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Biomarkers in Parkinson's disease: Advances and strategies

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ABSTRACT

Parkinson's disease (PD) is a neurodegenerative disorder characterized by progressive motor disturbances and affects more than 1% of the worldwide population. Despite considerable progress in understanding PD pathophysiology, including genetic and biochemical causes, diagnostic approaches lack accuracy and interventions are restricted to symptomatic treatments. PD is a complex syndrome with different clinical subtypes and a wide variability in disorder course. In order to deliver better clinical management of PD patients and discovery of novel therapies, there is an urgent need to find sensitive, specific, and reliable biomarkers. The development of biomarkers will not only help the scientific community to identify populations at risk, but also facilitate clinical diagnosis. Furthermore, these tools could monitor progression, which could ultimately deliver personalized therapeutic strategies. The field of biomarker discovery in PD has attracted significant attention and there have been numerous contributions in recent years. Although none of the parameters have been validated for clinical practice, some candidates hold promise. This review summarizes recent advances in the development of PD biomarkers and discusses new strategies for their utilization.

1. Introduction

The National Institutes of Health (NIH) defines a biomarker as "a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes or pharmacological responses to a therapeutic intervention" (2001). In other words, a biomarker is a tool to aid physicians, epidemiologists, and scientists in the study of human diseases by confirming a diagnosis and tracking disease progression, and may help to identify specific therapeutic targets or determine the efficacy of agents designed to influence disease progression. In general biomarkers involve measurements of biological samples (e.g., plasma, serum, cerebrospinal fluid (CSF) and biopsy) or measurements using brain imaging techniques to decipher changes in brain structure and function.

Parkinson's disease (PD) is the second most common neurodegenerative syndrome after Alzheimer's disease in the United States. It affects about 1 million Americans over age 65 and up to 10 million individuals worldwide, yet no cure exists and no disease-modifying therapies have been identified. With its prevalence expected to double within the next two decades due to the increasing age of the general population, PD is emerging as a socio-economic burden and a serious challenge for the public health system. The development of specific biomarkers that reflect disease progression and the discovery of new therapies are important for better clinical management of PD patients. As such, the establishment of reliable biomarkers is a subject of intensive investigation; the ideal biomarker being sensitive, reproducible, inexpensive, noninvasive and thoroughly validated.

2. Biomarkers in PD: from better clinical diagnosis to new therapeutics

PD is a progressive disease characterized by a complex motor disorder known as parkinsonism which is manifested by resting tremor, bradykinesia, rigidity and postural abnormalities. Additionally, many non-motor features are increasingly recognized as being integral components of the syndrome. The neuropathological hallmarks of PD are a loss of dopaminergic neurons in the substantia nigra (SN) and the formation of intraneuronal protein

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inclusions termed Lewy bodies (LB), which are composed primarily of alpha-synuclein (a-syn) [1]. Currently a clinical diagnosis of PD is made by the presence of motor disturbances, which remains the most important diagnostic marker. Unfortunately, due to overlap of symptoms with other neurodegenerative disorders such as multiple system atrophy and progressive supranuclear palsy, misdiagnosis is common and only autopsy can definitively confirm the disease. Moreover, motor deficits generally appear when a relatively advanced stage of neurodegeneration is present; indeed 50–60% of dopaminergic neurons in the SN are already lost prior to the clinical diagnosis, limiting the effectiveness of potential neuroprotective therapies [2]. It has become clear that PD is not just a movement disorder, but rather a complex syndrome non-motor symptoms (NMS) including olfactory deficit, sleep abnormalities, depression, autonomic dysfunction and cognitive disturbances. Indeed, more than 90% of patients experience NMS during the course of the disease [3]. Many of these NMS appear years before motor symptoms, and include gastrointestinal dysfunction, anosmia, and rapid eye movement (REM) sleep disturbances. NMS often become debilitating as the disease progresses, worsening the quality of life for PD patients. Additionally, neuropathological changes in the form of aggregated a-syn protein can be detected in peripheral tissues including skin, the olfactory bulb, and gastrointestinal tract, and predate the onset of motor symptoms [4]. At this early stage of the disease dopaminergic neurons are relatively spared. Consequently NMS and peripheral pathology might provide a window of opportunity for early neuroprotective intervention.

Although no specific biomarkers can be recommended in clinical practice yet, some interesting candidates exist. As mentioned earlier, PD is a complex disorder with different clinical subtypes and no clinical or pathological “gold standard” biomarker. Indeed, in the initial family in which the LRRK2 gene was discovered, all affected individuals manifested a PD phenotype. However, in the four affected individuals from this family in whom brain autopsies had already been performed, surprisingly there were four different neuropathological diagnoses described [5]. Therefore, it is unrealistic to expect that a single biomarker will fulfill all the criteria of accurate diagnosis and disease progression. Indeed, using a combination of biomarkers is the most likely rational approach (Fig. 1).

