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Review article

Towards a biological diagnosis of PD

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ABSTRACT

Since the original description by James Parkinson, Parkinson's disease (PD) has intrigued us for over 200 years. PD is a progressive condition that is incurable so far, and affects millions of people worldwide. Over the years, our knowledge has expanded tremendously, and a range of criteria have been put forward and used to try to define PD. However, owing to the complexity of the problem, it is still not consensual how to diagnose and classify a disease that manifests with diverse features, and that responds differently to existing therapies and to those under development. We are now living a time when 'biological' information is becoming abundant, precise, and accessible enabling us to attempt to incorporate different sources of information to classify different forms of PD. These refinements are essential for basic science, as they will enable us to develop improved models for studying PD, and to implement new findings into clinical practice, as this will be the path towards effective personalized medicine.

1. Introduction

Parkinson's disease (PD) is a progressive neurodegenerative disorder mostly known for typical motor features like rigidity, resting tremor, bradykinesia, and postural instability. These arise due to the loss of dopaminergic neurons in substantia nigra pars compacta (SNc), and the consequent deficit in dopamine in the basal ganglia circuitry [1–3]. However, PD also involves motor features that do not respond to dopamine replacement therapy and a large number of non-motor symptoms like hyposmia, constipation, anxiety, REM-sleep behavioral disorder (RBD), depression and cognitive dysfunction many of the latter arising years before the motor symptoms and therefore the diagnosis [1]. While some of these symptoms are related to the decline in dopamine levels, the underlying cause for most of them is not very well understood [4]. Hence, although PD has long been considered a movement disorder, it has now been accepted that clinical manifestations extend much beyond the characteristic motor symptoms thereby highlighting the involvement of more regions of the brain in addition to SNc as well as peripheral organs [1,5]. Neuropathologically, sporadic and some forms of genetic PD are characterized by the aggregation of the protein alpha-synuclein (aSyn) into inclusions called Lewy bodies (LBs) and Lewy neurites (LNs) [6–8] (Fig. 1). Interestingly, LBs and LNs have also been found in peripheral tissues like salivary glands, esophagus, stomach, colon, heart, bladder, and skin [9–12]. However, some forms of genetic PD lack evidence for aSyn aggregation using current evaluation methods.

Despite tremendous advancements in our understanding of the clinical complexity of PD, the community often still uses a nigral-centric view of the disease. Consequently, this strongly reflects in the way we model PD in the laboratory [13].

Based on the neuropathological analysis of postmortem tissue from individuals with PD, the progression of PD was predicted to start in the medulla oblongata and/or in the olfactory bulb, followed later by the SNc and midbrain [14]. Advanced stage PD is associated with damage to the cerebral cortex and symptoms like hallucinations, and cognitive impairment. It has been hypothesized that these symptoms arise due to

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aggregation of misfolded forms of aSyn that play an important role in disease progression [15]. Whether aSyn is causal to these clinical features or not is still unclear. However, the occurrence of these clinical features has major implications for disease classification and for clinical trials, which have been focusing primarily on assessing the effects of the interventions on motor features. Nonetheless, several ongoing trials are investigating possible treatments for non-motor symptoms of PD, such as mild deficits in attention, verbal fluency and visuospatial constructions using selective serotonin reuptake inhibitors (SSRIs) for psychiatric symptoms and cholinesterase inhibitors for cognitive decline for instance Refs. [16–19]. Several FDA approved drugs are also available to treat non-motor symptoms including depression, anxiety, excessive drooling, orthostatic hypotension, urinary incontinence and gastrointestinal problems in early stage PD [20–24].

Here, we discuss how different levels of biological information can now be used in order to aid in the diagnosis of PD.

2. Current criteria for PD

The most frequently applied criteria for PD diagnosis in the past have been the Gelb's criteria [3] and the UK Parkinson's Disease Society Brain Bank Diagnostic (UK Brain Bank) criteria [25]. These clinical criteria were created to facilitate the differential diagnosis of PD from other parkinsonian syndromes. Although these have been widely used in clinical practice, they were initially developed for research purposes.

