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Review

Parkinson's disease: Autoimmunity and neuroinflammation

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ABSTRACT

Parkinson's disease is a neurodegenerative disease that causes the death of dopaminergic neurons in the substantia nigra. The resulting dopamine deficiency in the basal ganglia leads to a movement disorder that is characterized by classical parkinsonian motor symptoms. Parkinson's disease is recognized as the most common neurodegenerative disorder after Alzheimer's disease.

PD ethiopathogenesis remains to be elucidated and has been connected to genetic, environmental and immunologic conditions.

The past decade has provided evidence for a significant role of the immune system in PD pathogenesis, either through inflammation or an autoimmune response. Several autoantibodies directed at antigens associated with PD pathogenesis have been identified in PD patients. This immune activation may be the cause of, rather than a response to, the observed neuronal loss.

Parkinsonian motor symptoms include bradykinesia, muscular rigidity and resting tremor. The non-motor features include olfactory dysfunction, cognitive impairment, psychiatric symptoms and autonomic dysfunction.

Microscopically, the specific degeneration of dopaminergic neurons in the substantia nigra and the presence of Lewy bodies, which are brain deposits containing a substantial amount of α-synuclein, have been recognized.

The progression of Parkinson's disease is characterized by a worsening of motor features; however, as the disease progresses, there is an emergence of complications related to long-term symptomatic treatment.

The available therapies for Parkinson's disease only treat the symptoms of the disease. A major goal of Parkinson's disease research is the development of disease-modifying drugs that slow or stop the neurodegenerative process. Drugs that enhance the intracerebral dopamine concentrations or stimulate dopamine receptors remain the mainstay treatment for motor symptoms.

Immunomodulatory therapeutic strategies aiming to attenuate PD neurodegeneration have become an attractive option and warrant further investigation.

Contents

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1. Introduction

Parkinson's disease is a neurodegenerative disease that results in the death of dopaminergic neurons in the substantia nigra pars compacta (SNpc). The resulting dopamine deficiency within the basal ganglia leads to a movement disorder characterized by classical parkinsonian motor symptoms.

Parkinson's disease was first medically described as a neurological syndrome by James Parkinson in 1817, although some aspects of Parkinson's disease were reported in earlier descriptions [1]. For example, Sylvius de la Boë wrote of resting tremor and Sauvages described festination [2,3]. Much earlier, traditional Indian texts from approximately 1000 BC and ancient Chinese sources also provided descriptions that were reminiscent of Parkinson's disease [4,5]. Over 50 years later, Jean-Martin Charcot was more thorough in his descriptions and distinguished bradykinesia as a separate cardinal feature of the illness [6].

2. Epidemiology

Parkinson's disease is recognized as the most common neurodegenerative disorder after Alzheimer's disease [7,8]. The incidence of Parkinson's disease ranges from 10 to 18 per 100,000 person-years [9]. Gender is an established risk factor, with a male-to-female ratio of approximately 3:2 [10]. Ethnicity is also a risk factor for the disease. In the USA, the incidence is highest in people of Hispanic ethnic origin, followed by non-Hispanic Whites, Asians and Blacks [9]. Age is the greatest risk factor for the development of Parkinson's disease. The prevalence and incidence increase nearly exponentially with age and peak after 80 years of age [11,12]. This trend has important public health implications; as the aging population and life expectancy increase worldwide, the number of people with Parkinson's disease is expected to increase by more than 50% by 2030 [7].

3. Ethiopathogenesis

Currently, PD ethiopathogenesis remains to be elucidated, and the destruction of dopaminergic neurons in PD has been connected to a variety of factors, including genetic, environmental and immunological conditions.

Genetic factors have been identified in familiar forms of PD, which contribute to approximately 10% of PD cases [13,14]. Environmental factors that were shown to be associated with a decreased risk were tobacco smoking, coffee drinking, non-steroidal anti-inflammatory drug use, calcium channel blocker use, and alcohol consumption [15]. Factors that increase the risk of developing PD were pesticide exposure, prior head injury, rural living, β-blocker use, agricultural occupation, and well-water drinking [15].

