ΚΛΙΝΙΚΟΙ ΒΙΟΔΕΙΚΤΕΣ ΣΤΗ ΝΟΣΟ ΠΑΡΚΙΝΣΟΝ ΚΑΙ ΣΤΟΝ ΑΤΥΠΟ ΠΑΡΚΙΝΣΟΝΙΣΜΟ

Μαρία Χονδρογιώργη [1], Σπυρίδων Κονιτσιώτης [1,2]

[1] Νευρολογική Κλινική, Πανεπιστημιακό Γενικό Νοσοκομείο Ιωαννίνων
[2] Τμήμα Νευρολογίας, Σχολή Επιστημών Υγείας, Ιατρική Σχολή Πανεπιστημίου Ιωαννίνων

Περίληψη

Η χρήση κλινικών βιοδεικτών στη διαφορική διάγνωση και πρόγνωση των παρκινσονικών συνδρόμων παραμένει πολύτιμη, παρά την εξέλιξη στον εντοπισμό εργαστηριακών, απεικονιστικών και γενετικών δεικτών. Στην παρούσα ανασκόπηση γίνεται αναφορά στα κριτήρια της Movement Disorders Society για την πρόδρομη νόσο Πάρκινσον (ΝΠ) τα οποία αποσκοπούν στην αξιολόγηση της πιθανότητας παρουσίας πρόδρομης ΝΠ σε άτομα χωρίς ή με πολύ ήπια κινητικά συμπτώματα. Περιγράφεται επίσης η προγνωστική αξία μεμονωμένων βιοδεικτών για την ιδιοπαθή ΝΠ, όπως η ηλικία έναρξης και ο κινητικός υπότυπος, καθώς και η προγνωστική αλλά και η διαφοροδιαγνωστική ικανότητα στο σύνολο των παρκινσονικών συνδρόμων της διαταραχής συμπεριφοράς ύπνου REM, της υποσμίας, των διαταραχών οφθαλμοκινητικότητας, της ορθοστατικής υπότασης, της στοματοφαρυγγικής δυσλειτουργίας και ποικίλων νευροψυχιατρικών εκδηλώσεων. Όσον αφορά τη διαταραχή συμπεριφοράς ύπνου REM, πέραν της υψηλότατης προγνωστικής της αξίας ως πρόδρομης κατάστασης α-συνουκλεϊνοπάθειας, σημαντική είναι και η χρήση της στην ταξινόμηση των ασθενών σύμφωνα με το προσφάτως προτεινόμενο μοντέλο κεντρικής ή περιφερικής έναρξης της παθολογίας α-συνουκλεΐνης στην ιδιοπαθή ΝΠ. Η χρήση του μοντέλου αυτού επιφυλάσσει χρήσιμες παθοφυσιολογικές και προγνωστικές προεκτάσεις όπως αυτές περιγράφονται συνοπτικά στο παρόν κείμενο. Τέλος, επισημαίνονται βασικές παράμετροι οι οποίοι καθοδηγούν τη θεραπευτική στρατηγική στην ιδιοπαθή ΝΠ, όπως η ηλικία, πιθανές συννοσηρότητες και ο τρόπος ζωής των ασθενών.

Λέξεις ευρετηρίου: νόσος Πάρκινσον; Άτυπα Παρκινσονικά σύνδρομα; Διαταραχή συμπεριφοράς ύπνου REM; κινητικός υπότυπος; Υποσμία

CLINICAL BIOMARKERS IN PARKINSON'S DISEASE AND ATYPICAL PARKINSONISM)

Maria Chondrogiorgi[1], Spyridon Konitsiotis[1,2]
[1] Department of Neurology, University General Hospital of Ioannina
[2] Department of Neurology, School of Health Sciences, Medical School, University of Ioannina

Abstract

The use of clinical biomarkers in the differential diagnosis and prognosis of parkinsonian syndromes remains valuable, despite the progress made in the identification of laboratory, imaging and genetic markers. The present review includes a reference on Movement Disorders Society criteria for prodromal Parkinson's disease (PD) which were designed to estimate the probability of prodromal PD in individuals with any or very mild motor symptoms. The prognostic value of individual biomarkers for idiopathic PD is also discussed, such as age of onset and motor subtype, as well as the role of REM sleep behavior disorder, hyposmia, oculomotor disorders, postural hypotension, oropharyngeal dysfunction and various neuropsychiatric manifestations in the differential diagnosis among parkinsonian syndromes. Regarding REM sleep behavior disorder, in addition to its high prognostic value as a state of an emerging α-synucleinopathy, its use in the classification of patients according to the recently proposed brain first and body first model for idiopathic PD is also important. The use of this model holds useful pathophysiological and prognostic implications which are also summarized in this review. Finally, key parameters that guide the therapeutic strategy in idiopathic PD are highlighted, such as patients' age and lifestyle and possible comorbidities.