Gelb's clinical diagnosis criteria suggests three levels of diagnostic confidence: definite, probable, and possible. However, it is mentioned in the same publication that there were no universally accepted histopathologic criteria for the diagnosis of PD, and the proposed criteria summarized above are only used for clinico-pathological diagnosis [3].

The UK Brain Bank criteria for the clinical diagnosis of neuropathologically defined PD [3] were proposed based on a clinico-pathological correlation study involving histopathological findings in 100 patients diagnosed with idiopathic PD (iPD), based on the demonstration of Lewy bodies in characteristic abundance and distribution within the brains of the affected patients. The statistical analysis supporting the criteria reported a 98,6% specificity and 91,1% sensitivity. Importantly, the application of these criteria was not well suited for early stages of PD, as they included aspects that depend on the way the motor disease progresses and its response to levodopa [26,27].

The International Movement Disorder Society (MDS) proposed new Clinical Diagnostic Criteria for PD that included the core of the UK Brain Bank criteria and incorporated further criteria based on non-motor features of the disease [1]. While these criteria were mainly developed for use in research, they could also be applied in clinical practice. The criteria defined two levels of diagnostic certainty: (i) clinically established PD and (ii) probable PD, and proposed a diagnostic approach based on three categories of diagnostic features: absolute exclusion criteria (which rule out PD), red flags (which must be counterbalanced by additional supportive criteria to allow diagnosis of PD), and supportive criteria (positive features that increase confidence of the PD diagnosis).

The most recent MDS criteria for PD suggest the diagnosis of PD using two different criteria – (i) diagnosis of PD in clinical practice with a sensitivity of 87.9% and a specificity of 91.3% and (ii) the recent MDS Clinical Diagnostic Criteria for PD with a specificity of 99.2%, and a satisfactory sensitivity to provide neuropathological validations [28]. The new criterions enable a slightly better separation of patients with atypical parkinsonism or secondary parkinsonism when compared with what is achieved using the UK Brain Bank criteria [29].