Furthermore, the results of epidemiological studies [15] showed that the use of anti-inflammatory medications, specifically non-steroidal anti-inflammatory drugs, reduced the risk of developing Parkinson's disease, supporting the hypothesis that inflammation might promote an underlying disease process (Fig. 1).

Currently, PD etiopathogenesis remains to be elucidated. Recently, reviews of the current literature have brought to light evidence for the possible role of the immune system, specifically autoimmune mechanisms, in the ethiopathogenesis of PD [16]. Previously, it was believed that PD is not mediated by autoimmune mechanisms [17]. However, data accumulated over the past decade regarding immune alterations in PD increased the interest in pursuing such an association. A series of independent observations has led to the convergence of the view that innate and adaptive immune mechanisms might play a role in the development of PD [18].

Neuroinflammation is a characteristic feature of Parkinson's disease pathology, but it has yet to be established whether neuroinflammation promotes or protects from neurodegeneration. A significant increase in the level of innate immune components, including complement and cytokines (e.g., IL-1, IL-2, IL-6, and TNF), in the substantia nigra and cerebrospinal fluid (CSF) of PD patients has been observed [18]. Elevation of γ/δ + T cells in the peripheral blood and CSF of PD patients was also reported [19]. Benkler et al. [20] then further pursued this quest and found evidence suggesting that an autoimmune mechanism, which may be mediated via humoral responses, might play a role in the ethiopathogenesis of PD.

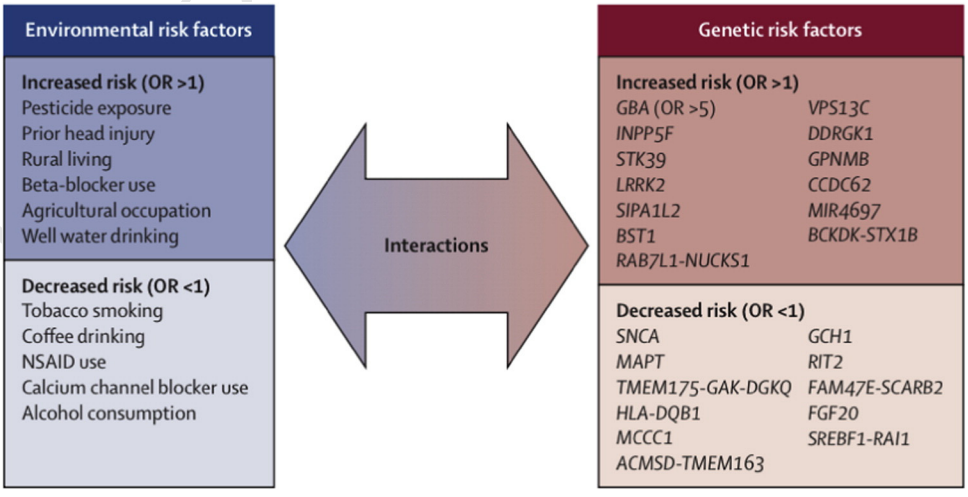

Fig. 1. Risk factors for the development of Parkinson's disease. Results of epidemiological studies have revealed various environmental exposures that increase (OR > 1) or decrease (OR < 1) the risk of developing Parkinson's disease (left). Findings of genome-wide association studies have identified genetic risk factors, which are polymorphisms within certain genes that influence risk for developing Parkinson's disease (right). The strongest genetic risk factor is the Asn370Ser mutation of β-glucocerebrosidase, which is associated with an OR greater than 5. The interplay between environmental and genetic risk factors is under investigation. OR = odds ratio. (*From:* Lancet 2015;386:896:912).

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Over the last decade, several autoantibodies directed at antigens associated with or related to PD pathogenesis have been identified in PD patients, including antibodies directed at melanin [21], a-synuclein [22,23], and GM1 ganglioside [24].

Interestingly, a recent placebo-controlled study demonstrated that GM1-ganglioside supplementation was effective in improving tremor-related motor functions, thus supporting a possible role for these antibodies in the pathogenesis of tremor in PD [24].

Autoreactive antibodies associated with PD have been found in the plasma and brain; a post-mortem analysis of brains from PD patients and controls showed that IgG was bound to dopaminergic neurons in tissues from patients with PD [25].

