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Prodromal Recognition of Non-Motor Symptoms and Biomarkers in Parkinson's Disease

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Abstract. The diagnosis of Parkinson's disease (PD) is often delayed due to over-reliance on motor manifestations, despite the fact that pathological changes including abnormal aggregation of alpha-synuclein (α-syn) and progressive dopaminergic neuronal loss in the substantia nigra pars compacta begin years before overt symptoms emerge. This interval, termed the prodromal phase, represents a critical window for potential intervention. This review summarizes the application value of non-motor symptoms (NMS) and their biomarkers in prodromal identification. Evidence on four NMS categories, namely isolated rapid eye movement sleep behavior disorder (iRBD), autonomic dysfunction, sensory impairment, and neuropsychiatric symptoms, is synthesized. Fluid biomarkers including cerebrospinal fluid (CSF) α-syn seed amplification assay, plasma proteins, and urine proteins, as well as neuroimaging tools including magnetic resonance imaging striatal metrics and meta-iodobenzylguanidine scintigraphy, are evaluated. The findings indicate that while iRBD and CSF α-syn seed amplification assay offer strong predictive value, no single modality suffices for reliable prodromal screening. A multi-modal strategy combining clinical symptoms, fluid markers, and imaging data appears more promising. By consolidating dispersed evidence across subspecialties, this review aims to offer clinicians and researchers an integrated reference for selecting and refining early detection strategies.

Keywords: Parkinson's Disease, Prodromal Stage, Non-Motor Symptoms, Alpha-Synuclein, Biomarkers

1. Introduction

Parkinson's disease (PD) is a neurodegenerative disorder predominantly affecting the middle-aged and elderly, characterized by progressive neurodegeneration and eventual loss of dopaminergic neurons in the substantia nigra pars compacta, resulting from the abnormal intraneuronal accumulation and deposition of alpha-synuclein (α-syn) [1]. PD is often diagnosed at an advanced stage, and existing medical technologies cannot achieve a complete cure. Motor symptoms include impaired motor control, movement execution, and postural balance. These symptoms are directly caused by dopamine deficiency in patients. The limitation of traditional PD diagnosis lies in its over-reliance on motor symptoms such as akinesia, bradykinesia, and resting tremor, which often leads to missing the optimal window for intervention [2]. Non-motor symptoms (NMS), in contrast, involve systems related to emotional and mental status, sensation, and cognition; although these symptoms

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do not directly affect limb movement, they significantly impair patients' quality of life. Increasing evidence shows that a considerable part of the above NMS can exist for a few years or even more than ten years before the typical motor performance, which is defined as the prodromal period of Parkinson's disease [3]. The significance of identifying this stage is that it may provide a key intervention time window for delaying or modifying the disease process.

Based on this, this paper focuses on the application of NMS and their related biomarkers in the identification of prodromal phase, reviewing the evidence of four types of NMS, namely isolated rapid eye movement sleep behavior disorder (iRBD), autonomic dysfunction, sensory impairment and neuropsychiatric symptoms, associated with prodromal phase, and evaluating the diagnostic performance and research progress of biofluid and neuroimaging biomarkers. The main contribution of this paper is to incorporate NMS and prodromal biomarkers scattered in various subspecialties into a unified review framework, and to reveal the relative value and applicable boundary of each index in prodromal identification, so as to provide an integrated reference for clinicians and researchers in the selection and optimization of early identification strategies.

2. Prodromal NMS

2.1. iRBD

Rapid eye movement sleep behavior disorder (RBD) is a parasomnia characterized by the loss of muscle atonia during rapid eye movement (REM) sleep, wherein patients exhibit violent dream-enacting behaviors during REM sleep, such as punching, kicking, and shouting [4]. Most patients display behaviors that may cause injury to themselves or others. iRBD refers to RBD for which no definitive etiology can be identified. In recent years, several biomarkers have been discovered that may indicate an elevated risk of progression from iRBD to overt α-synucleinopathy [5]. iRBD is commonly utilized for the prodromal identification of neurodegenerative disorders, including PD, dementia with Lewy bodies, and multiple system atrophy [6]. Currently, the most widely employed diagnostic technique for RBD is polysomnography. The characteristic presentation on video of complex motor behaviors accompanied by rhythmic, stereotyped limb twitching movements constitutes a crucial criterion for establishing the diagnosis of this disorder [7].

2.2. Autonomic dysfunction

Autonomic dysfunction includes gastrointestinal symptoms such as constipation, dysphagia, and delayed gastric emptying; cardiovascular issues including orthostatic hypotension and resting tachycardia; urinary dysfunction; and excessive or reduced sweating as well as increased sebaceous gland secretion due to autonomic dysregulation. These are important markers for identifying the prodromal stage of PD. In experiments using the M83 transgenic mouse model, injection of α-syn preformed fibrils can successfully induce severe central nervous system pathological damage in regions such as the spinal cord and brainstem. This model is characterized by widespread deposition of α-syn inclusions, prominent neuroinflammation, massive neuronal loss of motor neurons (loss rate 76%), and neuromuscular junction dysfunction (impairment rate 72%) as the main pathological features, accompanied by a behavioral phenotype of rapidly progressive paralysis [8].

