimmune inflammation in this disease. We discuss the question of preclinical markers of PD, including immunological, i.e., cytokines, HLA-DR and HLA-DQ antigens, autoantibodies, etc. The creation of algorithms for the presymptomatic diagnosis of PD and its prophylaxis and treatment at the presymptomatic stage will lead to the cessation or slowing of neuron death.

Keywords: autoimmune inflammation, cytokines, lymphocytes, blood–brain barrier, Parkinson's disease.

Parkinson's disease (PD) is a socially important progressive neurodegenerative disease, the second commonest such disease after Alzheimer's disease [1–3]. PD is characterized by progressive loss of dopaminergic neurons in the nigrostriatal system of the brain, which leads to impairment particularly of motor functions – resting tremor, hypokinesia, muscle rigidity, and postural instability [1–3]. Other disorders also appear in PD: autonomic, cognitive, behavioral, etc. [1–5], and these can appear at the very earliest stages of PD [1–5].

Depending on etiology, primary (idiopathic) parkinsonism (PD), secondary (symptomatic) parkinsonism, and parkinsonism in other neurodegenerative diseases are discriminated [1–3]. Primary parkinsonism accounts for 70–80% of all cases of parkinsonism [1–3]. Familial and sporadic forms of PD are identified [1–3]. According to different sources, the familial form affects 10–30% of patients, while the sporadic form occurs in 70–90% of patients [1–3].

From the point of view of pathological anatomy, PD is characterized by the accumulation of protein aggregates (so-called Lewy bodies) in the neuron cytoplasm, these containing α-synuclein (αS), ubiquitin, neurofilament proteins, and others [6–8]. The pathogenetic mechanisms associated with genomic, epigenetic, and ecological factors are believed to lead to conformational changes and deposition of key proteins because of anomalies in the ubiquitin-proteasome system, to impaired differentiation of dopaminergic neurons, and to dysregulation of mitochondrial functions and oxidative stress, with impairment to the normal functioning of synapses [9]. The etiology and pathogenesis of PD remain incompletely understood [10]. This review focuses on the immunological aspects of PD.

α-Synuclein. One of the main roles in the pathogenesis of PD is played by αS protein, which is seen mainly in presynaptic terminals [8, 11–13]. The exact physiological functions of this protein remain unknown [8, 12]. It has been suggested that in normal conditions, αS is involved in the processes of vesicular transport and regulation of dopaminergic transmission and in maintaining the presynaptic vesicular dopamine pool [8, 12]. αS can influence dopamine synthesis, operating as an inhibitor of tyrosine hydrox-

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ylase. αS is the main component of Lewy bodies and Lewy neurites, which are classical morphological markers of PD.

The role of αS in activating the inflammatory process in the central nervous system (CNS) has been studied in experimental models. The microglia of genetically modified animals with overexpression of αS or with transgenic human αS have been shown to be permanently in the activated state [14, 15]. The trigger mechanism for activation of the glia and macrophages is αS overexpression, which is accompanied by the appearance of aberrant forms of this protein with elevated aggregation ability, particularly nitro forms [16]. Experimental and clinical data have confirmed that αS aggregates induce the synthesis of reactive oxygen species (ROS) and nitric oxide (NO) in mice and activation of inducible nitric oxide synthase (iNOS) in human neurons, in turn promoting the formation of nitro derivatives of αS [17]. Overexpression of αS in the substantia nigra (SN) in the mouse brain by virus infection or genetic manipulation is accompanied by activation of the microglia and subsequent death of tyrosine hydroxylase-positive neurons [18]. Expression of αS under control of the Thy1 promotor leads to activation of the glia in the striatum in mice aged 1 month, with changes spreading to the SN over a period of 4–5 months and persisting in this location for further 14 months [14]. Thus, the formation of aberrant forms of αS can trigger neuroinflammation.

Inflammation. Progress in studies of the pathogenesis of PD has accumulated data showing that degeneration of SN cells may be associated with inflammation, which involves the cells of innate and adaptive immunity [19, 20]. The key role in the development of the immune response in the CNS is played by glial cells [21].

