Redefinition of Parkinson's Disease

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ABSTRACT

In 2015, a working group of the International Parkinson's and Movement Disorders Society (MDS) presented new clinical diagnostic criteria for Parkinson's disease (PD). This review outlines the key insights with regard to pathophysiology, various clinical manifestations and clinical progression which form the basis for a redefinition and the new, summarized clinical diagnostic criteria of Parkinson's disease. Essential findings, which led to the new diagnostic criteria, include (i) the recognition of the importance of non-motor symptoms, which may have a tremendous influence on the quality of life of patients and have an increasing relevance with regard to early and differential diagnosis of PD is stated. (ii) The categorization of dementia in the course of Parkinson's disease. While there has been a clear separation between Parkinson's disease and dementia with Lewy bodies so far, now a continuum is postulated which summarizes Parkinson's disease without, with late and with early (within the first year after the occurrence of motor symptoms) dementia under the umbrella term of Lewy Body Diseases (LBD). (iii) The realization of a slowly spreading process of neurodegeneration occurring throughout different parts of the nervous system. This resulted in the definition of different phases of the disease, the preclinical, prodromal and clinical phase. In particular, the definition of the prodromal phase, characterized by different clinical parameters and further biomarkers still to be implemented, opens up new possibilities for early diagnosis and in the long run early treatment of Parkinson's disease. (iv) The insight that the clinical phase is characterized by different forms of disease progression. For genetic variants (e. g., GBA or LRRK2) a separate clinical-genetic category is proposed, in idiopathic Parkinson's disease subtypes should be characterized by clearly distinct prognosis, progression and/or treatment strategies. The MDS Task Force proposes to keep the current gold standard of typical clinical motor symptom presentation and post-mortem verification of α-synucleinopathy for the diagnosis of PD. The new clinical diagnostic criteria were designed using a typical clinical expert as benchmark, codifying the expert diagnostic process to make it reproducible and easily applicable. The new diagnostic criteria now contain absolute exclusion criteria, supportive criteria and "red flags" in addition to the assessment of the cardinal motor symptoms. Specific ancillary diagnostic tests (e. g., imaging techniques) can be implemented; furthermore the time course and severity of symptoms are taken into account.

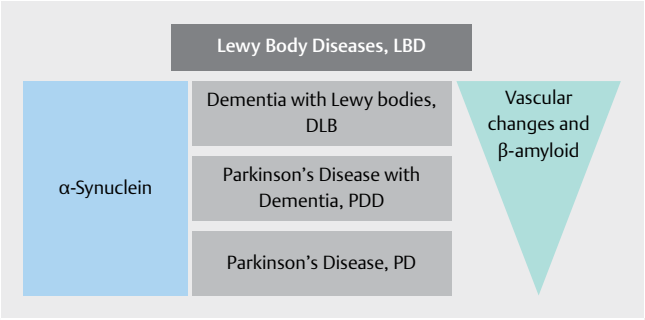
Introduction

200 years ago James Parkinson first described the clinical presentation of Parkinson's syndrome of a movement disorder, which was given his name: Parkinson's disease. Since that time, our understanding of the disease has changed fundamentally as to the possible causes, underlying pathomechanisms, forms of clinical progression, and the spread of the neurodegenerative process. This new state of knowledge calls for both the possibility as well as the necessity of redefining PD.

In order to meet this challenge, the International Parkinson's and Movement Disorder Society (MDS) formed a task force to summarize the current state of knowledge according to the essential aspects requiring a redefinition [1]. Based on this, new criteria for clinical diagnosis were developed proceeding from the results of this group's collaboration [2]. A further paper presented research criteria based on which a statistical method could be used to calculate the probability of a person to be in the prodromal state of Parkinson's disease [3]. The following presents the most important core aspects of the new state of knowledge and, in particular, the clinically significant diagnostic criteria of the MDS group.