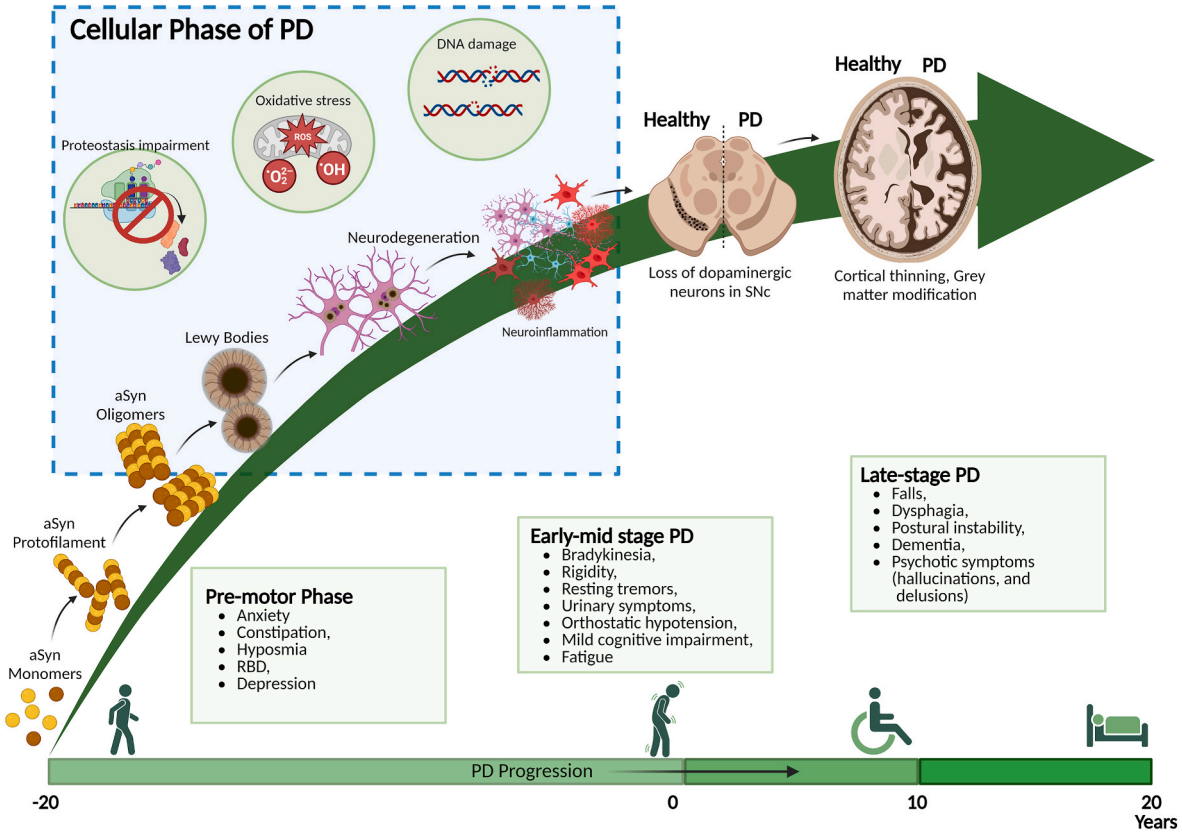

Fig. 1. The 'biology' of Parkinson's disease. The biochemical phase, in analogy to what happens in Alzheimer's disease, consists of the process of aSyn aggregation. Upon accumulation of aSyn, leading to both loss and gain of function, cellular alterations take place, leading to neuronal dysfunction, death, and neuroinflammation. When a threshold of neuronal loss is passed, the clinical phase manifests, with the typical motor and non-motor features of the disease. Figure created by Biorender.com.

3. The SynNeurGe classification system

With advancements in the field of diagnosis and in our understanding of the underlying biology of PD, several diagnostic methodologies have been proving to be useful for PD diagnosis, even at an early stage of the disease. A recent proposal for research use was based on three major components: **syn**ucleinopathy, **neur**odegeneration and **ge**netics, and was, therefore, named 'SynNeurGe' classification (pronounced "synergy" in order to highlight the important relationships between these major components) [30].

Several studies have highlighted the presence of aSyn-positive inclusions in PD and dementia with Lewy bodies (DLB) (in the form of LBs and LNs; the combination referred to as Lewy pathology) and in other synucleinopathies including multiple system atrophy (MSA) (in the form of glial cytoplasmic inclusions – GCIs) [31]. However, as mentioned above, neuropathological studies of certain PD brains (from patients carrying genetic alterations in selected PD-associated genes) suggest that aSyn pathology is neither sufficient nor necessary to define PD, because some cases of clinically-diagnosed PD are found to lack Lewy pathology as defined by current immunohistochemistry techniques [32]. Likewise, Lewy pathology has been found in post-mortem analyses of brains from individuals that had no clinical features of PD (known as incidental Lewy body disease) [33–36]. Neurodegeneration of dopaminergic neurons in the nigra is also an important alteration for diagnosing the disease with certainty, given the centrality of the motor features. Genetic alterations, which can be causative or risk factors, are also key factors in this classification system. Thus, in the following sections, we focus on these 3 main biological dimensions of PD: synuclein aggregation and pathological alterations in peripheral tissues like blood, CSF and skin, neurodegeneration measured using advanced imaging technologies like positron emission topography (PET) scan and magnetic resonance Imaging (MRI), and genetic predisposition including point mutations associated with familial forms and other genetic alterations associated with increased risk.

3.1. aSyn classifier

alpha-Synuclein (aSyn) is a presynaptic and nuclear protein with 140 amino acids that is abundant in the brain. Besides the central nervous system (CNS), aSyn is also present in skin and peripheral organs predominantly through the involvement of the peripheral autonomic nervous system [37–39]. aSyn is known to play a role in the regulation of synaptic vesicle dynamics at the nerve terminal, and in dopamine neurotransmission, however, its precise function is still debatable [40,41]. It is also present in abundance in different blood cell types which might suggest its involvement in other biological processes [42–44]. Given the occurrence of aggregated aSyn in the brains of patients with synucleinopathies, certain forms of aSyn have been regarded as toxic, based on observations in experimental models. The toxic forms are thought to consist of oligomeric or aggregated species [45,46] (Fig. 1). However, not all brains from clinically-diagnosed PD patients contain LBs or LNs upon neuropathological examination [47–51].