Previous studies have suggested that the cause of neurodegenerative diseases is the combination of chronic neuroinflammation and pathological aging, so-called inflammaging [22–25], which probably plays a triggering role in the mechanism of neurodegenerative disorders [26, 27], including in PD [22]. This is a low-level chronic proinflammatory status characterized by imbalance between inflammatory and anti-inflammatory mechanisms, is part of the set of complex adaptive mechanisms, and is primary in nature [25]. In contrast there is also anti-inflammaging: a state detected in long-lived people and associated with "healthy" aging [25]. The absence of adequate anti-inflammatory reactions may fuel inflammaging, which propagates at the local (cell to cell) and systems (for example, via exosomes and other molecules in the blood) levels [22]. The microglia play an important role in the pathogenesis of PD. Pathological activation of the microglia at the initial stages of disease has been suggested to develop into microglial dystrophy. The microglia become nonfunctional, and they are not in a state to carry out their physiological role of clearing neurotoxic aggregates, allowing the neurodegeneration process to progress [22–27].

As noted by Blandini [28], there is a limited series of biochemical mechanisms which might promote cell death in the nigrostriatal system. These mechanisms include mitochondrial damage and neuroinflammation. The first of these mechanisms leads to increases in ROS formation, oxidative damage, and derangement of protein aggregation [28]. In addition, or perhaps mingling with it, there is another mechanism – neuroinflammation [28]. Neuroinflammation receives ever more recognition in the pathogenesis of PD [28].

Many studies by different authors have confirmed the activated status of microglia and astrocytes in PD, this being accompanied by the synthesis of a variety of cytokines (TNF, IL-1β, IL-6, IFN-γ) and ROS, along with activation of enzymes, i.e., nicotinamide adenine dinucleotide phosphate-H-oxidase (NADPH oxidase), cyclooxygenases 1 and 2, and iNOS [29–31]. Accumulation of complement system proteins along with extracellular Lewy bodies suggests the involvement of the latter in activating immune cells [32]. Increased cytokine (IL-1β, IL-6, IL-2, IL-4, TNF, TGF-α) levels are detected in the cerebrospinal fluid (CSF) of PD patients [33, 34]. Serum from PD patients contained increased levels of IL-1β, IL-6, and TNF-α and decreases in IL-1RA levels, along with a correlation between IL-6 and disease severity on the Hoehn and Jahr scale [34, 35]. Data from a prospective study [36] indicate that an increase in the blood IL-6 concentration is linked with a higher risk of developing PD in men.

Relationships have been observed between measures characterizing the clinical variability of PD (disease severity, phenotype, cognitive impairments, presence of anxiety and depression) and CSF and serum IL-1β, IL-1RA, IL-6, IL-10, and TNF-α levels [34]. Rapid progression of PD has been linked with increased CSF TNF-α levels and serum IL-1β levels. A low IL-6 level was linked with a longer duration of PD. Anxiety, depression, the absence of tremor, and late onset of PD correlate with higher serum IL-10 levels. Serum TNF-α levels were lower in PD patients with moderate cognitive impairments than in controls [34]. Serum IL-1β, IL-6, and IL-10 levels correlated with CSF levels [34].

Researchers are currently inclined to the view that the inflammatory process in the central nervous system is the cause and not the consequence of PD [37]. An important role here is played by experimental data, as clinical material is available only at the later stages of the disease and post mortem. Models using administration of lipopolysaccharide (LPS) into the SN with altered αS expression provide for studies of the effects of activated glial cells on the state of neurons [38]. Conversely, models based on administration of neurotoxins provide information on how neuron damage can activate the inflammatory process [39, 40].

In animals with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced PD, neuron death precedes activation of the glia, cytokine synthesis, expression of adhesion molecules by endothelial cells, and migration of T-lymphocytes to brain tissue [39]. In this model, dexamethasone behaved as an anti-inflammatory agent able to prevent

the death of dopaminergic neurons [39, 40]. Other anti-inflammatory drugs were also effective in animals with MPTP- and 6-hydroxydopamine (6-HDA)-induced neuron damage [41]. Like MPTP, the toxin 6-HDA produced an increase in the content of proinflammatory cytokines and activation of the microglia [41, 42]. In these conditions, minocycline had neuroprotective effects, based on its ability to block microglial activation and inhibit cyclooxygenase-2 [43, 44].

Bacterial endotoxin had a direct activatory influence on glial cells, binding with Toll-like receptors for LPS (TLR4) [45]. In experimental animals, administration of LPS into the SN leads to rapid (seven days) decreases in the quantity of dopamine in the striatum and the number of tyrosine hydroxylase-positive neurons in the SN, these changes lasting a year [38, 45]. Administration of low-dose LPS into the SN for two weeks led initially to activation of the microglia and then to the death of dopaminergic neurons [38, 45]. Experiments in mixed cultures of glial cells and neurons confirmed that nerve cell damage could be induced by activated glia [46]. Medium conditioned by microglia activated via TLR4 was found to induce the death of dopaminergic cells in vitro [47].