Significance of Non-motor Symptoms

In his "Essay on the Shaking Palsy", James Parkinson described in addition to the cardinal motor symptoms of PD also non-motor symptoms. However, subsequently there was a focus on the motor symptoms, which over the course of decades has changed little, neither diagnostically nor therapeutically. Only in recent years has there been steadily growing awareness of the significance of non-motor symptoms of Parkinson's disease. In addition to the great number of autonomic functional disorders (constipation, hyperhidrosis, sialorrhea, orthostatic sexual and bladder dysfunction), a number of patients suffer from various forms of sleep dis-



▶ **Fig. 1** Lewy body disease spectrum.

turbance (REM sleep disorder, restless legs syndrome or insomnia), associated psychiatric symptoms (depression, anxiety) and sensory symptoms (e. g., hyposmia, various vision disturbances and chronic pain). These impose no less a burden on a large number of patients than motor deficits, and seriously influence the quality of life irrespective of the motor symptoms [4–6]. Moreover, the early occurence of non-motor symptoms in the course of the disease is gaining increased relevance in early diagnosis and differential diagnosis.

Dementia and Parkinson's Syndrome

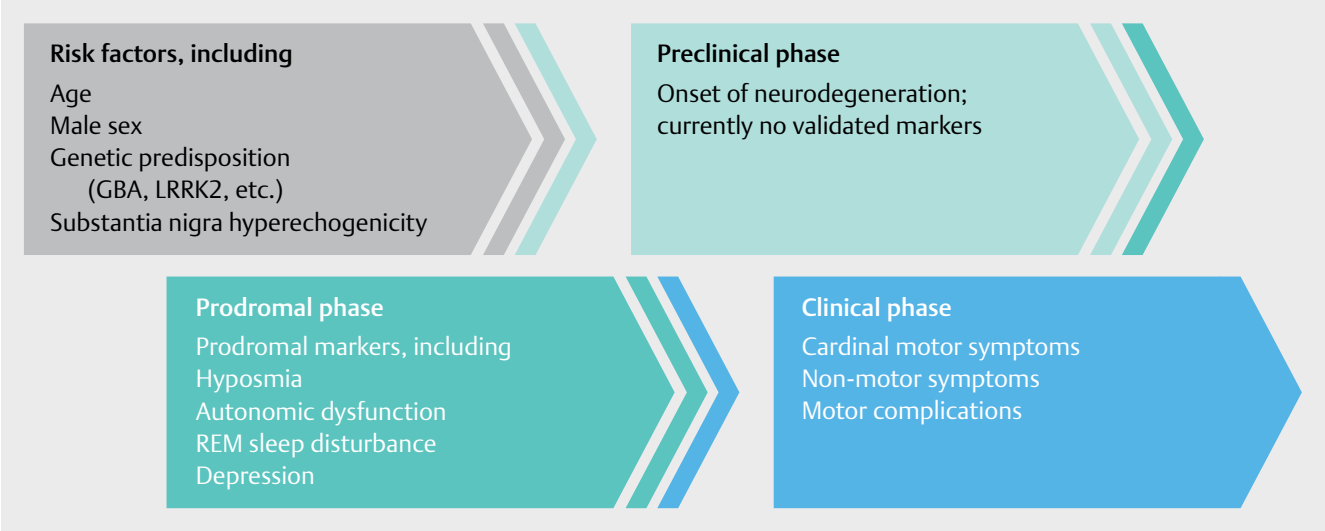
Dementia is one of the most clinically important non-motor symptoms of Parkinson's disease, the understanding of which has changed significantly in recent years. Until McKeith set forth his criteria, there had been a clear diagnostic distinction between Parkinson's dementia and Lewy body dementia according to the one-year rule [7]. Signs of dementia appearing prior to or during the first year of appearance of Parkinson's disease resulted in the diagnosis of Lewy body disease; if they occurred later in the course of motor manifestation, then it was considered to be Parkinson's dementia. The observation that both diseases have overlapping and clinical characteristics resulted in the much-discussed hypothesis that contrary to the previous definition, these are not 2 distinct disease entities [8]. The MDS Task Force [1] instead postulated, based on this hypothesis, a continuum or spectrum of diseases subsumed under the category Lewy body diseases (LBD), containing Parkinson's disease without (PD) and Parkinson's disease with dementia (PDD) as well as dementia with Lewy bodies (DLB). Clinically, in addition to the typical motor symptoms these disease forms have other non-motor symptoms such as hyposmia or REM sleep behavior disorder in common. With regard to pathology, this hypothesis is supported by the observation that other pathologies (vascular changes and/or β-amyloid deposits) can often be found in the development of dementia in Parkinson's disease in addition to the known neuronal α-synuclein pathology. According to the MDS Task Force, their time of onset, extent and localization have an influence on the beginning and course of the dementive process. Thus, dementia in Parkinson's disease can occur not only in later stages of the disease, but also early, or even before manifestation of motor symptoms. In the presence of typical Parkinson's symptoms, the MDS Task Force mentions Parkinson's disease with e. g., early onset of dementia. The concept of DLB can additionally be applied, but should no longer be considered an alternative diagnosis to Parkinson's disease. Refer to ▶ **Fig. 1** (based on [1]).