One potential target structure for an immune attack against dopaminergic neurons is the pigment neuromelanin (NM) that accumulates in dopaminergic neurons as a by-product of catecholamine metabolism [26].

Oberlander et al. recently showed that NM triggers the functional DC maturation in vitro, as NM-treated DCs were able to trigger a proliferative T cell response. They also showed that DCs can phagocytose NM [27].

These experiments demonstrate that the first criterion for DCs to initiate an adaptive autoimmune response directed against NM-associated structures was fulfilled. Koutsilieri et al. [28] hypothesize that activated DCs migrate from the brain into the cervical lymph node, where they present the potential (auto-)antigens to T and B cells. The recognition of NM as a pathogen or dangerous molecule and its uptake by DCs would allow the DCs to migrate, and its presentation in the cervical lymph nodes triggers an adaptive autoimmune response if NM-reactive T or B cells are present. This autoimmune response against NM would be directed against NM-rich cells in the brain, leading to dopaminergic cell death. This auto-aggressive loop would be enhanced by NM-triggered activation of microglia [29,30], resulting in an amplification of the adaptive immune response against NM and the local reactivation of the immigrating effector T cells (Fig. 2). There is accumulating evidence for an immunogenic role of NM in PD pathogenesis. Antibodies directed at catecholamine-based melanins have been detected in the sera from PD patients [21].

In another study, CSF derived auto-Abs that react with dopaminergic neurons in the substantia nigra were present in 78% of patients compared with 3% of the controls [31].

Moreover, the CSF of PD patients exerted a cytotoxic effect on dopaminergic neurons, which enhanced the substantia nigra degeneration in a time- and dose-dependent manner [31,32]. This cytotoxic effect was further demonstrated by neuronal labelling with IgG, which correlated with neurodegeneration in PD [25].

Early experimental evidence in favour of an autoimmune background of PD came from Chen et al., who reported that the transfer of plasma antibodies isolated from PD patients to the substantia nigra of rats induced a marked loss of dopaminergic neurons. In contrast, animals that were treated with antibodies from healthy controls exhibited much less neuronal damage, suggesting that autoantibodies that recognize dopaminergic cells are present in patients with PD [33].

Furthermore, several immune-mediated mechanisms were proposed to explain the possible mechanisms by which autoantibodies may induce dopaminergic cell death, such as activation of apoptosis, enhanced complement function, accelerated attack of the surrounding microglia cells [31,32,34,35], and competitive binding inhibition [36,37].

Microglia cells, the tissue macrophage population of the brain, are the main glial cell type that participates in the inflammatory response in the brain. Microglial activation through an FCγ receptor pathway can be induced by IgG derived from PD patients, which subsequently causes substantia nigra cell injury [34]. The plausible notorious effect of antibodies on the dopaminergic system was further highlighted in a series of in vitro and in vivo studies utilizing synthetic antibodies (Abs) [36]. These engineered Abs were able to bind native dopamine receptors and competitively inhibit the dopamine receptors' ability to bind their natural agonists [37,38].

Taken together, these results might suggest a role for autoantibodies, which are a prominent feature of autoimmunity, in the ethiopathogenesis of PD. However, recent studies suggest that this immune activation may be the cause of, rather than a response to, the observed neuronal loss.