Keywords: Parkinson's disease; Atypical Parkinsonian syndromes; REM sleep behaviour disorder; motor subtype; Hyposmia

Κύρια σημεία της ανασκόπησης

- *Ο εντοπισμός και η χρήση κλινικών βιοδεικτών παραμένει ουσιώδης παρά την εξέλιξη στον εντοπισμό εργαστηριακών βιοδεικτών*
- *Η εφαρμογή των κριτηρίων της Movement Disorders Society για την πρόδρομη ΝΠ επιτρέπουν τον πολύ πρώιμο εντοπισμό επίνοσων ατόμων*
- *Το μοντέλο διαχωρισμού των ασθενών με ΝΠ σε κεντρικής και περιφερικής έναρξης νόσο (brain first/ body first) παρέχει ενδιαφέροντα παθοφυσιολογικά και προγνωστικά στοιχεία*
- *Η διαταραχή συμπεριφοράς ύπνου REM, η υποσμία, η ορθοστατική υπόταση, η διαταραχή της οφθαλμοκινητικότητας και της στοματοφαρυγγικής λειτουργίας και το πρότυπο πιθανών νευροψυχιατρικών διαταραχών συμβάλλουν σημαντικά στη διαφοροδιάγνωση και πρόγνωση των παρκινσονικών συνδρόμων*

Αξιοποιήσιμα σημεία στην κλινική **πράξη**

- Η πρώιμης έναρξης ΝΠ σχετίζεται με βραδύτερη εξέλιξη της νόσου αλλά ταυτόχρονα σημαντική επιβάρυνση της ποιότητας ζωής
- Ο κινητικός υπότυπος παρέχει χρήσιμα προγνωστικά στοιχεία αλλά πιθανώς όχι μακροπρόθεσμα λόγω της δυνητικής μεταβλητότητάς του στην πορεία του χρόνου
- Η διαταραχή συμπεριφοράς ύπνου REM αποτελεί σε ένα εξαιρετικά υψηλό ποσοστό πρόδρομη εκδήλωση α-συνουκλεϊνοπάθειας
- Η παρουσία διαταραχής συμπεριφοράς ύπνου REM ως προκινητικό σύμπτωμα στη ΝΠ σχετίζεται με βαρύτερη διαταραχή του αυτόνομου νευρικού συστήματος και ταχύτερη γνωστική εξασθένιση
- Η υποσμία είναι συχνότερη στην ιδιοπαθή ΝΠ παρά στον άτυπο παρκινσονισμό
- Η ορθοστατική υπόταση όταν προηγείται του παρκινσονισμού και της γνωστικής έκπτωσης υποστηρίζει τη διάγνωση της ατροφίας πολλαπλών συστημάτων
- Το πρότυπο της γνωστικής έκπτωσης συμβάλλει στη διαφορική διάγνωση μεταξύ των άτυπων παρκινσονικών συνδρόμων

Review highlights

- The identification and use of clinical biomarkers remains essential despite the advances in the identification of laboratory and imaging biomarkers
- Application of the Movement Disorders Society criteria for prodromal PD allows the very early identification of individuals about to develop clinical PD
- Brain first and body first model provides valuable pathophysiological and prognostic clues
- REM sleep behavior disorders, hyposmia, orthostatic hypotension, oculomotor and oropharyngeal dysfunction, and the pattern of neurophychiatric disorders contribute significantly to the differential diagnosis and prognosis of parkinsonian syndromees