Phases of Parkinson's Disease

The diagnosis of PD is still based on the clinically examined cardinal motor symptoms. Generally, these are only identifiable when more than 50 % of the dopaminergic cells in the substantia nigra have degenerated. Exceptions to this are top athletes (for example, Ray Kennedy, in whom typical signs of Parkinsonism were evident during soccer matches 14 years prior to diagnosis) [9], virtuoso musicians or others who at specific times require above-average quantities of dopamine. Thus there is a prodromal phase lasting years or decades in which neurodegeneration progresses slowly, although this phase is not asymptomatic clinically. Non-specific symptoms may occur, including hyposmia, depression or mild motor signs such as reduced arm swing, as well as more specific symptoms such as REM sleep behavior disorder (RBD). Based on the findings of Braak et al. a large number of studies have shown that Parkinson's disease, as a developing process, leads to neurodegeneration and α-synuclein deposits in large parts of the nervous system. According to H. Braak's model the course of the disease exhibits a pattern ascending from the lower brain stem or enteral nervous system into the neocortex [10]. Another model suggests that the spread of Parkinson's-typical pathology begins in olfactory structures and from there affects either the limbic cortex or the lower brain stem [11], thus explaining the different clinical progressions of the disease, such as early dementia. Regardless of the point of origin of the spreading pathology, there appears to be a cell-to-cell transmission of neurodegenerative information. Analogous to prion diseases in which protein deficiency information is also passed along as cell-to-cell transmission, a "prion-like" propagation is discussed [12, 13].

In any case, the pathological changes found are in line with the clinical observation that Parkinson's patients have a number of non-motor symptoms such as a hyposmia or constipation for years or even decades before their "clinical phase." In the presence of symptoms prior to diagnosis which may be an expression of the affected regions, this phase of advancing neurodegeneration prior to diagnosis is referred to as the prodromal phase of the disease and can vary individually in terms of both manifestation and progression over time. The phase of neurodegeneration in which there are no defining symptoms is referred to as the preclinical phase for which there are as yet no unambiguous markers. There are studies discussing α-synuclein aggregation in various tissues such as the gastrointestinal tract [14–16], cerebrospinal fluid markers such as changed α-synuclein level [17, 18], or imaging markers, which are indicative of the neurodegenerative process preceding the development of initial clinical symptoms [19, 20].

All of these phases should be distinguished from the basic risk of developing Parkinson's disease which, depending on a person's age, can achieve a prevalence between 0.4 % (age 50–54 years) and 4.0 % (age over 80 years, summarized in [3]). This basic risk can increase if there are for example certain genetic changes, certain behaviors (abstinence from coffee or tea), or if transcranial sonography discloses hyperechogenicity of the substantia nigra [21]. Based



▶ **Fig. 2** Possible phases of parkinson's disease.