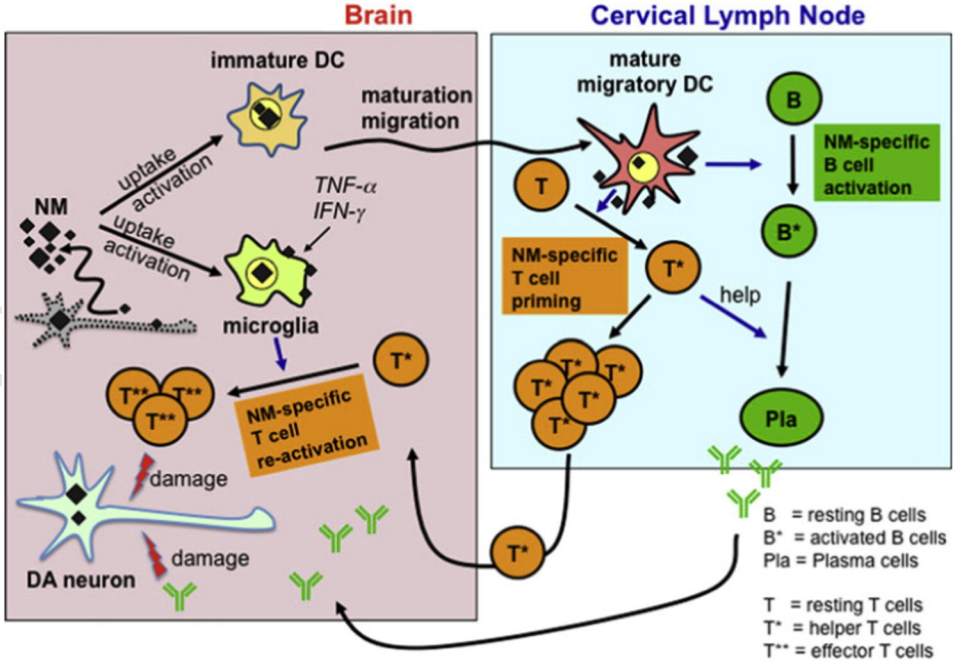

Fig. 2. How activation of DCs by NM could trigger autoimmunity directed at dopaminergic neurons. Contact of DCs with NM triggers the maturation of these cells that subsequently migrate from the brain into the cervical lymph nodes where they present NM to B- and T-lymphocytes.

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4. Clinical features

Parkinsonian motor symptoms include bradykinesia, muscular rigidity and resting tremor [39]. The non-motor features include olfactory dysfunction, cognitive impairment, psychiatric symptoms, sleep disorders and autonomic dysfunction.

Non-motor features are also frequently present in Parkinson's disease before the onset of the classical motor symptoms (Fig. 1) [40]. The premotor phase can be prolonged; for example, the average latency between the onset of the early symptoms and occurrence of parkinsonian motor symptoms is 12–14 years [40].

In late-stage Parkinson's disease, treatment-resistant motor and non-motor features are prominent and include axial motor symptoms, such as postural instability, freezing of gait, falls, dysphagia, and speech dysfunction. After approximately 17 years of disease, up to 80% of patients with Parkinson's disease have a freezing of gait and falls, and up to 50% of patients report choking [41]. Dementia is particularly prevalent, occurring in 83% of patients with Parkinson's disease who have had a disease duration of 20 years [42] (Fig. 3).

5. Histopathology

The loss of dark pigmentation in the substantia nigra and frontal atrophy are typical examples of macroscopic brain aberrations that develop in PD [43].

Microscopically, two predominant features have been recognized: a specific degeneration of dopaminergic neurons in the substantia nigra and the presence of Lewy bodies, which are brain deposits that contain a substantial amount of α-synuclein [43]. In its misfolded state, α-synuclein becomes insoluble and aggregates to form intracellular inclusions within the cell body (Lewy bodies) and processes (Lewy neurites) of neurons [44]. Lewy pathology is not restricted to the brain, but can also be found in the spinal cord and peripheral nervous system [45].

6. Diagnosis

A clinical diagnosis of Parkinson's disease is based on the presence of parkinsonian motor features, namely, bradykinesia, rigidity and resting tremor.

Strategies to develop biomarkers for the diagnosis of Parkinson's disease are under investigation, particularly to enable diagnosis early in the disease course, even before the onset of motor symptoms. Potential clinical markers include olfactory impairment, as measured by standard methods, such as the University of Pennsylvania's smell identification test [40]. The proposed pathological markers are being tested on the basis of earlier findings of α-synuclein within the peripheral nervous system. The concentrations of α-synuclein, DJ-1, tau and β-amyloid [46,47], as well as the β-glucocerebrosidase activity in the cerebrospinal fluid are being tested as potential biochemical biomarkers of early Parkinson's disease [48,49] (Fig. 4).

Candidate imaging markers include positron emission tomography (PET) or single photon emission computed tomography (SPECT) methods to measure the reduction in the number of SNpc dopaminergic nerve terminals projecting to the striatum [50]. Standard MRI has a marginal role in Parkinson's disease diagnosis, but high and ultra-high-field (7 Tesla) MRI combined with advanced techniques, such as diffusion tensor imaging, are being explored for early diagnosis of Parkinson's disease [51,52].

