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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.

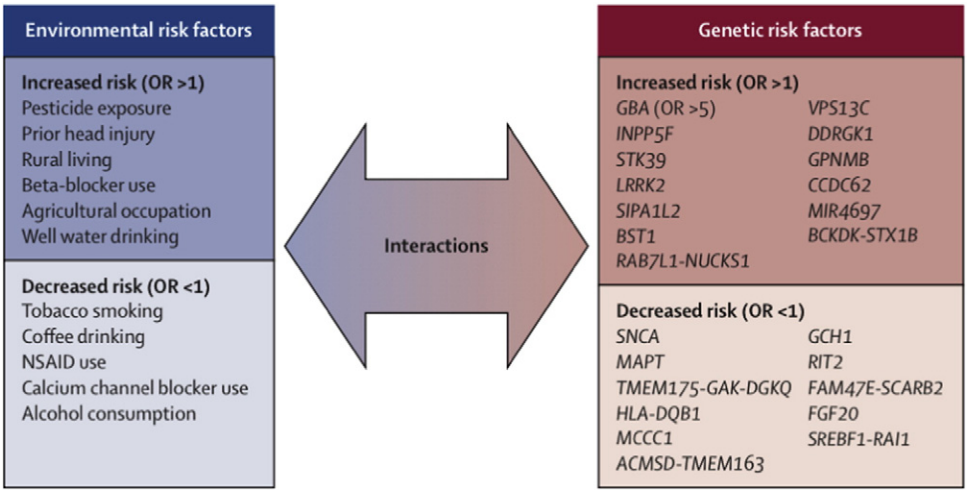

Fig. 1. Risk factors for the development of Parkinson's disease. Results of epidemiological studies have revealed various environmental exposures that increase (OR > 1) or decrease (OR < 1) the risk of developing Parkinson's disease (left). Findings of genome-wide association studies have identified 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).