In patients with incidental Lewy body disease (LBD), α-syn aggregates appear most frequently in the distal axons of cardiac sympathetic nerves, particularly affecting tyrosine hydroxylase (TH)-immunoreactive axons. Furthermore, in this group, α-syn aggregates are significantly more abundant in cardiac distal axons than in neuronal cell bodies; in some cases, virtually no α-syn aggregates are

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found within ganglia, whereas they are abundantly present in the heart [9]. Moreover, apart from the olfactory nerve, the vagus nerve and the enteric nerve plexus it innervates are among the earliest sites of α-syn accumulation in the pathological progression of PD, and their dysfunction occurs almost synchronously with brainstem pathology [10].

In summary, autonomic dysfunction is an important differential marker of the prodromal stage of PD. Studies in transgenic mouse models have confirmed that abnormal aggregation of α-syn can lead to extensive neural damage, neuronal apoptosis, and motor dysfunction. Tissue specimens from patients with LBD also exhibit a characteristic distribution pattern of this protein aggregate in peripheral nerve axons. During the progression of PD, α-syn first accumulates in the peripheral autonomic nervous system. Its pathological changes are highly correlated with brain lesions, ultimately resulting in the clinical manifestations of multisystem autonomic dysfunction.

2.3. Sensory impairment

Sensory impairment includes hyposmia, pain, altered temperature perception, and reduced tactile sensitivity. Olfactory function tends to decline with age, and hyposmia has the highest prevalence in patients with PD, with males being more affected than females [11]. The neurobiological mechanisms underlying PD-related pain are highly complex. The basal ganglia circuitry is directly involved in the central processing and modulation of nociceptive signals, and degenerative changes in the nigrostriatal pathway may partially mediate the development of pain abnormalities. In addition to dopaminergic dysfunction, imbalances in multiple neurotransmitter systems, including serotonergic, noradrenergic, glutamatergic, and GABAergic pathways, also contribute to this pathological process [12]. Although dopaminergic replacement therapy has been widely used to manage PD-related sensory symptoms, evidence suggests that such treatments do not effectively reverse proprioceptive processing deficits and may even exacerbate functional disturbances. Proprioceptive impairment in PD may be more closely related to dysfunction of the supplementary motor area circuitry than solely to dopaminergic neuron degeneration in the basal ganglia [13].

2.4. Neuropsychiatric symptoms

In recent years, an increasing number of symptoms such as depression, anxiety, as well as apathy have been identified in patients with PD. These neuropsychiatric symptoms often appear before the motor symptoms of PD and are therefore recognized as one of the identifying markers of its prodromal stage [14]. The underlying mechanism of such abnormalities is highly complex, manifesting on the one hand as dysfunction of neural circuits mediated by dopamine, serotonin, and norepinephrine, and on the other hand as observable organic damage to brainstem nuclei such as the raphe nuclei and locus coeruleus [15]. Currently, no fully validated criteria have been established to distinguish between depression and anxiety associated with the prodromal stage of PD, making it impossible to effectively differentiate pathological prodromal neuropsychiatric symptoms from ordinary mood fluctuations [16]. Sertraline is a highly selective serotonin reuptake inhibitor that also possesses weak dopamine reuptake inhibitory effects, a mechanism of action that aligns with the pathophysiological basis of impaired dopaminergic pathways in PD. This drug demonstrates favorable tolerability in elderly populations, with manageable adverse effects. Clinical intervention can significantly reduce patients' scores on the Beck Depression Inventory, while the Unified Parkinson's Disease Rating Scale (UPDRS) motor subscale and energy-related parameters show no significant deterioration, indicating that sertraline does not exacerbate motor impairment [17].

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3. Prodromal biomarkers for PD

3.1. Body fluid biomarkers

Real-time quaking-induced conversion assay targeting α-syn aggregates in cerebrospinal fluid achieves high sensitivity and 100% specificity for the diagnosis of PD and dementia with Lewy bodies. This approach can effectively discriminate synucleinopathies from tauopathies, based on its capability to detect the seeding activity of misfolded α-syn [18]. Based on the DeNoPa cohort study, the cerebrospinal fluid α-syn seed amplification assay (αS-SAA) demonstrated a sensitivity of 94.6% and a specificity of 98% for the diagnosis of synucleinopathies, with an overall accuracy of 98%. In patients with iRBD, the baseline positivity rate was 92.6% and the overall positivity rate was 93.1%. This method can detect α-syn seeds as early as 8-9 months after the onset of iRBD symptoms, making it suitable for screening the prodromal phase of PD [19]. Analyses of plasma and urine can serve as effective approaches for fluid biomarker discovery in PD. Multiple proteins, including dopa decarboxylase (DDC), are significantly upregulated in the plasma and urine of patients with PD and individuals at high risk in the prodromal phase. Urinary biomarkers can also dynamically reflect the pathological progression of the disease, and combining both types of fluid samples may facilitate the early detection of PD [20].