Thus, inflammation accompanying the production of cytokines and other damaging agents can directly result in neuron death. It should be noted that dopaminergic neurons in the midbrain are quite sensitive to the toxic actions of TNF and IFN-γ [48, 49]. It would appear that there is a double link between inflammation and neuron dysfunction. Neuroinflammation leads to the death of nerve cells, while the death of nerve cells accompanied by the release of intracellular proteins can induce responses by innate immunity cells, which may in turn promote the development of the adaptive immune response and selective neuron damage.

Inflammatory mediators produced by mast cells also elicit neurodegeneration, leading ultimately to PD. The interactions of mast cells with glia, neurons, and 1-methyl-4-phenylpyridine (MPP+) – a metabolite of MPTP – were studied [50, 51]. MPP+ induced significant neurodegeneration, with release of monocyte chemoattractant protein 1 (MSP-1) and brain-specific serine protease 4 (BSSP-4) from mouse and human mast cells [51]. BSSP-4 in turn induced MCP-1 release from astrocytes and combined glia/neuron cultures. Interaction of mast cells with neurons and glia may likely provide a new therapeutic target for PD [50].

Impairments to the Blood–Brain Barrier. Inflammation may underlie impairments to the blood–brain barrier (BBB), attraction of adaptive immunity cells, their activation, and antigen-dependent damage to other areas of the brain. Thus, PD may involve propagation of the inflammatory process by a positive feedback mechanism [52]. Confirmation of BBB damage in patients with PD has been obtained by positron emission tomography of P-glycoprotein-mediated uptake and by studies of blood and CSF albumin contents [53, 54]. BBB impairments were accompanied by thinning of capillary basement membranes and accumulation of collagen [55], along with endothelial cell proliferation [56]. Increased expression of intercellular adhesion molecule 1 (ICAM-1) in the endothelium of vessels in the SN has been detected in brain autopsy specimens from PD patients and MPTP models in rodents and primates [57, 58]. Impairments to the integrity of the BBB promote migration of immunocompetent cells to neurodegenerative plaques [59] and the development of autoimmune processes. Impairment to the BBB can also promote "leakage" of antigens from the CNS into lymph nodes, where they can trigger adaptive immune responses.

Autoimmune Inflammation. The first evidence for autoimmune inflammation in the idiopathic form of PD was obtained by McGreer et al. [60]. Autopsy SN contained not only Lewy bodies, but also reactive glial cells containing human leukocyte DR antigens (HLA-DR-positive cells). Further studies noted elevated expression of class II major histocompatibility complex antigens (MHC II) – HLA-DR and HLA-DQ – by blood monocytes and in the CSF of PD patients [20, 61]. In health, HLA-DR expression is barely detected, while in PD, HLA-DR$^+$ microglia were detected in the SN and other parts of the CNS, including the hippocampus and entorhinal cortex [60, 62]. Early genetic studies demonstrated a link between a high risk of PD and mutations in the HLA-DRA gene (at the PARK18 locus) [63, 64]. However, a meta-analysis did not reveal any significant link between the HLA-DRA/PARK18 gene (rs3129882) and the risk of developing PD [65]. The authors came to the conclusion that more detailed primary research was required. However, it remains unknown whether these mutations correspond to increases in the expression of histocompatibility molecules or whether they underlie the "inappropriate" immune response to autoantigens or "weak" alloantigens.

The Role of the Microglia. In physiological studies, the "resting" state of the microglia is maintained by interaction with undamaged neurons, which involves the chemokine fractalkine (CX3CL1), the CD47, CD200, and CD22 molecules, which are expressed by neurons, and the corresponding receptors – CX3CR1, CD172, CD200R, and CD45 on the surfaces of glial cells [66]. Neuron death leading to loss of these interactions and accompanied by αS release, induces microglial activation. The cells start to produce cytokines [67, 68], ROS [69, 70], prostanoids [71], and chemokines, which stimulate the recruitment of immune cells [72, 73]. Neuron death may be mediated by binding of TNF with Fas "death" receptors, the harmful actions of ROS, and macrophage and glial cell phagocytic activity [67, 72]. Chronic activation of the microglia (microgliosis) occurs in patient consuming MPTP-contaminated heroin [74] and primates given this toxin [75]. Human brain samples collected post mortem showed positive correlations between disease duration and the level of expression of activation marker CD68 by glial cells and between the level of HLA-DR expression by microglial cells and the quantity of αS [76]. Activation of microglial cells was found to be most marked in areas of

accumulation of damaged neurons with Lewy bodies [62]. Positron emission tomography data indicate that the extent of midbrain microglial activation in PD patients is linked with the severity of motor disorders [77].