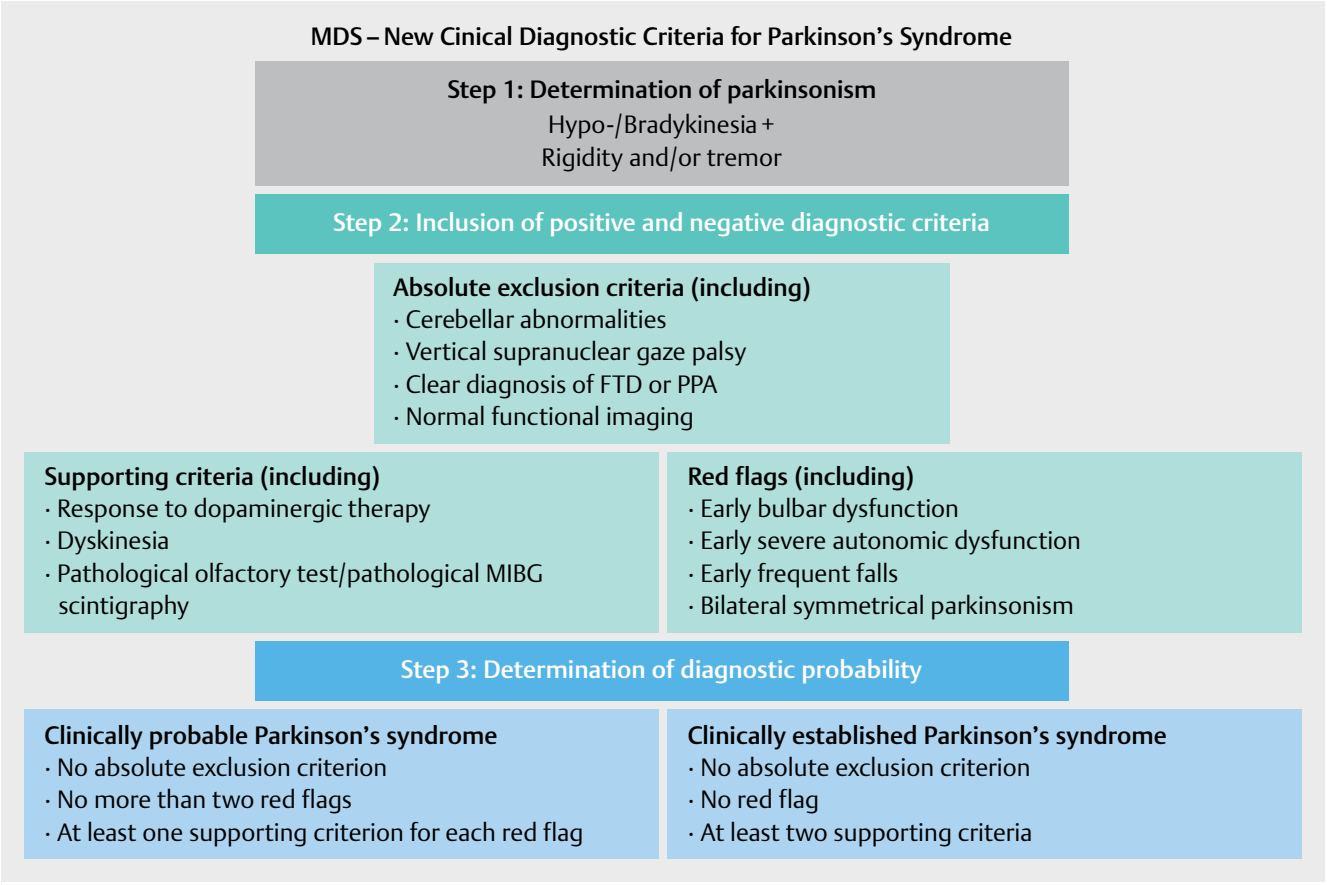
on epidemiological data and clinical cohort studies, the MDS Task Force, presented an initial model in the form of research criteria which in theory will make it possible to calculate the probability of a person developing Parkinson's syndrome. This model is based on risk factors and prodromal markers while taking into account prior probability, that is, the basic likelihood of a person to develop Parkinson's disease [3]. Prognostically the strongest prodromal marker in this calculation is the occurence of REM sleep behavior disorder, if it could be ascertained by polysomnography. Prospective studies have indicated that between 75 to 91 % of individuals suffering from idiopathic REM sleep behavior disorder will also develop an α-synucleinopathy later in life [22, 23]. To date, however, the individual appearance of the different markers, their chronological sequence and duration prior to the appearance of motor symptoms appear unclear and are probably strongly variable depending on the individual, so that no blanket statement can be made regarding a person's development of a clinical Parkinson's syndrome. See ▶ **Fig. 2**.