Useful points to clinical practice

- Early-onset PD is associated with a slower disease progression but at the same time with a significant burden on the quality of life
- Motor subtypes provide useful prognostic evidence in the short term but probably not in the long term due to their potential variability over time
- REM sleep behavior disorder represents at a high percentage an early stage of α-synucleinopathy
- The presence of REM sleep behavior disorder as a promotor symptom in PD is associated with more severe autonomic dysfunction and faster cognitive decline
- Hyposmia is more common in idiopathic PD than in atypical parkinsonism
- Orthostatic hypotension preceding parkinsonism and cognitive decline supports the diagnosis of multiple system atrophy
- The pattern of cognitive decline contributes to the differential diagnosis among atypical parkinsonian syndrom

Introduction

Despite the significant advances in the identification of laboratory, imaging and genetic biomarkers, the diagnosis of Parkinson's disease (PD) and atypical parkinsonism is still heavily relied on clinical examination. However, the diagnostic procedure can be proved demanding due to a substantial overlap among parkinsonian syndromes, with misdiagnosis rates even by movement disorders experts approaching the percent of 20% [1]. The neurodegenerative process that underlies these diseases is known to start many years before the emergence of motor symptoms [2] and specific non-motor symptoms that arise from this long-term procedure serve either as supportive criteria of the diagnosis of PD or as red flags for atypical parkinsonism. The identification of subtle motor symptoms is also crucial for the early and precise diagnosis. In the pursuit of precision medicine and personalized therapeutic approaches, clinical biomarkers have emerged as promising candidates for unraveling the intricate pathophysiology of PD and atypical parkinsonism.

This paper aims to depict the evolving landscape of clinical biomarkers in the context of PD and atypical parkinsonism. By delving into the current state of

knowledge surrounding these biomarkers, we seek to elucidate their potential role in not only diagnostic precision but also in prognostication, disease monitoring, and targeted therapeutic interventions.

Movement Disorders Society research criteria for prodromal PD

In 2015 the Movement Disorders Society published the first research criteria for prodromal PD [3]. Using a Bayesian classifier approach, the study provided likelihood ratios (LRs) for specific markers supposed to increase the probability for prodromal PD. The marker with the highest positive likelihood ratio was found to be polysomnography-proven REM sleep behavior disorder (LR 130), followed by a clearly abnormal dopaminergic PET/SPECT (LR 40), and possible subthreshold parkinsonism (LR 10). Other factors that were reported to increase the probability of prodromal PD included the presence of a sibling with PD with age at onset <50, olfactory loss, constipation, excessive daytime somnolence, symptomatic hypotension, severe erective dysfunction, depression, pesticide or solvent exposure, nonuse of caffeine, and male sex. In 2019 the criteria were updated, providing updated predictive values of the markers referred in the original criteria, while four new markers were also introduced, which included diabetes mellitus, cognitive deficits, physical inactivity, and low plasma urate levels in men [4].

Age of onset in PD

Age of onset was among the first clinical characteristics that were hypothesized to associate with different disease phenotypes and prognosis. The age of 40 was initially set as the cut-off to define young-onset PD (YOPD) but most recent studies have used a cut-off of 50 or even 55 years of age [5]. YOPD represents a maximum percentage of 10% of the entire PD population and a considerable variability exists within this group due to different genetic substrate etc. Despite this rather small sample size and the existing heterogeneity, YOPD has been associated in general with a favorable prognosis regarding both the motor and the non-motor part of the disease. Specifically, the large body of literature suggests that YOPD patients exhibit slower disease progression with less postural instability and autonomic dysfunction, more preserved cognitive function and less severe hyposmia [5,6]. In the study of Pagano et al [7] that used a dataset of Parkinson Progression Markers Initiative (PPMI), greater dopaminergic dysfunction on DaTSCAN and greater reduction of CSF α-syn and t-tau levels were observed in patients with PD of later onset. In the same study, the Hoehn and Yahr stage and the unified Parkinson's disease rating scale (UPDRS)-part III score was higher at the time of diagnosis in older patients. On the other hand, YOPD patients tend to develop earlier motor complications and dyskinesias and the impact of the disease on quality of life is more severe due to possible implications on employment, higher rates of depression and anxiety and more affected emotional well-being [5,6]. The frequency of RBD and other sleep problems was found to be similar among PD patients regardless of the age of disease onset [7]. At any case, comparisons of clinical characteristics according to age at disease onset should always be made under the light of changes that accompany the normal aging. To end with, the study of Kempster et al [8] found that YOPD patients delay to reach the disability milestones that define the advanced stage PD, but once this stage is reached the progression accelerates to match that of the older onset patients.