Like other antigen-presenting cells, microglial cells take part in processing and presenting antigens with class II MHC $CD4^+$ lymphocytes and in triggering specific immune responses. In mice with overexpression of human αS, knockout of class II MHC prevents activation of microglia and T lymphocytes, the accumulation of immunoglobulins in the SN, and neurodegeneration [78]. Data from both clinical and experimental studies have demonstrated the presence of lymphocyte infiltrates in brain tissues in PD and their link with the formation and expression of HLA-DR antigens by glia [57, 60]. Stratum specimens obtained from PD patients have been found to contain increased contents of β2 microglobulin, which is involved in stabilizing class I histocompatibility molecules (MHC-I) [79], which suggests involvement of cytotoxic $CD8^+$ T-lymphocytes in the process of neurodegeneration, along with $CD4^+$ lymphocytes.

Dopaminergic Neurons. Dopaminergic neurons in certain conditions can function as antigen-presenting cells for cytotoxic T-lymphocytes [80]. Activated microglia release factors which can lead to induction of MHC-I molecules on neurons. Dopaminergic neurons can take up foreign antigens and present them via MHC-I, triggering dopaminergic neuron death in the presence of the corresponding cytotoxic T-lymphocytes. Thus, neuronal MHC-I molecules can trigger antigen responses [80].

The Role of Lymphocytes and Their Subpopulations. In MPTP models of parkinsonism, animals showed accumulation of T-cells, mainly $CD8^+$, in the CNS, with elevated expression of integrin, i.e., lymphocyte function-associated antigen 1, which has a role in the migration of cells across the BBB [39]. The death of dopaminergic neurons was significantly less marked in mice with knockout of RAG2 (recombination-activating gene 2), which lack T and B cells, and in mice with deficiency of T cells and isolated deficiency of $CD4^+$ lymphocytes [57, 81], though deficiency of $CD8^+$ T-lymphocytes did not lead to such consequences. Administration of RAG1 (recombination-activating gene 1) mutant splenocytes but not IFGγ–/– splenocytes to –/– FasL (first apoptosis signal ligand, the ligand of the Fas receptor) mice had neuroprotective actions. These data emphasize the importance of $CD4^+$ $FasL^+$ T-cells in mediating cytotoxic effects in the CNS in PD.

Overexpression of human αS in a mouse model of PD, as noted above, induced glial activation. This was accompanied by accumulation of T- and B-lymphocytes, evidencing the development of a specific immune response [18]. Studies reported by Bennet et al. [82] showed that the C-fragment of nitro-modified αS induced a specific immune response in mice, while adaptive transfer of Th1 and Th17 from a synuclein-immunized donor led to acceleration of the neurodegenerative process in the recipient; at the same time, transfer of regulatory T-cells (T_{reg}) had the opposite action [73]. Immunization of mice with αS was found to lead to a decrease in the quantity and a reduction in the activity of $CD4^+CD25^+$ T_{reg} cells, assessed in terms of their ability to suppress the proliferation of effector T-lymphocytes in vitro [83].

The importance of T_{reg} cells in organizing neurodegeneration in PD has been clearly demonstrated in animal models. Studies using an MPTP model of PD showed a decrease in the number of Th1 cells producing IFNγ, which was accompanied by an increase in the number of T_{reg} cells ($CD4^+C25^+$) in lymphoid tissues [84, 85]. In mice with knockout of aquaporin-4, the number of $CD4^+C25^+$ cells was decreased as compared with wild-type mice, and this was linked with a stronger reaction by the microglia and greater loss of dopaminergic neurons in the MPTP model as compared with wild-type mice [86]. Systematic increases in the number of T_{reg} cells in this same model led to a decrease in microglial activation and overcame the degeneration of dopaminergic neurons in the SN [83, 85, 87].