For people with family members with a known monogenic form of Parkinson's disease, genetic testing can assist in the diagnosis.

A single measure might not suffice for an accurate and early diagnosis of such a complex disease. Instead, a combination of imaging, biochemical and genetic biomarkers might be required.

7. Prognosis

The progression of Parkinson's disease is characterized by the worsening of motor features, which can initially be managed with symptomatic therapies. However, as the disease progresses, there is an emergence of complications related to long-term symptomatic treatment, including motor and non-motor fluctuations, dyskinesia and psychosis [41]. Symptoms of late-stage Parkinson's disease substantially contribute to disability and are strong predictors of a need for admission to an institution and mortality [53].

8. Treatment

The available therapies for Parkinson's disease only treat the symptoms of the disease. A major goal of Parkinson's disease research is the development of disease-modifying drugs that slow or stop the underlying neurodegenerative process. Drugs that can slow or stop the neurodegenerative process in Parkinson's disease are not yet available, but such disease-modifying drugs are anticipated to be most effective if patients can be diagnosed and treated during this prodromal premotor period. Drugs that enhance intracerebral dopamine concentrations or stimulate dopamine receptors remain the mainstay treatment for motor symptoms. These drugs include levodopa, dopamine agonists,

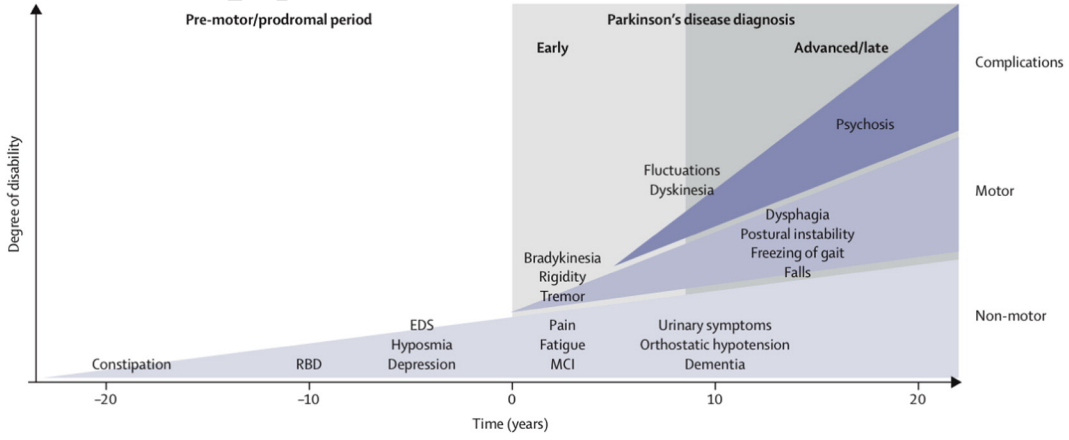

Fig. 3. Clinical symptoms and time course of Parkinson's disease progression. Diagnosis of Parkinson's disease occurs with the onset of motor symptoms (time 0 years) but can be preceded by a premotor or prodromal phase of 20 years or more. This prodromal phase is characterized by specific non-motor symptoms. Additional non-motor features develop following diagnosis and with disease progression, causing clinically significant disability. Axial motor symptoms, such as postural instability with frequent falls and freezing of gait, tend to occur in advanced disease. Long-term complications of dopaminergic therapy, including fluctuations, dyskinesia and psychosis, also contribute to disability. EDS = excessive daytime sleepiness; MCI = mild cognitive impairment; RBD = REM sleep behaviour disorder. (*From:* Lancet 2015;386:896:912).

