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Comment on "Classification of Advanced Stages of Parkinson's Disease: Translation into Stratified Treatments"

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Abstract

Parkinson's disease (PD) is increasingly recognized as a heterogeneous disorder combining equally diverse motor and non-motor symptoms, with a complex interplay and different individual presentations, especially in the advanced stages of the disease. Current classifications and related stage-adapted therapeutic recommendations still lack of precision, as traditional concepts of advanced PD (advPD) are mainly based on milestones of motor disabilities. In this short review, we present the concepts delineated by Krüger and colleagues published in the 'Journal of Neural Transmission' on current classifications for advPD and novel directions for future clinical trials, a precision medicine approach by empowerment of patients and their involvement in therapeutic decisions.

Advances stages of Parkinson's disease (PD) still represent a challenge due to their complexity and heterogeneity in their clinical presentation and therapeutic demands. Traditional classifications and disease progression of PD consider mostly motor symptoms as milestones for defining advanced PD (advPD), as for example motor-fluctuations, freezing of gait or falls. However, PD is more than 'just a movement disorder', as a large variety of non-motor symptoms completes the phenotypic spectrum of the disease. This phenotypic variety is paralleled by the diversity of neurodegenerative patterns and the involvement of different neurotransmitters in the pathomechanism of the disease [1,2]. The current used classifications for PD do not describe the full range of the clinical variety of motor and non-motor symptoms.

Current concepts of evidence-based medicine are guided by the results from classical clinical trials, which may not represent real life situations, as potentially biased according to well selected and strict inclusion and exclusion criteria. Thus, these cohorts may not represent completely the general population of PD patients as a whole, with its continuous and multi-dimensional spectrum of motor and non-motor symptoms and especially in the advanced stages-numerous comorbidities and polymedication (a general issue in the elderly population). Given the complexity of the patient's demands and the great variability of the phenotypic presentation in the advanced stages of PD (as every patient is different), classical trial designs fall short in their representation, so new concepts are needed for classification of PD.

A novel concept consists in an in-depth phenotyping in order to have a precise and comprehensive analysis of the patient's symptoms, enable a stratification into disease subclasses and in the end to guide physicians towards the best available care tailored for the individual patient considering his needs and requirements (the so-called 'precision medicine' concept) [3]. According to the 'patient-and-physician partnering perspective' of the Parkinson Net in the Netherlands [4], advPD would rather reflect critical phenotypic presentations (including motor, non-motor, quality of life, psychosocial and contextual aspects) needing therapeutic adjustment, than disease milestones represented in classical clinical scales (e.g. Hoehn and Yahr staging).

Current strategies to define disease stages and classify PD use categories as age of onset, disease severity, predominant clinical phenotype (motor or non-motor) or the different neuropathological alterations. For instance, the age at onset classifies PD as juvenile if the disease develops until the age of 20 years and early onset PD until 40 years. The disease severity on the other hand, is often classified using the broadly accepted five Hoehn and Yahr stages [5]. However, the transition from one stage to the other is not linear; especially from stage II to III typically marks an important milestone for the patient, as gait and balance impairment due to PD can result in severe complication and impact on quality of life [6]. Therefore, different classification systems have been developed, such as the Unified Parkinson Disease Rating Scale (UPDRS) and the modified form proposed by the Movement Disorders Society (MDS-UPDRS) [6-8]. The latter does not only focus on the cardinal motor symptoms of PD (bradykinesia, resting tremor, rigidity and postural instability), but also take in account non-motor domains, such as cognition, mood and activities daily living, as PD is now widely regarded as a complex disorder including neuropsychiatric and other non-motor features [9]. For more detailed assessment of non-motor symptoms one has to use more specific scales, such as the patient self-questionnaire NMS-Quest [10] or the physician-assisted NMS scale [11], capturing the non-motor burden of the disease, which has a strong influence on the overall disease severity [12,13]. Lastly, neuropathological staging of the disease progression and severity is widely performed by the Braak stages describing the neuronal degeneration and Lewy body spreading in the central nervous system [14,15]. However, the extent of synucleinopathy including Lewy bodies does not correlate with the clinical disease severity and may also be present in healthy subjects, questioning the Braak staging as unifying concept [16].