With the aim of identifying the role of adaptive immunity in the pathogenesis of PD in humans, lymphocytes in brain specimens, CSF, and peripheral blood from patients with PD were typed. SN autopsies from PD patients showed $CD8^+$ cells and a smaller population of $CD4^+$ T-lymphocytes, and cells were located in the immediate vicinity of dead neurons and activated glia [57, 60, 88]. Lymphocyte accumulation in brain tissue can only partly be explained in terms of disruption of the BBB [54], as the $CD4^+/CD8^+$ ratios in the CNS and bloodstream are different. These data suggest predominant migration of $CD8^+$ lymphocytes to brain tissue via an as yet unidentified pathway. A decrease in the total lymphocyte content in the blood has been demonstrated, due to reductions in both B- and, to a lesser extent, T-lymphocytes, the content of T-cells decreasing because of constriction of the helper population [89, 90]. A decrease in the relative number of naïve T-cells and an increase in the content of memory cells in the peripheral blood of PD patients were described by Fiszer et al. [91]. It is interesting that selective loss of the $CD45RA^+$ population of naïve T-cells has also been detected in other CNS diseases, i.e., multiple sclerosis and Down's syndrome [91, 92]. The cause of the reduction in the number of naïve T-cells may be the high density of membrane Fas molecules, which induce apoptosis when FasL binds to them [90]. An increase in the number of $CD4^+Fas^+$ T-lymphocytes was demonstrated by Hisanaga et al. [93]. A decrease in the $CD4^+/CD8^+$ ratio and an increase in the IFGγ-producing T-cell content in PD provide evidence of shift towards $CD8^+$ cytotoxic T-lymphocytes [89, 90, 94]. Within the population of $CD4^+$ lymphocytes, expansion of the $CD45RO^+$ population has been demonstrated, this including activated cells and memory cells [95]. A link between the content of $CD45RO^+$ T-lymphocytes and the severity of motor impairments was demonstrated. Other changes in relation to measures of cellular immunity in PD were: increases in the number of acti-

vated $CD4^+CD8^+CD45RO^+$ and $CD25^+$ T-cells [94], an increase in the Th1/Th2 ratio, and increases in the blood concentrations of IL-15, IL-10, and the chemokine RANTES [96, 97]. Fiszer et al. [98] found an increase in the γδ T-cell population in the CSF of PD patients, these cells expressing the activation marker CD25. Overall these observations support the view that an inflammatory autoimmune process takes place in PD.

Clinical analysis of peripheral blood lymphocyte subpopulations was run in 268 patients with sporadic PD and 268 healthy subjects with the aim of assessing potential markers for the development of PD in Chinese patients [99]. Immunostaining and flow cytometry analysis methods were used to determine the numbers of natural killers (NK), $CD3^+$, $CD3^+CD4^+$, as well as $CD3^+CD8^+$ subpopulations, and $CD19^+$ B-lymphocytes in human peripheral blood, and their percentage compositions were computed. Flow cytometry analysis determined the ratios of regulatory T-cells and helper T17 cells (T_{reg}/Th17) in 64 patients with PD and 46 healthy people. The study results showed that the proportion of NK cells was greater in patients with progressive PD than in controls, while the percentage of $CD3^+$ T-cells was decreased. The percentage composition of $CD19^+$ B-lymphocytes in patients at the late stages of PD was lower than in patients in the early stages. The T_{reg}/Th17 ratio in female patients was higher than that in women in controls. These results suggest that the proportions of NK, $CD3^+$ T-lymphocytes, and $CD19^+$ B-lymphocytes, along with the Treg/Th17 ratio in peripheral blood, may be useful for predicting the risk of developing PD in the Chinese population, in detecting new diagnostic biomarkers, and in suggesting novel therapeutic developments [99].

Data on the activity of T_{reg} cells in PD are contradictory. Rosenkranz et al. [100] showed that T_{reg} cells have elevated suppressor ability in people with PD. Another study identified a decrease in the number of T_{reg} cells in PD [101]. A decrease in T_{reg} cell suppressor activity was also identified [95]. Studies seeking to increase the activity of T_{reg} cells in PD have significant potential in the battle with this disease [85].

The available literature as yet lacks data on the specificity of human T-cell clones in PD, while sequencing of the repertoire of T-cell receptors in PD has not been carried out. One study showed a low content of cells with the Vβ8 T-cell receptor variant [102]. Analysis of the T-cell proteome in PD allowed biomarkers for the disease to be identified, including β-fibrinogen and transaldolase [103], though the pathogenic roles of these proteins have not been studied.

