Journal of Parkinson's Disease 14 (2024) S253–S255
DOI 10.3233/JPD-249011
IOS Press

Editorial

Introduction: The Earliest Phase of Parkinson's Disease: Possibilities for Detection and Intervention

Daniela Berg[a,*], Bastiaan R. Bloem[b], Lorraine V. Kalia[c] and Ron B. Postuma[d,*]
[a]*Department of Neurology, Christian-Albrechts-University of Kiel, Kiel, Germany*
[b]*Radboud University Medical Centre, Donders Institute for Brain, Cognition and Behaviour, Department of Neurology, Centre of Expertise for Parkinson and Movement Disorders, Nijmegen, The Netherlands*
[c]*Krembil Research Institute, Edmond J. Safra Program in Parkinson's Disease and the Morton and Gloria Shulman Movement Disorders Clinic, Toronto Western Hospital, University Health Network, Toronto, Canada*
[d]*Department of Neurology, Montreal General Hospital, Montreal, Quebec, Canada*

Pre-press 26 September 2024
Published 1 October 2024

This is an exciting time in Parkinson's disease (PD) research. Real progress has been made in our understanding of the pathophysiology, manifestations, progression and biomarkers of Parkinson's disease in the last two decades. We now recognize PD as the second most common neurodegenerative disorder and the world's fastest growing neurological condition. We are starting to understand the heterogeneity of disease, in which the main features that distinguish one person's path from another can start to be identified (noting that many of these features are not even motor). Most critically, we are beginning to gain the ability to recognize pathobiologic processes of PD long before the classic signs and symptoms emerge. The transition from the definition of PD as a clinical syndrome of bradykinesia, rigidity and rest tremor, to a biologic entity that can be diagnosed with biomarkers is a critical step. It could increase the probability of developing neuroprotective treatments that could ultimately alter the underlying degenerative course. For people already affected, this could lead to a slowing of disease progression. For those at risk of developing PD, it could lead to a postponement or perhaps even a complete prevention of a diagnosis of PD as we currently define it.

These changes in the understanding of this still relentlessly progressive disorder are especially relevant because the global prevalence of PD continues to rise as our world's population ages and many lifestyle and environmental contributors have changed and keep changing. We need early diagnosis and the best possible treatment options to lessen the individual and global disability burden. Moreover, a strong scientific basis for disease detection will facilitate a research agenda focusing on a better understanding of disease promoting factors and possible prevention strategies.

With this in mind, this special issue of JPD is focused on summarizing our recent understanding of the earliest phases of PD.

The supplement starts with an historical overview by Kulcsarova et al. [1], which summarises our understanding of PD combined with predictions of what our future understanding may look like. This is followed by three sections, each of which covers the essential aspects of early diagnosis. These include: (i) clinical

*Correspondence to: Daniela Berg, Department of Neurology, Christian-Albrechts-University of Kiel, Kiel, Germany. E-mail: Daniela.Berg@uksh.de; Ron B. Postuma, Department of Neurology, Montreal General Hospital, Montreal, Quebec, Canada. E-mail: ron.postuma@mcgill.ca.

ISSN 1877-7171

diagnosis, (ii) biomarker diagnosis and (iii) therapeutic issues. Each section comprises 4 articles, authored by two or more experts with complementary expertise.

The clinical section describes current knowledge and future research challenges in several areas. In the first article, Frasnelli et al. [2] cover hyposmia and RBD, the two most common markers for the early diagnosis of PD in *Opportunities and pitfalls of REM sleep behavior disorder and hyposmia as early markers in Parkinson's disease*. The second covers challenges in the definition, measurement and recording of early motor symptoms in *Identifying subtle motor deficits before Parkinson's disease is diagnosed: What to look for?* by Maetzler et al. [3]. The third deals with the still unresolved issue of subtyping in *Approaches to early Parkinson's disease subtyping* by Hu et al. [4]. In the fourth article, Schäffer et al. [5] discuss the necessity to prudently approach ethical issues in the early phase in *Ethical considerations for identifying individuals in the prodromal/early phase of Parkinson's disease: A narrative review*.

The biomarker section comprises an overview of the current knowledge and limitations of major classes of biomarkers specific to the earliest stages of PD. New biomarkers have been the basis for recently-proposed classification/staging systems of PD, including the SynNeurGe PD classification and the Integrated Staging System of Neuronal Synuclein Disease (NSD-ISS) [6, 7]. Biomarker classes covered in this supplement start with the α-synuclein seeding assays in (1) *Biofluid detection of pathological α-synuclein in the prodromal phase of synucleinopathies by* Kluge *et al*. [8]. Then, Pilotto et al. [9] cover the remaining fluid and tissue markers in *Biofluid markers and tissue biopsies analyses for the prodromal and earliest phase of Parkinson's disease*. The large field of genetics and its importance in early PD diagnosis is summarized by Seibler et al. [10] in *Combining biomarkers with genetics in prodromal/earliest phase Parkinson's disease.* Finally, imaging biomarkers, including those that are already used in clinical practise and those showing potential for research are discussed by van Eimeren et al. [11] in *Imaging biomarkers in prodromal and earliest phases of Parkinson's disease*.

