Parkinson's disease cluster: the wind of change

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Abstract
This paper aims at demonstrating that “Parkinson's disease” (PD) is an umbrella designation for a number of heterogeneous disorders sharing an important number of clinical features, but separated by significant differences.

In fact, PD should probably be regarded as a “Parkinson's disease cluster”, and the core clinical features termed Parkinson syndrome. Disease manifestations, genetic underpinnings, and pathological findings argue against a unique disease process and, hence, a unique management approach, especially one that aims solely at the improvement of later (i.e. motor) disease manifestations.

We propose that true therapeutic innovation in PD calls for a leap in concepts and shift in research efforts. Disease-specific neuroprotective agents targeting early molecular and pathological events should ideally be developed.

Keywords: Parkinson’s disease, Parkinson’s disease cluster, Genetics, Pathophysiology, Neuropathology, Therapeutics, Clinical trials, Neuroprotection.
Parkinson’s disease (PD) is a common, disabling neurodegenerative disorder [1]. Although remarkable progress has been made in the fields of genetics, imaging, and neuropathology, the intimate causes of PD have not yet been elucidated. Far from being solely a disorder associated with the loss of dopaminergic neurons in the substantia nigra (SN), PD involves multiple neural systems, causing derangements of olfaction, sleep, mood, visual perception, cognition, and autonomic regulation, in addition to the classically recognized motor symptoms [2, 3]. The timeline of pathological progression proposed by Braak and coworkers has greatly contributed to our understanding of the overall disease process, although it fails to explain a significant proportion of cases [4]. According to Braak et al., PD pathology emerges initially at the myenteric plexus, vagus nerve, and olfactory bulb and nucleus, as evidenced by findings of abnormal α-synuclein deposits in these regions at early disease stages, subsequently spreading until the ultimate involvement of neocortical areas [4, 5]. As the disease progresses rostrally within the central nervous system (CNS), including the SN, the motor symptoms ensue, but at this stage the disease is already neuropathologically advanced.

Non-motor features, such as hyposmia, REM sleep behavior disorder, depression, and dysautonomia may be present at earlier disease stages, even decades before motor changes become apparent, correlating with less extensive CNS pathology [4]. Despite the awareness that these features could assist diagnosis earlier in the course of disease, the main therapeutic strategies remain essentially the same: treating motor manifestations of the disease is the essential aim for which solid evidence-based data exists [1]. Ongoing research for new therapeutic targets and strategies, including drugs targeting non-dopaminergic systems, as well as gene and cell therapies, is focused on preventing or reducing motor complications [6, 7]. None of these therapies have, so far, shown to be getting any closer to preventing disease progression and are, therefore, essentially symptomatic or palliative. Despite the efficacy of dopaminergic therapies in improving motor function and overall quality of life, they fail to prevent disease progression, and are associated with important complications [8-10]. This is consistent with the notion that the upstream molecular processes responsible for the cascade of pathological events are not yet being targeted by therapies currently available or under clinical development. Much of the difficulty in developing truly neuroprotective therapies lies in the fact that the mechanisms behind disease initiation and progression remain elusive and patients are diagnosed in late stages of pathological progression, when motor symptoms have already surfaced. Unfortunately, the deficits are probably irreversible at this stage, thus disease recognition and treatment in its premotor and even preclinical stages—according to the classification proposed by Stern et al. [11]—should ideally be sought.

The heterogeneity in clinical presentation, as well as the numerous genetic underpinnings and variable neuropathological findings in PD highlight the complex nature of the disorder, thus pointing towards a cluster of related diseases rather than a single clinical entity (Figure 1) [12-15]. There is growing awareness that both genetic and spo-

![Figure 1. Proposal for a new classification of Parkinson’s disease sub-forms, illustrating conceptual relationships between different disorders](Image)
radic forms of the disease have sub-forms that substantially differ from one another and may, therefore, have different responses to treatment [11, 16-18]. This heterogeneity probably reflects different disease-specific etiologies and pathological processes, and should therefore have implications in future research and development, as well as the design and interpretation of clinical trials, with a special focus on population homogeneity. Although the genetic mutations identified so far account for only a small portion of PD cases, there is evidence that these same genes may play a role in the much more common sporadic forms of the disease. Also, common variants in genes responsible for autosomal dominant (AD) parkinsonian syndromes represent risk factors for sporadic PD [16, 19].

The genetic findings in PD patients contributed to the knowledge about possible different disease mechanisms. Protein misfolding, aggregation and cell-to-cell spread of α-synuclein are considered central in the pathogenesis of PD [20]. Mutations in the α-synuclein gene (SNCA) cause aberrant expression of the protein, while other mutations may disrupt α-synuclein degradation by interfering with the ubiquitin proteasome system, as may be the case for PARK5 and PARK15, or with the autophagy-lysosome pathway. Mutations in the leucine-rich repeat kinase 2 (LRRK2) and β-glucocerebrosidase (GBA) genes may have a role in the latter, although LRRK2 mutations may also interfere with microtubule stability [16, 21]. Even though these different mutations may result in significant α-synuclein accumulation, they differ significantly with regard to clinical, imaging and neuropathological features, suggesting that despite our advances in molecular genetics, their role in the cascade of events could be broader than identified so far. Patients carrying SNCA mutations usually present early-onset disease, initially with good response to levodopa, but soon display an aggressive course, with cognitive decline and atypical features at times, such as central hypoventilation and myoclonus [21]. Their brain pathology is characterized by abundant α-synuclein-positive neuronal inclusions, frequently involving cortical areas, with a propensity for the hippocampal formation, which may explain the emergence of dementia observed in these patients [13]. However, patients with LRRK2 mutations usually manifest in a fashion similar to the more common sporadic PD, although less rapidly progressing and more prone to suffer from dystonia or tremor [14, 21]. Also, neuropathological findings are not uniform, ranging from pure nigral degeneration to widespread Lewy body disease, sometimes with tau- and ubiquitin-containing inclusions [21]. Patients with GBA mutations have been reported to develop early-onset, symmetrical clinical signs, with increased incidence of neuropsychiatric symptoms, although the clinical manifestations may be indistinguishable from idiopathic PD [22, 23].