In recent attempts to identify biomarkers for the diagnosis and early-detection of PD, aSyn emerged once again as a key molecule. aSyn seeding competent species are detected in blood, cerebrospinal fluid (CSF), skin and saliva using current versions of seeding amplification assays (SAAs) [52–55]. Skin and CSF SAAs have shown highest sensitivities (92% and 90% respectively) when compared to the other bio-specimens [56]. While at this point in time, aSyn SAAs are simply binary, and not quantitative, there is hope that future versions may be improved to yield quantitative information reflecting the aSyn seeding burden in the central nervous system of individual patients, thereby expanding the information provided.

In addition to SAAs, imaging techniques like immunohistochemistry and immunohistofluorescence for aSyn in skin are also important advancements in the diagnosis of PD [57]. Skin biopsies using selected methodologies provide adequate >90% sensitivity and specificity to be considered as diagnostic tools and to aid in the biological definition of PD. Due to the differences in the immunohistochemical staining pattern of aSyn aggregation and distribution, skin biopsies appear to be useful in differentiating PD from MSA [58] and, therefore, can be used as biomarkers due to the reproducibility and consistency within laboratories [58,59].

While measuring the levels of total aSyn seems to lack specificity, it is possible to measure aSyn in a variety of samples, including extracellular vesicles like exosomes present in different biofluids – this holds immense potential for aiding in the field of diagnosis [60–63].

4. Neurodegeneration classifier

About half a century ago, neurochemical studies during autopsy of individuals with Parkinsonism showed dopaminergic denervation even in patients with mild Parkinsonism [64]. In another similar study, a reduction of 68–82% of dopamine was observed in caudate when compared with age-matched controls [65]. Consistently, functional MRI activation maps during a self-paced motor task of assessment of ^{18}F-DOPA uptake suggests a decline in activity in both hemispheres in PD patients when compared with age-matched controls [66]. Likewise, ^{18}F-DOPA scans show a longitudinal decline in functional connectivity, and an asymmetric pattern of dopaminergic dysfunction in the putamen of PD individuals [67,68]. Additionally, a radiopharmaceutical for dopamine transporter (DAT) imaging, ^{18}F-FE-PE2I ([^{18}F]-(E)-*N*-(3-iodoprop-2-enyl)-2β-carbofluoroethoxy-3β-(4′-methyl-phenyl) nortropane) has been established as a suitable radioligand for DAT quantification and imaging of the nigrostriatal pathway to differentiate between early PD patients and healthy controls [69–71].

Interestingly, PD and DLB patients have reported cardiac sympathetic denervation in the early stages of the disease. Studies carried out early in the field have shown decreased cardiac uptake of ^{123}I-meta-iodobenzylguanidine (MIBG), a physiological analogue of norepinephrine in patients with PD and DLB [72–77]. Also, tyrosine hydroxylase (TH)-immunoreactive nerve fibres in fascicles of the epicardium from the anterior wall of the left ventricle are significantly reduced in PD and DLB [76,78]. In total, loss of neurons in the nigra and dopamine terminals in the stratum, selective glucose metabolic patterns, and cardiac sympathetic denervation, are important biological characteristics of PD and can, therefore, contribute to diagnosis.