Biomarkers of PD are diverse and can be categorized into four main subgroups: clinical, biochemical, genetic, and imaging. When one group is considered alone the utility of the biomarker is often limited, but when combined and considered collectively, biomarkers for PD may be more useful. Also, multimodal assessments may be pivotal for reliable measures of progression and determination of disorder modification. In the following sections, a brief summary of existing molecular and imaging biomarkers is presented along with discussion concerning novel approaches driving the field forward.

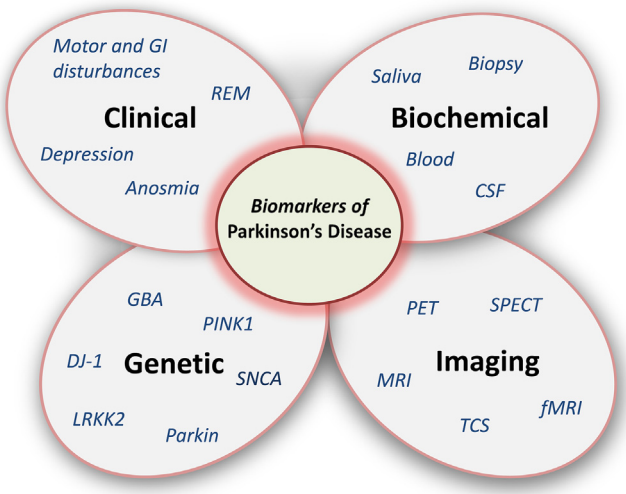

Fig. 1. Biomarkers of Parkinson's disease: A single biomarker cannot reflect the complexity of the disorder. Clinical, laboratory, imaging, and genetic data need to be judiciously combined to accurately predict disease status and progression.

2.1. Genetic biomarkers

The etiology of PD is not entirely understood with 90–95% of cases being idiopathic, resulting from complex interactions between genes and environmental factors. Nevertheless a clear genetic component has been identified in the last 15 years. Genetic mutations leading to familial forms of PD combine a-syn (SNCA), Parkin, PTEN-induced kinase 1 (PINK1), DJ-1, and Leucine-rich repeat kinase 2 (LRRK2), and account for 2–3% of all cases with classical parkinsonism, which is often clinically indistinguishable from idiopathic PD [6]. These discoveries were followed by population-based genome-wide association studies (GWAS) that identified an additional 20 PD risk loci. Houlden and Singleton [7] recently summarized the genetic, clinical, and pathological findings of autosomal dominant and recessive mutations and discussed the discovery of genetic risk loci for PD with an emphasis on LRRK2 and GBA (glucocerebrosidase). Indeed 5–10% of PD patients have GBA mutations, numerically making this the most important risk factor for the disease [8]. Even though this might represent a small percentage of PD cases, genetic studies are invaluable to elucidate the pathways contributing to clinical diagnosis and most importantly to identify populations at risk. Genetic causes of parkinsonism may reside in individuals for years and often decades prior to any development of symptoms, as such “gene positive at-risk” individuals comprise a unique population in which to study biomarker efficacy in reflecting disorder progression from asymptomatic to end-stage disease. In this regard, detection of multiple misregulated genes and their messenger RNA or protein expression may allow the identification of networks of interacting proteins that reflect the underlying disease process. Further, proteins associated with disease pathophysiology can be identified as candidate biomarkers.

2.2. Biochemical markers

Searching for biomarkers in body fluids and tissues provides a relatively noninvasive examination of proteins levels and other molecules specific to the disease. Investigators have evaluated various potential biomarkers in blood, saliva, cerebrospinal fluid (CSF) and biopsies. Because molecular changes in the brain are often reflected in CSF, it represents a potential source of biomarkers. The identification of proteins associated with PD has been informed by advances in genetics (Section 2.1), as witnessed in the discovery of SNCA or DJ-1 genes.

a-Syn was the first gene to be linked to PD. A direct link between a-syn and PD is strongly supported by the discovery that point mutations or multiplications of the gene cause parkinsonism. a-Syn can be detected in PD patient's CSF, saliva, serum, urine, and also in the gastrointestinal tract [9]. Seemingly discrepant findings have revealed that PD patients have significantly lower a-syn levels in CSF than control groups [10] and no association between a-syn levels and disease severity has been found. The reproducibility of the data remains challenging with the main issues being sampling protocols, blood contamination and different operating procedures. Several studies have also attempted to measure a-syn in blood cells and plasma, but so far the results have been inconsistent. Lastly,

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