In fact, GBA mutations appear to heterogeneously affect PD risk, milder mutations conferring increased susceptibility or behaving as AD PD genes with reduced penetrance, while severe mutations could be considered strong risk factors or AD with higher penetrance [24, 25]. Hence, the actual role of GBA mutations in genetic PD is still in debate and the search for mutations in this gene is not routinely performed in clinical practice. Neuropathologically, they are associated with extensive Lewy body pathology in a pattern identical to that seen in sporadic PD, although a larger proportion of cases have neocortical Lewy body pathology [23].

Mutations in the vacuolar protein sorting 35 (VPS35) cause a phenotype similar to typical PD, with asymmetric onset, significant benefit with levodopa, and typical motor complications. Cognitive deterioration seems to be rare in these patients. The protein seems to be involved in endosomal trafficking and recycling of synaptic vesicles, suggesting it may be impaired in this form of PD [14, 26].

Further heterogeneity within Parkinson’s disease becomes apparent when considering the autosomal recessive (AR) forms. Patients carrying parkin gene mutations (PARK2) have a clinical phenotype that typically resembles early onset idiopathic PD, with slowly progressive levodopa-responsive disease and high likelihood of developing dyskinesias. However, atypical clinical characteristics are frequently seen, with prominent dystonia and hyperreflexia. Unlike the more common forms of PD, dementia and dysautonomia seem to be rare [21, 27, 28]. Also, the majority of parkin post-mortem examinations failed to demonstrate synucleinopathy, but rather display significant neuronal loss in the SN and locus coeruleus [13, 14]. The clinical phenotype of PINK1 and DJ-1 related PD appears to be similar to that of parkin disease. In vitro studies have implicated parkin and PINK1 in the same mitochondrial pathway, suggesting a role in selective elimination of damaged mitochondria [21]. Mitochondrial dysfunction, excess mitophagy and increased oxidative stress have been proposed as mechanisms for parkin, PINK1 and DJ-1 related parkinsonism [16]. Despite the obvious common features, the only reported PINK1 autopsy presented Lewy body pathology, in clear contrast with parkin cases [29].

Intriguingly, heterozygous mutations in recessive genes are more frequently found in PD patients than in controls, raising the question of their role in the development of the disease. It has been proposed that these mutations may represent risk factors, further contributing to the complexity of the genetics of the disease [30]. To further complicate matters, digenic inheritance of AR genes has also been implicated in early-onset PD and the functional interaction between gene products has been proposed as a possible mechanism [31]. These fascinating findings challenge the traditional rules of Mendelian genetics in PD, suggesting a continuum of inheritance, ranging from dominant and recessive inheritance to oligogenic and complex additive and synergistic inheritance, influenced by other genetic, epigenetic, and environmental modifiers.

The PARK system here mentioned has been criticized for a number of reasons [32]. It brings together several dis-
orders, although some of them cannot even be considered true PD forms (such as the above mentioned PARK15), due to noteworthy differences in clinical, imaging, and neuropathological features, although parkinsonism (mostly levodopa responsive) is a common characteristic to all of them.

Similarly to Alzheimer’s disease (AlzD), the prevalence of PD is growing in the aging population. The lack of available neuroprotective interventions contributes to the general apprehension regarding the rising prevalence of age-related brain disease. Nonetheless, unlike the research carried out in AlzD, where novel drugs have been designed to target specific molecular disease mechanisms (without clinical success so far), no similar effort has been seen for PD yet [33, 34]. The lack of reproducible biomarkers used to detect disease early in its course, and to monitor its progression, is a major obstacle. Alpha-synuclein in the cerebrospinal fluid is promising, but there are still some aspects to address before it can be reliably used. Other diagnostic strategies may be used to further improve early diagnosis of PD [35].

In summary, we aimed at demonstrating that “Parkinson’s disease” is actually an umbrella designation for a sum of heterogeneous disorders sharing an important number of clinical features, but separated by significant differences among them at various levels. In fact, PD should probably be regarded as a “Parkinson’s disease cluster”, and the core clinical features termed “Parkinson’s syndrome”. Disease manifestations, genetic underpinnings, and pathological findings argue against a unique disease process and, hence, a unique management approach, especially one that aims solely at the improvement of later (i.e. motor) disease manifestations. We propose that true therapeutic innovation in PD calls for a leap in concepts and shift in research efforts. Disease-specific neuroprotective agents targeting early molecular and pathological events should ideally be developed. Solid scientific knowledge of genetics and pathology will be paramount for this purpose.

Abbreviations
AD: Autosomal dominant; AlzD: Alzheimer’s disease; AR: Autosomal recessive; CNS: Central nervous system; GBA: β-glucocerebrosidase; LRRK2: Leucine-rich repeat kinase 2; PD: Parkinson’s disease; SN: Substantia nigra; SNCA: α-synuclein; VPS35: Vacuolar protein sorting 35

Competing interests
The authors declare no conflict of interest.

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