4.1. Genetics classifier

Approximately 15% of PD are associated with genetic mutations [79]. Out of the various genes associated with familial forms of PD, four are associated with dominantly-inherited forms with pathogenic gene variants in *SNCA*, *LRRK2*, *VPS35*, or *CHCHD2*, and three are associated with recessively-inherited forms with pathogenic gene variants in *PRKN*, *PINK1*, or *PARK7* [80]. Furthermore, these variants can be subcategorised into high penetrance, variable penetrance and genes that are although linked to PD, are not strongly pathogenic. While, monoallelic variants in *SNCA*, and biallelic variants in *PRKN*, *PINK1* and *PARK7*, are generally fully penetrant, variants in *VPS35*, *CHCHD2* and *LRRK2* provide a strong predisposition, while selected *GBA1* variants a more moderate risk for developing PD [81]. The *SNCA* gene is of particular importance as it encodes for aSyn, the main component of LBs and LNs (Lewy-type pathology). Three types of mutations have been identified in *SNCA* – point mutations (such as A53T, A30P, or E46K, among several others discovered more recently), duplications, and triplications. The point mutations might change the function and/or aggregation propensity of aSyn, while duplication and triplication lead to increased aSyn levels, thereby potentiating its accumulation and associated detrimental effects [82–88].

Intriguingly, PD associated with monoallelic or biallelic *LRRK2* variants is not always associated with Lewy pathology, as determined by

post-mortem studies [49].

5. Implications of an accurate biological definition of PD for disease modelling

The development of therapeutic strategies for any disease often relies on the availability of pre-clinical models that need to recapitulate relevant disease features. Given the complexity of many diseases, it is not uncommon for both cell and animal models to suffer limitations that may hinder the success of drug-development. Yet, preclinical studies are usually required before clinical trials can proceed, and animal models are needed to identify and test pathophysiological mechanisms that cannot be directly studied in humans [89,90]. Modelling a disease like PD has proven to be highly challenging, as it is not always clear which aspects of the disease should be modeled [90].

5.1. Animal models

The difficulties in defining PD demonstrate that no model can be seen as a "perfect" model of such a complex disease. A "good" model should, at least, be based on an established molecular mechanism underlying at least some forms of the disease. However, even such models are unlikely to recapitulate the complexity of the disease [91].

Originally, genetic forms of PD were thought to be not only rare but also irrelevant to the sporadic cases. We now know that this is not the case, largely based on data from GWAS studies where pleomorphic risk loci have been identified in genes associated with monogenetic forms of PD, such as *SNCA* and *LRRK2* [92]. Thus, mechanisms uncovered by studying rare genetic forms turn out to also contribute to our understanding of sporadic forms PD and genetic models became highly relevant for testing hypotheses and neuroprotective treatments. The difficulty remains to define which aspect(s) of PD need to be present for the model to qualify as a "good" model of the disease. Ideally, loss of dopaminergic neurons should occur, since this is a feature associated with motor symptoms of PD. Indeed, many different models based on PD-associated genetic mutations have been shown to develop loss of nigrostriatal dopaminergic neurons [93,94]. But is this really necessary for a model to be considered 'useful' for the development of neuroprotective strategies? We now know that the demise of dopaminergic neurons in the substantia nigra is preceded by years of progressive pathology in many other areas of the central and peripheral nervous system. A model that reproduces these early pathological alterations can be very useful for discovering drug targets and testing potential candidates. Furthermore, a slowly progressing model with robust early deficits would enable preclinical studies in younger animals, hence at lower cost, long before neurodegeneration occurs.

A diverse range of animal models is extremely important for addressing different aspects of the disease. For example, simple and versatile model organisms such as the invertebrates *C. elegans* and *Drosophila* are useful to elucidate genetic interactions and mechanisms; mammalian models including mice, rats and, in some cases, non-human primates, are essential to reproduce circuit-level alterations [93,95]. Importantly, even some mammalian models suffer from limitations, such as the absence of neuromelanin [96–98], which is characteristic in primates.

The study of non-motor symptoms of PD likely requires mammalian models that develop central pathology outside of the substantia nigra, such as transgenic animals using a broadly expressed and, ideally, endogenous promoter driving the expression of the gene of interest. Models based on the injection of protein species of interest (e.g. preformed fibrils – PFFs), are well suited to test blockers of cell-to-cell transmission, but less so for analyzing drugs thought to interfere with the early steps of protein misfolding or aggregation. Although important, these models rely on the injection of likely non-physiological concentrations of material directly into the brain, which does obviously not happen in PD.

In conclusion, at the present moment, the "best" model of PD is one that enables us to address the specific question being asked, since none of the existing models reproduce all phenotypical aspects of PD. Since those aspects are not necessarily present in all patients or forms of the disease, a useful model should rather reproduce mechanisms that are disease-relevant and match the intended drug target.