Motor subtype

The predominance of specific motor symptoms was also very early acknowledged as a valuable criterion to categorize patients into groups with different prognosis. The akinetic-rigid and tremor-dominant subtypes were the first motor subtypes described. The development of UPDRS allowed a more thorough classification, that included the tremor-dominant, postural instability and gait difficulty (PIGD), the axial-dominant, appendicular-dominant and rigidity dominant subtypes. However, the appendicular-dominant and rigidity dominant subtypes were largely replaced in clinical practice by the intermediate type. Patients with tremor-dominant phenotype are generally considered to present a more benign course with slower disease progression and lower rates of hyposmia, dementia, depression and other non-motor symptoms than those of PIGD subtype [6]. The term "benign tremulous parkinsonism" has been also used to describe a type of the disease with tremor predominance, absence of gait disorder and a relatively mild progression over many years [9]. Nevertheless, the predictive value of a motor subtype is compromised by its possible instability in the long term, as some longitudinal studies have provided related evidence. Specifically, the study of Simuni et al [10] showed that after one year of the diagnosis 39% of the patients with PIGD subtype and 18% of the tremor-dominant subtype shifted to another subtype, while another more recent study with a follow-duration of 3 years reported a conversion rate of 50% and 38% for PIGD and tremor-dominant patients respectively [11]. As additional factors are involved in the general prognosis of PD, in 2017 Fereshtehnejad et al [12] using data from PPMI proposed a new subtyping method encompassing both motor and non-motor features. A motor summary score and three non-motor characteristics (cognitive impairment, RBD, and dysautonomia) were used for the classification to "mild motor-prodominant",

"diffuse malignant" and "intermediate" subtype. During the follow-up period, patients classified under "diffuse malignant" and "intermediate" subtypes showed a significantly greater and more rapid progression of motor symptoms, as assessed by UPDRS-Part II. A similar progression of non-motor symptoms assessed with UPDRS – Part I was also observed. Particularly within the "diffuse malignant" subtype, the steeper decline was observed in cognition and in the activities of daily living.

REM Sleep Behavior Disorder (RBD)

RBD is a parasomnia characterized by dream-enacting behaviors. It is attributed to impairment of locus subcoeruleus and other pontine structures including magnocellular reticular formation as these nuclei are involved in the regulation of sleep-wake cycle and the maintenance of muscle atonia during REM sleep. Post-mortem studies on patients with idiopathic RBD have identified α-synouclein pathology in these areas [13] indicating RBD as a prodromal manifestation of α-synoucleinopathies. Multiple cohort studies have also reported a percentage of 73.5-92.5% of idiopathic RBD converting to PD, DLB, or MSA within 10-14 years [14,15]. Under this prism RBD has been proposed as the strongest predictor of α-synoucleinopathies and contributes significantly to their differentiation from tauopathies. The percentage of idiopathic RBD cases that convert to PD or DLB is similar, while phenoconversion to MSA is more unusual (about 5% of total RBD cases). RBD is such a rare phenomenon in PSP and CBD that the occurrence of RBD in patients with other clinical characteristics suggestive of CBS has been attributed to diffuse Lewy body disease manifesting as CBS [16]. Moreover, significantly reduced cardiac MIBG uptake, consistent with sympathetic denervation of the same magnitude as that in patients with diagnosed PD has been observed in subjects with idiopathic RBD [17]. Notably, a history of RBD preceding parkinsonism is also used to distinguish body-first PD from brain-first PD as discussed more extensively below.