3.2. MRI biomarkers

Neurodegeneration in PD exhibits a dying-back pattern of injury, in which damage to dopaminergic axon terminals and synaptic function occurs earlier than the loss of neuronal cell bodies in the substantia nigra pars compacta. α-syn oligomers can disrupt synaptic transport at an early stage and downregulate the expression of dopamine transporter (DAT) on the cell membrane, resulting in a significant decrease in striatal DAT uptake as early as the prodromal phase, before the onset of overt motor symptoms. Thus, this decrease can serve as an in vivo imaging biomarker for prodromal synaptic dysfunction [21].

Magnetic resonance imaging (MRI) quantitative metrics based on cortico-striatal projection–based parcellation of striatal subregions can serve as highly sensitive diagnostic and progression imaging biomarkers for PD. Conventional global volumetric parameters of the whole striatum, caudate, putamen, and nucleus accumbens fail to differentiate PD patients from healthy controls; in this study, the striatum was parcellated into seven functional subregions using a semi-automatic segmentation protocol. As the region with the earliest and most severe dopamine loss in PD, the caudal-motor striatum exhibits volume atrophy, inward surface deformation, and a significant decrease in fractional anisotropy of the cortico-striatal white matter tracts, making it suitable for PD diagnosis. Only the limbic striatum, which is innervated by the late-degenerating ventral tegmental area, shows progressive atrophy, and its volume correlates negatively with OFF-state UPDRS Part III motor scores, thus enabling objective assessment of disease progression. All structural and diffusion measurements demonstrate good test-retest reliability, meeting the reliability requirements for valid biomarkers [22]. Although [^{123}I]-meta-iodobenzylguanidine (MIBG) scintigraphy is not an MRI-based technique, its quantitative cardiac parameters can reflect peripheral sympathetic nerve damage in PD, demonstrating potential as a peripheral imaging biomarker. The results of this controlled study show that in early-stage PD patients with a disease duration of less than one year, reduced cardiac tracer uptake is observed only on early imaging, with no abnormality detected on delayed imaging. In patients with type 2 diabetes mellitus, cardiac uptake is significantly decreased at both time points; therefore, relying solely on this parameter makes it difficult to differentiate PD

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patients with comorbid diabetes, and tracer washout rate may serve as a supplementary differential parameter. Based on the pathological feature of abundant Lewy body deposition in peripheral sympathetic ganglia in PD, the degree of cardiac sympathetic denervation can be quantified by MIBG uptake levels, and this metric can reflect disease progression and thus has value for disease staging. Owing to ionizing radiation, this imaging modality cannot achieve non-invasive screening comparable to MRI; it can be combined with MRI and dopamine positron emission tomography to perform multimodal assessments of prodromal autonomic dysfunction [23].

4. Conclusion and future perspectives

This article reviews the application status of NMS and corresponding biomarkers in the identification of PD in the prodromal stage. In general, iRBD is currently the most well-documented premotor manifestation, and its association with the risk of synucleinopathy conversion has been supported by multicenter cohort studies. Sensory abnormalities such as autonomic dysfunction and hyposmia have unique advantages in prodromal screening due to their early onset and ease of clinical detection. Although neuropsychiatric symptoms are common, they are difficult to be used for differential diagnosis alone due to their lack of specificity. In terms of biomarkers, cerebrospinal fluid α-syn seed amplification analysis showed extremely high diagnostic accuracy and is currently the most promising prodromal detection method; various proteins such as DDC in plasma and urine also show good early screening potential. In terms of imaging, MRI quantitative indicators based on the division of striatum subregions can reflect axonal and synaptic damage earlier than cell body loss, while MIBG scintigraphy provides an important supplement for evaluating peripheral sympathetic nerve involvement.

However, it must be acknowledged that the field still faces several key challenges. First, most of the current studies are still at the cross-sectional or retrospective level, and there is a lack of prospective cohort verification of large samples and long-term follow-up. The evidence base for translating prodromal markers into clinical practice remains insufficient. Second, the sensitivity and specificity of a single NMS or a single biomarker have their own shortcomings, and false positives and false negatives coexist. How to construct a feasible multi-modal joint identification model remains to be further explored. Thirdly, some detection methods (such as cerebrospinal fluid obtained by lumbar puncture, radiation exposure from MIBG imaging) limit its large-scale screening application in asymptomatic population.

The following directions are worthy of focus in the future. First, community-based prodromal cohort construction should be promoted, with systematic collection of clinical, fluid and imaging multidimensional data to clarify the predictive efficacy of each marker in the real-world settings. Secondly, develop more sensitive and more accessible peripheral detection methods (such as optimizing plasma and urine detection schemes) to lower the threshold for screening; thirdly, with the help of machine learning and other algorithms to integrate multi-dimensional information, an individualized risk assessment tool for the prodromal phase is established; fourth, explore the feasibility and safety of early intervention strategies based on the identification of the precursor period. Only by building a bridge between accurate identification and effective intervention can precursor research truly translate into clinical benefits for patients.

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