Finally, early detection enables a new path towards treatment strategies. The goal is to interfere with the progressive pathology before substantial portions of the nervous system are lost. The third part of this special issue covers aspects of treatment development. This includes a summary of disease models by Yamakado et al. [12] entitled *Experimental animal models of prodromal Parkinson's disease*. Specifics of disease modification trial design are discussed in *Designing the First Trials for Parkinson's Prevention by* Crotty et al. [13]. Potential and pitfalls of non-pharmacological interventions, particularly exercise, are discussed by Oosterhof et al. [14] in *Considerations on how to prevent Parkinson's disease through exercise*. Finally, a summary *of* the major potential pharmacological interventions and their possible limitations is provided by Mahlknecht et al. [15] in *Pharmacotherapy for disease-modification in early Parkinson's Disease – how early should we be?*

Of course, none of this supplement can be considered as anything close to a final statement on early PD. Our goal is to summarize and compile the current understanding of early PD, focusing on open questions and limitations of these topics. This can serve as the basis for further discussion and research. As the editors of this issue, we are confident that the field of early detection and intervention of PD will develop rapidly, and we hope that this issue will help further spark research in this important field.

REFERENCES

[1] Kulcsarova K, Skorvanek M, Postuma RB, Berg D (2024) Defining Parkinson's disease: Past and future. *J Parkinsons Dis* **14**, S257-S271.

[2] Orso B, Brosse S, Frasnelli J, Arnaldi D (2024) Opportunities and pitfalls of REM sleep behavior disorder and olfactory dysfunction as early markers in Parkinson's disease. *J Parkinsons Dis* **14**, S275-S285.

[3] Maetzler W, Mirelman A, Pilotto A, Bhidayasiri R (2024) Identifying subtle motor deficits before Parkinson's disease is diagnosed: What to look for? *J Parkinsons Dis* **14**, S287-S296.

[4] Hu M, Skjærbæk C, Borghammer P (2024) Approaches to early Parkinson's disease subtyping. *J Parkinsons Dis* **14**, S297-S306.

[5] Schaeffer E, Yilmaz R, St. Louis EK, Noyce AJ (2024) Ethical considerations for identifying individuals in the prodromal/early phase of Parkinson's disease: A narrative review. *J Parkinsons Dis* **14**, S307-S319.

[6] Hoglinger GU, et al. (2024) A biological classification of Parkinson's disease: The SynNeurGe research diagnostic criteria. *Lancet Neurol* **23**, 191-204.

[7] Simuni T, et al. (2024) A biological definition of neuronal alpha-synuclein disease: Towards an integrated staging system for research. *Lancet Neurol* **23**, 178-190.

[8] Kluge A, Iranzo A (2024) Biofluid detection of pathological α-synuclein in the prodromal phase of synucleinopathies. *J Parkinsons Dis* **14**, S323-S331.

[9] Pilotto A, Zanusso G, Antelmi E, Okuzumi A, Zatti C, Lupini A, Bongianni M, Padovani A, Hattori N (2024) Biofluid markers and tissue biopsies analyses for the prodromal and earliest phase of Parkinson's disease. *J Parkinsons Dis* **14**, S333-S344.

[10] Seibler P, Streubel-Gallasch L, Klein C (2024) Combining biomarkers with genetics in prodromal/earliest phase Parkinson's disease. *J Parkinsons Dis* **14**, S345-S351.
[11] Theis H, Pavese N, Rektorová I, van Eimeren T (2024) Imaging biomarkers in prodromal and earliest phases of Parkinson's disease. *J Parkinsons Dis* **14**, S353-S365.
[12] Yamakado H, Takahashi R (2024) Experimental animal models of prodromal Parkinson's disease. *J Parkinsons Dis* **14**, S369-S379.
[13] Crotty GF, Ayer SJ, Schwarzschild MA (2024) Designing the first trials for Parkinson's prevention. *J Parkinsons Dis* **14**, S381-S393.
[14] Oosterhof TH, Darweesh SKL, Bloem BR, de Vries NM (2024) Considerations on how to prevent Parkinson's disease through exercise. *J Parkinsons Dis* **14**, S395-S406.
[15] Mahlknecht P, Poewe W (2024) Pharmacotherapy for disease modification in early Parkinson's disease: How early should we be? *J Parkinsons Dis* **14**, S407-S421.