Olfactory dysfunction

Hyposmia presenting as impairment of odor detection, odor identification, odor discrimination and odor-recognition memory has been recognized as a common feature of PD and may antedate clinical diagnosis by even more than 20 years [18]. Borghammer and Van Den Berge [19] recently hypothesized that the olfactory bulb might be an entry point of pathogens and toxins that initiate the α-synoulein pathology and then swallowed nasal secretions expose gastrointestinal lining to the same pathogens. Odor identification threshold corresponds to the level at which subjects are able not only to detect but also to recognize a stimulus. Odor identification testing has been found to provide high diagnostic accuracy in distinguishing PD patients from healthy individuals. Marked deficits in odor identification have been also associated with impaired visuospatial and executive function, revealing a potential of hyposmia for its use as biomarker of PD-related cognitive decline [20]. Cholinergic denervation in temporolimbic areas is strongly associated with both of hyposmia and cognitive impairment and appears to play and an important role in the correlation of these conditions along with degenerative changes in the orbitofrontal cortex [21]. Moreover, post-mortem studies have shown that the degree of olfactory impairment does not reflect the degree of α-synouclein pathology in the olfactory bulb but is mostly associated with a more widespread cortical and subcortical α-synouclein pathology [22,23]. Hyposmia is also a significant predictor of phenoconversion in patients with idiopathic RBD [15]. Furthermore, in the study of Kim et al [24] MIBG uptake was independently related to hyposmia in de novo PD patients. Olfactory deficits are less prominent in MSA than PD and affect less than 25% of the patients [25]. Similarly, hyposmia is infrequent in PSP and CBD. In the study of Shill et al [26] a sensitivity of 93.4% and specificity of 64.7% was suggested for PSP among patients presenting with parkinsonism and normosmia. The use of standardized olfactory tests and consideration of confounding factors including age increase the prognostic accuracy of hyposmia.

Oculomotor dysfunction

Oculomotor disturbances are mostly prominent in PSP with the typical vertical supranuclear gaze palsy combined with astonished facial expression. Macro square wave jerks, curved vertical saccades and slow velocity of vertical saccades are also strongly suggestive of PSP. Eyelid opening apraxia is possibly indicative for either PSP or CBS. Apraxia of saccades and slow velocity of vertical saccades can also be present in CBS. Hypermetric saccades, reduced VOR-suppression and saccadic eye sequences are probably indicative for MSA. Additional features of MSA, despite more infrequent can be the presence of downbeat or rebound nystagmus [27]. DLB has not been linked with any specific oculomotor dysfunction.

Orthostatic hypotension

Individuals with orthostatic hypotension have been found to run an about 2-fold higher risk of PD than healthy population. In a longitudinal study performed at an autonomic disorders clinic, it was found that 19% of patients with orthostatic hypotension and 25% of patients with delayed orthostatic hypotension converted to an α-synoucleinopathy within 10 years of diagnosis [28]. In a study that compared patients with PD and atypical parkinsonian syndromes,

the prevalence of orthostatic hypotension was 81% among MSA patients and lower in the other patient groups (PD 18%, DLB 31%, PSP 26%, CBD 7%) [29]. Despite the occurrence of orthostatic hypotension at a considerable percentage in almost all types of degenerative parkinsonism, its early manifestation is mostly supportive of MSA since in it typically antedates motor symptoms in PD and cognitive impairment in DLB [30].

Oropharyngeal dysfunction

Inspiratory stridor, usually nocturnal, is a symptom highly specific for MSA. Due to its high positive predictive value, it has been included in the diagnostic criteria as additional feature of possible MSA. Moreover, it has been proposed that the early occurrence of laryngeal stridor contributes to reduced survival. On the other hand, dysphagia can present in either PD, MSA-P or PSP patients with the proposed shared mechanism being the degeneration of the cholinergic neurons of the pedunculopontine nucleus [31]. Early dysphagia argues against PD and indicates additional dysfunction of brainstem related to atypical parkinsonism syndromes.

Neuropsychiatric symptoms

Obvious cognitive dysfunction should not be an early symptom in PD but can be a key feature in the diagnosis and differential diagnosis of atypical parkinsonian syndromes. Regarding PSP, executive deficits are typically prominent at the time of diagnosis and frequently precede it up to three years [32]. In the study of Rittman et al [33] impairment in verbal fluency was found to strikingly distinguish PSP from PD patients. Progressive non-fluent aphasia can be a presentation of either PSP or CBD underlying pathology [34]. Apraxia of speech, agraphia and social cognition impairment are particularly supportive of CBD [35]. The cognitive pattern of the prodromal phase of DLB on the other hand typically includes attention, executive and visual processing deficits and relatively preserved memory and object naming. Depression is an independent predictor of quality of life in all parkinsonian syndromes and is associated with a higher frequency of other non-motor symptoms such as sleep disturbances, anxiety, and cognitive decline [36]. The prevalence of depression has been found to be significantly higher in MSA and PSP compared to PD and other parkinsonian syndromes [35]. However, in a study that investigated non-motor symptoms preceding cognitive impairment in DLB, about one third of the patients had depressive symptoms with a mean duration of 4.5 to 10.7 years [30]. Apathy is also most frequent in PSP and an apathetic profile has been associated with increased mortality among these patients [37]. Among PSP subtypes, the PSP-RS subtype was found in a comparative study to comprise in total more neuropsychological and neurobehavioural deficits than the PSP-P subtype [38]. Delirium and visual hallucinations or even depression and anxiety can occur during the predementia stage of DLB and correspond to the delirium-onset and psychiatric-onset types of prodromal DLB [39].