The clinical distinction between PD and atypical parkinsonism (AP) still remains a challenge, especially in light of the overlap syndromes like 'minimal change' multiple system atrophy (MSA) or progressive supranuclear palsy with predominant parkinsonism (PSP-P) [17,18]. The differentiation of AP from advPD is critical as related to therapeutic consequences: advPD defines a stage of the disease where intensified therapies should be proposed, such as pump-systems or deep-brain-stimulation (DBS). Here patients with AP do typically not respond to

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dopaminergic or Neuromodulation treatments and therefore the risk of these interventional therapies overweighs the achievable benefit, as shown in a series of pathologically confirmed 'benign' MSA cases, who underwent a DBS intervention [19]. Combination of diagnostic tests, like magnetic resonance imaging (MRI) or single photon emission tomography (SPECT), without being sufficient to their own, can help do differentiate between PD and AP and increase the diagnostic accuracy. Future longitudinal cohorts using deep phenotyping approaches (with for example additional device-based assessments) are needed to improve the definition of the different diseases and subtypes.

Stratification of the disease is of therapeutic importance and better definitions of subtypes of PD will help to assign treatments according to the best individual outcome. Disease stage and age of the patients are major criteria for assigning a therapy approach, as for example it has been shown in the EARLYSTIM study, that DBS was superior to best pharmacological treatment in younger patients with early motor fluctuations [20]. Besides these clinical stratification parameters genetic stratification has already proven effective in this matter in the cancer therapy, by stratifying the patients according to the tumor subtype or the methylation profile of specific genes predicting the therapeutic response [21]. In PD, a first similar approach in the ADAGIO study has shown that a polymorphism in the dopamine D2 receptor gene is predictive for the response to rasagiline treatment as monotherapy [22]. Another, smaller study has recently shown that a certain polymorphism in the alpha-synuclein gene may predict a positive outcome of DBS after two years of treatment [23]. Interestingly, the same genetic variant is linked to less alpha-synuclein protein accumulation in different brain areas and less cognitive impairment, arguing in favor of more preserved basal ganglia circuits [24-26].

Future trials need therefore to shift from the classical 'large number of patients with a handful of parameters measured' scheme, to a more in-depth approach, to capture a large number of different parameters on a smaller group of patients. Highly selective clinical studies based on strict inclusion and exclusion criteria, do seldom allow translation into real-life patients with numerous accompanying health issues, disease related disabilities and potential drug-drug interactions due to polypharmacy. A more individualized approach, without preselection of the patient cohort, is therefore needed, that includes (i) a detailed clinical assessment of motor and non-motor symptoms including objective measurements via wearable technologies, and (ii) 'omics'-based assays for detailed biological assessments and stratification approaches (i.e. genetic polymorphisms). These strategies might become a valuable asset to the classical clinical trials and help to predict more precisely side effects and drug-drug interaction.

In the emerging area of healthcare technology and wearable device-based assessments of patient's motor and non-motor symptoms, objective measurements come more and more into the spotlight of PD research [27,28]. Although, most of these technologies need yet to be validated and lack the required readiness level [29], the way more and more data are generated will foster 'big data' in PD and pave the way for the future diagnostic and treatment strategies. Thus, new IT-based communication strategies need to be developed, in order to connect and harmonize the different stakeholders in the next-generation healthcare. The integration of interactive communication and information platforms is an important step in new integrative healthcare concepts, allowing transparent feedback and empowerment of patients in their own ambulatory healthcare provision [30]. In the future, these empowered and (due to device-aided assessments) highly connected patients will shape a new concept of clinical studies, allowing a better and more 'real-life' definition of advPD. Using novel mobile devices (integrated in their daily life for more objective health data) and 'omics'-based assessments (metabolome, genome, transcriptome, proteome), and by the engagement of patients themselves in clinical research (patient's empowerment), individualized trials (so-called 'one-person trials) with deep phenotyping will complete the classical clinical trials to generate valuable and highly needed new medical evidence for novel therapies and in the end establish precision medicine [31].

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