A better characterization of the prodromal phase should lead to an early diagnosis of Parkinson's syndrome, which in turn can lead to a benefit for patients. It was shown that pre-Parkinson's patients 3 to 4 times more visits to medical practitioners than those for whom there was no Parkinson's diagnosis [24]. In addition, important compensation mechanisms (particularly physical and cognitive training) could be strengthened early on. Furthermore, the prodromal phase and with it the early detection of PD will in the future be a critical point of attack for pharmacological interventions. Whereas in recent years significant advances have been made in the area of symptomatic therapy for PD, no breakthrough has been made as yet in causative therapy. Promising therapeutic approaches to slow down or even stop the course of the disease medically have hitherto failed, presumably because they have been tried on patients already suffering from Parkinson's, i. e., in cases of advanced neurodegeneration. In the meantime, other promising therapeutic approaches are in clinical trial, including immunization strategies to stop the spread of α-synucleinopathy [25–27]. A clearly-defined patient cohort in the prodromal phase would be an ideal group for these types of pharmacological interventions.

Various Subtypes of Parkinson's Disease

Presentation of symptoms and progression of Parkinson's disease vary widely. The manifestation of motor symptoms appears to predicate the course of the disease to a certain extent; thus patients with a tremor-dominant Parkinson syndrome have a better chance of experiencing a benign disease course compared to patients with pronounced akinetic-rigid symptoms, postural instability or gait disturbance [28]. The new understanding of the importance of non-motor symptoms also gives rise to the suggestion that there are also different subtypes and developmental forms in this area. For example, Ferehstehnejad et al. described an association of RBD and orthostatic dysregulation with a malignant progress of the disease [29]. Despite this variability, affected patients continue to be largely treated the same. In this case a clear definition of subtypes should support a more strongly individualized therapy.

According to the MDS Task Force, in order to discuss a subtype, there should be a clear distinction with respect to the disease manifestation, prognosis or treatment strategy which is not unambiguously possible in the large group of idiopathic Parkinson syndrome. Much more promising, however is the possibility of making a clear distinction by including genetic alterations. Clinically, patients with certain genetic variations exhibit different manifestations of symptoms; for example, patients with a GBA mutation have a greater risk of developing neuropsychiatric symptoms such as dementia or depression [30]. On the other hand, carriers of LRRK2 mutations are usually distinguished by a comparatively benign course of the disease [31]. The hope exists that through patient stratification and therapy strategies specifically addressing the metabolic pathways involved, individualized and causal therapies will be possible. The MDS Task Force has offered its own clinical-genetic nomenclature which has been implemented by another working group [32].



▶ **Fig. 3** New clinical diagnostic criteria of the MDS

The Gold Standard for Establishing a Diagnosis

The key issue when defining a disease is what the gold standard is for the establishment of a diagnosis. The previous gold standard for diagnosing parkinsonism was the presentation of classical levadopa-responsive cardinal motor symptoms based on the loss of dopaminergic cells in the substantia nigra pars compacta with evidence of α-synuclein deposits. Examinations of patients with certain forms of genetic parkinsonism (carriers of parkin or LRRK2 mutations) exhibit little or no typical α-synucleinopathy, even though the clinical pattern distinctly correlates with Parkinson's disease [33].

Moreover, according to the above-mentioned models of spreading neurodegeneration, the prodromal phase (at least in its early phase) is not yet associated with α-synuclein deposits in the substantia nigra. On the other hand, over a period of 50 years Lewy body pathology was diagnosed in about 10 % of deceased patients even though typical symptoms of Parkinson's disease were not evident during the patients' lifetime (incidental Lewy body disease) [34, 35]. The counter-argument against defining clinical presentation of the patient as the absolute gold standard is that clinical presentations of Parkinson's syndromes can also be based on other pathologies determined post mortem.

After evaluation of all arguments, the MDS Task Force for the redefinition of PD postulates to keep the current clinical-pathological gold standard and expanded it by an additional clinical-genetic diagnosis category. There is also indication that progress in the research of possible biomarkers (visualization and histological evidence of α-Synuclein pathology in other parts of the nervous system) can in the future provide additional diagnostic certainty.