Brain-first and body-first model

The brain-first and body-first hypothesis arose from the observation that Braak's theory was found to be not valid for all PD cases at post-mortem [40]. Specifically, some cases of PD and DLB were found to lack Lewy pathology in dorsal motor nucleus of the vagus nerve despite presenting pathology in substantia nigra and other structures corresponding to higher Braak stages [41]. Moreover, in some patients RBD is not prominent at the time of diagnosis but appears during the course of the disease. Third, severe autonomic dysfunction is observed in individuals with idiopathic RBD but a significant percentage of early PD patients show normal cardiac sympathetic innervation with deterioration at more advanced stages of the disease [17, 42,43]. Considering the above findings, it was hypothesized that PD comprises two subtypes according to the initial origin of α-synouclein pathology [40]. The two subtypes are supposed to differ at the early stages of the disease in some clinical and imaging markers but in later stages the two subtypes converge due to the spreading of α-synouclein pathology. The presence of RBD was proposed as the key clinical symptom to differentiate the two subtypes. The body-first subtype is defined by an established history of RBD preceding the symptoms of parkinsonism. On the other side, brain-first subtype is characterized by nigrostriatal dopaminergic dysfunction prior to involvement of the autonomic peripheral nervous system and patients under this subtype should not present RBD at the time of PD diagnosis. The early involvement of the autonomic system and lower brainstem structures in the body-first patients manifests in general with a higher burden of autonomic symptoms including orthostatic hypotension, constipation, urinary and sexual dysfunction. Moreover, body-first patients present higher rates of cognitive decline and a more rapid progression to dementia than patients of the brain-first subtype. A higher frequency of depression has been also found by some studies in the body-first subtype but the link between antidepressant use and RBD demasking should be taken into account in the interpretation of such findings. A tremor-dominant subtype has been reported to be more pronounced in brain-first patients. However literature is still inconclusive on the ability of brain-first and body-first model to predict accurately the PD motor subtype.

"One size does not fit all" in PD treatment

Despite the concept of precision medicine is relatively new in PD, a personalized medicine strategy according to basic patient characteristics is already followed by the majority of neurologists. The spectrum of these clinical characteristics that define clinical decisions is constantly growing. Age is usually the first characteristic that attending physician considers in order to decide a treatment plan. To begin with, the use of dopamine agonists is typically limited in older patients due to the high frequency of side-effects. Deep-brain stimulation is also usually avoided in patients of more than 70 years of age. At any case we suggest that differences between "chronological" and "biological" aging should be considered at every single patient, as well as possible comorbidities (e.g. diabetes mellitus with secondary autonomic dysfunction, osteoporosis with increased risk of fracture in case of fall, hyperomocysteinaemia possibly worsened by high dose levodopa therapy). Personality traits that predispose to impulse control disorders, dopamine dysregulation and punding should also be taken into account, with such including high alcohol consumption, novelty seeking behavior and history of substance or drug addiction [44]. Certain lifestyle and daily routine should also be considered particularly for younger patients for which side effects such as sedation during working hours can be incapacitating, while the opportunity of rescue therapy should also be offered [45].

Conclusion

The incorporation of biomarkers in Parkinson's disease research and clinical practice serves several crucial purposes. It facilitates a deeper comprehension of mechanisms, aids in the design of optimal treatment strategies, helps in avoiding medications with a high likelihood of side effects, and enables a more precise guidance to patients and caregivers. The Movement disorders criteria for prodromal PD provide a framework for the identification of individuals with early signs of PD, even during the crucial for research premotor phase. The brain-first and body-first model, by categorizing the PD patients into two different categories according to their initial symptoms provides prognostic clues since the body-first subtype has been associated with a higher burden of autonomic symptoms and more rapid cognitive decline.RBD is a biomarker with high prognostic value that tends to be considered as a stage of an emerging α-synoucleinopathy. The use of additional biomarkers such as olfactory disruption, orthostatic hypotension and cognitive decline can assist the differential diagnosis among α-synoucleinopathies. Oculomotor disturbance and specific patterns of neuropsychiatric manifestations are particularly helpful in the early diagnosis of PSP and CBD. PD motor subtypes provide insights into disease prognosis, but their long-term stability may be limited. Finally, age, comorbidities, personality traits, and lifestyle are recognized as critical factors influencing treatment decisions in PD. Research on several promising candidate markers may improve the accuracy in the early diagnosis and prognosis of parkinsonian syndromes.