Autoantibodies and Brain Antigens. The autoimmune concept of the development of parkinsonism is reinforced by data showing increases in titers to antibodies to brain autoantigens [104]. No data evidencing infiltration of the CNS with B-cells have been obtained [57, 60]. As noted above, the number of circulating B-lymphocytes is decreased in PD [89, 90], and the cause and consequences of this phenomenon require further investigation. Analysis of antibody specificity demonstrated heterogeneity, i.e., interactions with different proteins [104]. The blood and CSF of patients with PD were found to contain antibodies specific for different types of αS, melanin [105], heat shock proteins HDP-65 and HSP-70 [106], and brain-associated antigens, i.e., GM1, S100B, glial fibrillary acidic protein, nerve growth factor, neurofilaments, myelin basic protein, tau protein, and calcium channel proteins [107, 108]. No universal "parkinsonism antigen" was found among these. The situation is made more difficult by the impossibility of running studies in humans in the early stages of the disease. Most publications provide evidence that autoantibodies have pathogenetic rather than protective properties. Analysis of brain sections from PD patients is evidence for the existence of immunoglobulin molecules associated with pigmented dopaminergic neurons and $Fc\gamma R^+$ microglia. Endogenous antibodies appear to be able to cross the BBB and react with targets within dopaminergic neurons. Data from immunohistochemical analysis indicate that dopaminergic neurons in the SN bind IgG but not IgM [109]. The number of neurons binding IgG correlated with the content of MHC II^+ microglial cells, which suggests the existence of mechanisms common to antigen presentation and antibody-mediated neuron death. Binding of antibodies to the corresponding targets on neuron surfaces may lead to their elimination by phagocytosis by microglia or macrophages. Microglial cells have been shown to be able to synthesize the C1q component of complement [110], and this, binding with Fc immunoglobulin fragments, triggers the "classical" pathway of complement activation. Complement activation may be an additional factor promoting nerve cell death. Pigment granules have been detected in microglial cells, which may point to antibody-dependent phagocytosis of neurons [109]. Administration of immunoglobulins obtained from the serum of PD patients into the SN in rodents led to the death of tyrosine hydroxylase-positive neurons, dependent on the expression of Fcγ receptors [111]. Mice with activated Fcγ receptors were resistant to the neurodegenerative action of MPTP given chronically [81]. These animals showed less marked activation of the microglia and nerve cell damage [111]. Overexpression of human αS in mice also induced immunoglobulin accumulation and neurodegeneration [81], while additional knockout of Fcγ led to better protection of the nervous system [112]. Some studies have demonstrated the protective role of autoantibodies in PD. Thus, mouse experiments showed that microglial cells clear pathogenic αS complexed with antibodies [113]. Attempts to find PD biomarkers among autoantibodies specific only for this disease have been unsuccessful [104]. Some data indicate that the search for such biomarkers is appropriate for the inherited but not for the sporadic forms of PD [114].

According to the autoimmune theory of the pathogenesis of PD, various actions leading to damage to nervous cells may ultimately uncouple immunological tolerance

from the development of autoimmune inflammation. The autoimmune hypothesis for the development of PD is reinforced by reports of increases in the incidence of this disease when other autoimmune diseases are present – systemic lupus erythematosus, Sjögren's syndrome, and pemphigoid [115–117]. Genetic risk factors common to PD and Crohn's disease have been observed. Some investigators take the view that viruses and parasites (influenza virus, Epstein–Barr virus, *Toxoplasma*) may be able to provoke the development of PD [118–120].

Conclusions. PD develops over tens of years. By the time of onset of the first clinical symptoms, more than 50% of the bodies of dopaminergic neurons in the SN have already been lost. It is therefore important to detect the disease before clinical manifestations are apparent. Preclinical signs, i.e., disease markers, need to be found. Immunologists are also seeking immunological markers. A number of cytokines are candidates for this role as their CSF and serum levels change; Class II MHC antigens, i.e., HLA-DR and HLA-DQ, whose expression is elevated in blood and CSF monocytes, autoantibodies, etc., are also candidates. Changes in blood contents of lymphocyte populations and subpopulations are known to occur. This may also serve as a prognostic sign. As noted in the excellent monograph on neurodegenerative diseases edited by Ugryumov [10], development of presymptomatic diagnosis of PD, with prophylaxis and treatment at the presymptomatic stage, will hopefully lead to termination or slowing of neuron death.

The authors have no conflicts of interests.

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