New Clinical Diagnostic Criteria

In order to optimize the relevant everyday clinical diagnosis based on the current state of knowledge (clinically a proper diagnosis is made in only 75–95 % of cases, depending on the expertise of the physician [36]), the MDS Task Force has developed a new algorithm for the clinical definition of PD [2]. The basic concept of the criteria was to mimic the approach of an experienced clinician, who, in addition to recognizing the cardinal symptoms leading to a diagnosis, also incorporates various aspects of the patient's history and physical examination when establishing the diagnosis.

The basis for the diagnosis is the determination of the presence of cardinal motor symptoms, that is the presence of hypo-/bradykinesia in combination with rigidity, rest tremor or both. Postural instability is no longer considered a cardinal symptom, since in the case of idiopathic Parkinson's syndrome this generally appears later

in the progression of the disease. In addition, five further primary elements are implemented when making a diagnosis: 1) Inclusion of positive and negative characteristics (i. e., aspects that support or exclude the presence of a Parkinson's syndrome), 2) Counterbalancing the significance of characteristics (differentiation of clear exclusion criteria and red flags), 3) Correct interpretation of characteristics (i. e., inclusion of information into a general context), 4) Inclusion of the time factor (since certain symptoms have a very different significance, depending on the time of appearance in the course of the disease), and 5) the optional inclusion of supplementary examinations (including smell testing or imaging), see ▶ **Fig. 3**.

Summary

The redefinition of Parkinson's disease presented here means that the disease is to be viewed in its diversity. Research and everyday clinical practice should take into account the manifold motor and non-motor symptoms, subtypes and pathogens, genetic and pathophysiological foundations of the disease. This will form the basis for the growing understanding of the disease as well as the development of new therapeutic strategies.

An accurate early diagnosis is a prerequisite for any symptomatic therapy. In addition, an understanding of the heterogeneity of the clinical presentation, the course, underlying pathology, or the progression of pathophysiological changes is essential for individual and conclusive causal therapy.

In coming years the definition of Parkinson's syndrome PD will continue to undergo change. The establishment of biomarkers is particularly promising, as this will support the diagnosis and prediction of the course of the disease. These include advances in obtaining biopsies with α-synuclein changes, such as specimens of intestinal mucosa, salivary glands or skin samples [37–41], which could be especially useful in the early detection of parkinsonism. In the future, changes in cerebrospinal fluid might predict the development of dementia within the context of Parkinson's syndrome [42, 43]. Finally, advances are expected in structural and functional imaging. While structural MRI imaging, partly in combination with nuclear medical procedures (FDG-PET, FP-CIT (DaTscan) SPECT, or cardiac 123I-MIBG-SPECT), has been established in the clinical routine for the differential diagnosis with respect to distinguishing Parkinson's disease from atypical Parkinson's syndromes or other forms of parkinsonism, early detection and progression markers based on functional imaging are still under investigation. Particular hope is in place regarding the development of a sensitive imaging marker for demonstrating expanding neurodegeneration and α-synuclein deposits which would be of great value as target parameters for therapy studies.

To date, ethical issues which arise with increased knowledge have yet to be fully addressed. In particular, in the absence of reliable prognostic statements and causal therapy strategies, it is necessary to establish the extent to which carriers of risk or prodromal markers should be informed of their individual disease prospects as well as patients who have already been diagnosed with Parkinson's disease. The more precisely Parkinson's disease can be defined in the future, and the more clearly individual prognoses and therapeutic consequences can be described, the more important it will be to actively address these aspects of patient care.

Conflicts of Interest

Eva Schäffer declares no conflicts of interest. Daniela Berg declares grants, honoraria and/or support from the following: Janssen Pharmaceutica; Michael J. Fox Foundation; German Parkinson's Disease Association (dPV); BMWi; BMBF; Parkinson Fonds Deutschland GmbH; UCB Pharma GmbH; TEVA Pharma GmbH; Novartis Pharma GmbH; Boehringer Ingelheim Pharma GmbH; Lundbeck, independently of the current article.

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