References

[1] Rizzo G, Copetti M, Arcuti S, Martino D, Fontana A, Logroscino G. Accuracy of clinical diagnosis of Parkinson disease: A systematic review and meta-analysis. ***Neurology***. 2016;86(6):566-576

[2] Kalia LV, Lang AE. Parkinson's disease. ***Lancet***. 2015;386(9996):896-912.

[3] Berg D, Postuma RB, Adler CH, Bloem BR, Chan P, Dubois B, et al. MDS research criteria for prodromal Parkinson's disease. Mov Disord. 2015;30(12):1600-1611

[4] Heinzel S, Berg D, Gasser T, Chen H, Yao C, Postuma RB; MDS Task Force on the Definition of Parkinson's Disease. Update of the MDS research criteria for prodromal Parkinson's disease. Mov Disord. 2019;34(10):1464-1470

[5] Schrag A, Schott JM. Epidemiological, clinical, and genetic characteristics of early-onset parkinsonism. ***Lancet Neurol***. 2006;5(4):355-363

[6] Fereshtehnejad SM, Postuma RB. Subtypes of Parkinson's Disease: What Do They Tell Us About Disease Progression?. ***Curr Neurol Neurosci Rep***. 2017;17(4):34

[7] Pagano G, Ferrara N, Brooks DJ, Pavese N. Age at onset and Parkinson disease phenotype. ***Neurology***. 2016;86(15):1400-1407

[8] Kempster PA, O'Sullivan SS, Holton JL, Revesz T, Lees AJ. Relationships between age and late progression of Parkinson's disease: a clinico-pathological study. ***Brain***. 2010;133(Pt 6):1755-1762

[9] Josephs KA, Matsumoto JY, Ahlskog JE. Benign tremulous parkin- sonism. Arch Neurol. 2006;63(3):354–357

[10] Simuni T, Caspell-Garcia C, Coffey C, Lasch S, Tanner C, Marek K, et al. How stable are Parkinson's disease subtypes in de novo patients: analysis of the PPMI cohort? Parkinsonism Relat Disord. 2016;28:62–67

[11] Kohat AK, Ng SYE, Wong ASY, Chia NSY, Choi X, Heng DL, et al. Stability of MDS-UPDRS Motor Subtypes Over Three Years in Early Parkinson's Disease. ***Front Neurol***. 2021;12:704906

[12] Fereshtehnejad SM, Zeighami Y, Dagher A, Postuma RB. Clinical criteria for subtyping Parkinson's disease: biomarkers and longitudinal