The difficulty in providing a simple and universal definition of PD constitutes a major limitation in the development of animal models: What specific aspect(s) of the disease should the model reproduce? How meaningful and robust are the endpoints? To what extent can the findings in a particular model be generalized to other forms of PD? These are only but a few questions one is faced with, and that would greatly benefit from a biological classification of PD.

5.2. Cell models of PD

Cell models of autosomal dominant forms of genetic PD, mainly of those associated with mutations in the *SNCA* and *LRRK2 genes*, typically rely on the overexpression of disease-associated mutant forms of the proteins. In fact, overexpression of proteins is not necessarily artificial as some may consider, since in the case of the *SNCA* gene, overexpression of the wildtype (WT) form of aSyn occurs in patients carrying multiplications of the *SNCA* gene [99,100]. There are also cases where genetic alterations in non-coding regions of the gene may lead to increased expression of the protein, increased protein burden [101,102].

Given the recent suggestion that overactivation of WT LRRK2 is detectable in sporadic PD [103], findings pertaining to the overexpression of WT LRRK2 may also have some value. Nevertheless, overexpression models may lead to non-specific effects, unrelated to the disease process, but rather to increased protein levels.

Seeding models based on the inoculation of cells with aggregated forms of aSyn have been developed, in an attempt to mimic the spreading of pathology that is thought to occur during disease progression in PD patients. These cell models have achieved the formation and accumulation of protein inclusions that are enriched in aSyn phosphorylated on serine 129, a typical feature of LBs and, therefore, have provided a significant step forward in modelling the process of aSyn aggregation [104,105].

In cell-based systems, outcome measures include, primarily, detrimental effects on cellular functions, such as protein folding and degradation systems, mitochondrial function and oxidative stress, neuronal activity and integrity, or overall cellular toxicity, assuming that the disease modeled in these cases represents, at least in part, a gain of toxic function (GoF) – proteinopathy. However, it is important to consider that loss of normal protein function (LoF) may occur, for example due to a molecular "sink" effect whereby proteins are trapped in aggregates – proteinopenia [106]. These mechanisms are not mutually exclusive and, most likely, co-occur in the biology of PD (Fig. 1).

6. Concluding remarks

PD is a heterogeneous clinical entity presenting with diverse features, from different clinical domains. Despite tremendous progress in our understanding of pathological mechanisms and of clinical features, the precise underlying cause(s) for PD is/are unknown. Strikingly, almost all diagnostic criteria applied in clinical practice and research are based on clinical criteria, case series, and limited clinico-pathological correlations. To date, there are no established disease subtype classifications, which questions the adequacy of the current clinical and biological factors used for the definition of progression models. Therefore, current classifications are mainly generated by clinical data analysis with very limited cohort sizes and lack of extensive neuroimaging, neurophysiological and wet-laboratory markers, including genetics as well as autopsy confirmation. This results in weak correlation with biological markers and problems of replicability. Interestingly, new prodromal criteria strengthen the association with potential biological

markers [107,108], but do not reliably confirm the disease, the direction (i.e., iRBD developing into MSA, PD, DLB) or the time of conversion. Protective factors (such as resilience genetic factors) have also not been studied extensively in this regard.

Recent efforts, like the "SynNeurGe" classification system, constitute important progress towards integrating biological information that can be readily collected to improve our understanding and modelling of PD. However, there is still a tremendous need to improve our understanding of the underlying biology leading to PD and other synucleinopathies. This knowledge, together with clinical, genetic, and detailed pathological examinations, will enable us to better define PD and, ultimately, to identify novel diagnostic and therapeutic strategies.

CRediT authorship contribution statement

Avika Chopra: Writing – review & editing, Writing – original draft. **Anthony E. Lang:** Writing – review & editing, Writing – original draft. **Günter Höglinger:** Writing – review & editing, Writing – original draft. **Tiago F. Outeiro:** Writing – review & editing, Writing – original draft, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors have no relevant conflicts of interest to declare.

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