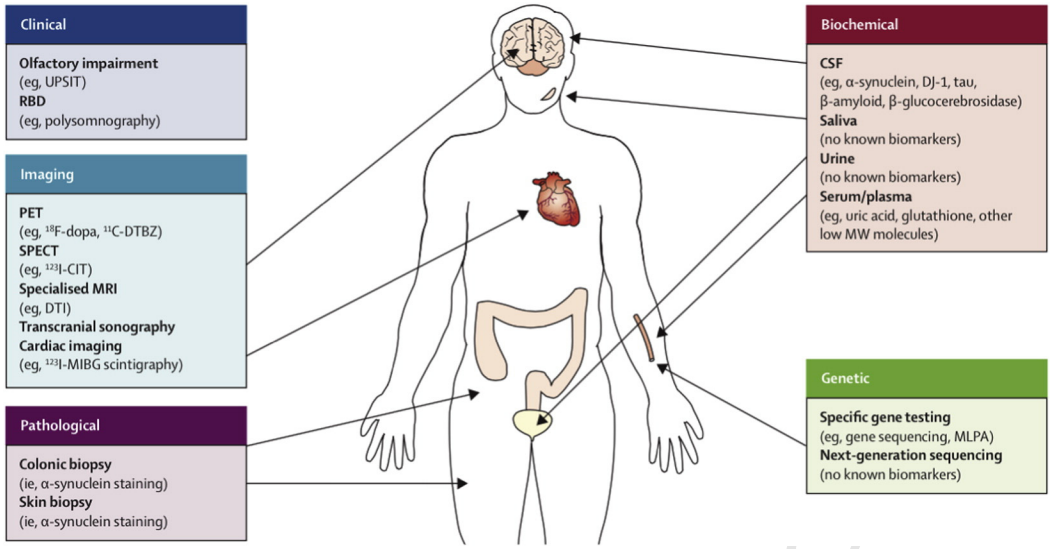

Fig. 4. Potential biomarkers for diagnosis of Parkinson's disease. A variety of biomarkers for Parkinson's disease diagnosis are currently under investigation. These biomarkers can be classified as clinical, imaging, pathological, biochemical and genetic. Midbrain hyperechogenicity detected by transcranial sonography is a proposed diagnostic biomarker for Parkinson's disease, but many experts have found this method to have reliability and replicability issues. Combinations of biomarkers are likely to be necessary for accurate diagnosis of premotor or early PD. 11C-DTBZ = 11C-dihydrotetrabenazine; CSF = cerebrospinal fluid; DTI = diffusion tensor imaging; 123I-CIT = 123I-2β-carbomethoxy-3β-(4-iodophenyl)tropane; 123I-MIBG = 123I-metaiodobenzylguanidine; MLPA = multiplex ligation-dependent probe amplification; MW = molecular weight; PET = positron emission tomography; RBD = rapid eye movement sleep behaviour disorder; SPECT = single photon emission computed tomography; UPSIT = University of Pennsylvania's smell identification test. (*From:* Lancet 2015;386:896:912).

monoamine oxidase type B inhibitors and, less commonly, amantadine [54,55]. Because none of these drugs have proven to be neuroprotective or disease-modifying, therapy does not need to be started at the time of diagnosis for all patients. However, there is little justification for delay. Treatment should be initiated when symptoms cause disability or discomfort to the patient, with the goal of improving function and quality of life.

The past decade has provided accumulating evidence for a significant role of the immune system in PD pathogenesis, either through inflammation or an autoimmune response. Thus, immunomodulatory therapy strategies aiming to attenuate PD disease progression have become an attractive option and warrant further investigation. However, the negative results of non-steroidal anti-inflammatory drugs in late PD [56] strongly suggest that early immunomodulation is the key to preventing PD onset and progression.

Minocycline, a broad-spectrum tetracycline antibiotic, has been tested in experimental models and PD patients. Minocycline effectively crosses the blood–brain barrier (BBB) and shows potent anti-inflammatory effects in neurotoxin models of PD [57]. A randomized, double-blind, Phase II clinical trial showed that minocycline offers a clinical benefit to early PD patients, which warrants further consideration of minocycline for use in Phase III clinical trials [58].

Leucine-rich repeat kinase 2 (LRRK2) is an enzyme that is highly expressed in peripheral macrophages and monocytic cells, as well as central microglia, suggesting a functional role for LRRK2 in the innate immune system [59,60]. Inhibition or attenuation of LRRK2 is a promising therapeutic strategy as an anti-inflammatory treatment for PD.

Peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α) is a potential new target for anti-inflammatory therapy in PD patients. PGC-1α activity is mainly controlled by the peroxisome proliferator-activated receptors (PPARs), 5′ AMP-activated protein kinase (AMPK), and sirtuin 1 (Sirt1) [61]. Hence, pharmacological activators for these proteins have the potential to exert anti-inflammatory effects by activating PGC-1α. These activators include fibrates and rosiglitazone (PPAR) [62,63], metformin [64], pyrroloquinoline quinone [65], 5-aminoimidazole-4-carboxamide ribonucleotide (AICAR) (AMPK) [66] and resveratrol (Sirt1) [67].

As PPAR agonists (fibrates and rosiglitazone) and AMPK activators (metformin and AICAR) are already routinely used in clinical practice for the treatment of metabolic syndrome and type 2 diabetes, these drugs could be readily translated from animal models to PD patients. Preclinical CNS distribution and efficacy studies using inflammatory animal models of PD will be sufficient to warrant clinical trials on these drugs.

9. Conclusions

Parkinson's disease is a debilitating disease of unknown cause, despite major scientific and therapeutic advances. The extensive damage to the dopaminergic system in PD seems to be interconnected with genetics, environmental and immunological factors, which is described as a mosaic of many autoimmune diseases [68]. In this review, we pursued the evidence for immune- and autoimmune-mediated mechanisms that are associated with PD. A unique observation indicated that olfactory dysfunction may be a consequence of an autoimmune mechanism. As decreased olfaction is one of the earliest non-motor signs of PD, this observation might shed more light on a possible association between autoimmunity and PD.

The prevalence of several brain-associated autoantibodies in the sera of PD patients further support the possible role of immunoglobulin-mediated autoimmune mechanisms in the ethiopathogenesis of PD. Not only can these autoantibodies serve as biomarkers of disease but our renewed understanding of the nature of this complex disease might also be useful for the early diagnosis and treatment of PD patients. It is even safe to say that novel therapeutics targeted at specific autoantibodies may be able to differentiate between PD subgroups. Further studies to evaluate a larger number of patients and preferably a wider profile of brain-associated autoantibodies might enable a better understanding of the precise ethiopathological mechanism of PD.

Thus, although PD pathogenesis remains to be fully elucidated, it seems that the inflammation and neuronal degeneration associated with PD could be induced by autoimmune mechanisms, mainly via brain-specific auto-Abs.

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Take-home messages

- Parkinson's disease is a neurodegenerative disease that causes the death of dopaminergic neurons in the substantia nigra pars compacta (SNpc). The resulting dopamine deficiency in the basal ganglia leads to a movement disorder that is characterized by classic parkinsonian motor symptoms.
- PD ethiopathogenesis remains to be elucidated and has been connected to genetic, environmental and immunological conditions. Recently, the role of autoimmune mechanisms in the ethiopathogenesis of PD has garnered more attention. Thus, it seems that neuronal degeneration could be induced by autoimmune mechanisms, mainly via brain-specific autoantibodies.
- Parkinsonian motor symptoms include bradykinesia, muscular rigidity and resting tremor. The non-motor features include olfactory dysfunction, cognitive impairment, psychiatric symptoms and autonomic dysfunction. Olfactory impairment is one of the first symptoms and allows an early diagnosis of PD many years before the onset of motor symptoms.
- Microscopically, two predominant features have been recognized: a specific degeneration of dopaminergic neurons in the substantia nigra and the presence of Lewy bodies, which are brain deposits containing a substantial amount of α-synuclein.
- Therapies for Parkinson's disease only treat the symptoms of the disease. Drugs that enhance the intracerebral dopamine concentrations (levodopa) or stimulate dopamine receptors (dopamine agonists) remain the mainstay treatment for motor symptoms. A major goal of Parkinson's disease research is the development of disease-modifying drugs that stop the neurodegenerative process.

If NM-reactive lymphocytes are present, they get activated (primed) and secrete NM-specific antibodies (B cells) or exert NM-specific cytotoxic functions (T cells). Activation of microglia by NM would result in a proliferation of NM-specific T cells after contact with NM-presenting microglia. NM-specific antibodies and T cells may recognize NM-positive neurons and trigger their degradation. (*From:* J Neural Transm 2013;120:75–81).

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