progression. ***Brain***. 2017;140(7):1959-1976
[13] Turner RS, D'Amato CJ, Chervin RD, Blaivas M. The pathology of REM sleep behavior disorder with comorbid Lewy body dementia. ***Neurology***. 2000;55(11):1730-1732
[14] Iranzo A, Fernández-Arcos A, Tolosa E, Serradell M, Molinuevo JL, Valldeoriola F, et al. Neurodegenerative disorder risk in idiopathic REM sleep behavior disorder: study in 174 patients. ***PLoS One***. 2014;9(2):e89741
[15] Postuma RB, Iranzo A, Hu M, Högl B, Boeve BF, Manni R, et al. Risk and predictors of dementia and parkinsonism in idiopathic REM sleep behaviour disorder: a multicentre study. Brain. 2019;142(3):744-759
[16] Kasanuki K, Josephs KA, Ferman TJ, Murray ME, Koga S, Konno T, et al. Diffuse Lewy body disease manifesting as corticobasal syndrome: A rare form of Lewy body disease [published correction appears in Neurology. 2018 Nov 20;91(21):986]. ***Neurology***. 2018;91(3):e268-e279
[17] Miyamoto T, Miyamoto M, Inoue Y, Usui Y, Suzuki K, Hirata K. Reduced cardiac 123I-MIBG scintigraphy in idiopathic REM sleep behavior disorder. ***Neurology***. 2006;67(12):2236-2238
[18] Fereshtehnejad SM, Yao C, Pelletier A, Montplaisir JY, Gagnon JF, Postuma RB. Evolution of prodromal Parkinson's disease and dementia with Lewy bodies: a prospective study. ***Brain***. 2019;142(7):2051-2067
[19] Borghammer P, Van Den Berge N. Brain-First versus Gut-First Parkinson's Disease: A Hypothesis. ***J Parkinsons Dis***. 2019;9(s2):S281-S295
[20] Mao CJ, Wang F, Chen JP, Yang YP, Chen J, Huang JY, et al. Odor selectivity of hyposmia and cognitive impairment in patients with Parkinson's disease. ***Clin Interv Aging***. 2017;12:1637-1644
[21] Lee JE, Cho KH, Ham JH, Song SK, Sohn YH, Lee PH. Olfactory performance acts as a cognitive reserve in non-demented patients with Parkinson's disease. ***Parkinsonism Relat Disord***. 2014;20(2):186-191
[22] Nag S, Yu L, VanderHorst VG, Schneider JA, Bennett DA, Buchman AS, et al. Neocortical Lewy bodies are associated with impaired odor identification in community-dwelling elders without clinical PD. ***J Neurol***. 2019;266(12):3108-3118.
[23] Tremblay C, Serrano GE, Intorcia AJ, Sue LI, Wilson JR, Adler CH, et al. Effect of olfactory bulb pathology on olfactory function in normal aging. ***Brain Pathol***. 2022;32(5):e13075
[24] Kim JS, Park HE, Park IS, Oh YS, Ryu DW, Song IU, et al. Normal 'heart' in Parkinson's disease: is this a distinct clinical phenotype?. ***Eur J Neurol***. 2017;24(2):349-356
[25] Zhang L, Cao B, Ou R, Wei QQ, Zhao B, Yang J, et al. Non-motor symptoms and the quality of life in multiple system atrophy with different subtypes. ***Parkinsonism Relat Disord.*** 2017;35:63-68
[26] Shill HA, Zhang N, Driver-Dunckley E, Mehta S, Adler CH, Beach TG. Olfaction in neuropathologically defined progressive supranuclear palsy. ***Mov Disord***. 2021;36(7):1700–1704
[27] Schröter N, van Eimeren T, Classen J, Levin J, Redecker C, Wolz M, et al. Significance of clinical symptoms and red flags in early differential diagnosis of Parkinson's disease and atypical Parkinsonian syndromes. ***J Neural Transm (Vienna)***. 2023;130(6):839-846
[28] Gibbons CH, Freeman R. Clinical implications of delayed orthostatic hypotension: A 10-year follow-up study. ***Neurology***. 2015;85(16):1362-1367
[29] Ha AD, Brown CH, York MK, Jankovic J. The prevalence of symptomatic orthostatic hypotension in patients with Parkinson's disease and atypical parkinsonism. ***Parkinsonism Relat Disord***. 2011;17(8):625-628
[30] Chiba Y, Fujishiro H, Iseki E, Ota K, Kasanuki K, Hirayasu Y, Satoa K. Retrospective survey of prodromal symptoms in dementia with Lewy bodies: comparison with Alzheimer's disease. Dement Geriatr Cogn Disord. 2012;33(4):273-81.
[31] Alfonsi E, Versino M, Merlo IM, Pacchetti C, Martignoni E, Bertino G, et al. Electrophysiologic patterns of oral-pharyngeal swallowing in parkinsonian syndromes. ***Neurology***. 2007;68(8):583-589
[32] Street D, Whiteside D, Rittman T, Rowe JB. Prediagnostic Progressive Supranuclear Palsy - Insights from the UK Biobank. ***Parkinsonism Relat Disord***. 2022;95:59-64
[33] Rittman T, Ghosh BC, McColgan P, Breen DP, Evans J, Williams-Gray CH, et al. The Addenbrooke's Cognitive Examination for the differential diagnosis and longitudinal assessment of patients with parkinsonian disorders. ***J Neurol Neurosurg Psychiatry***. 2013;84(5):544-551
[34] Santos-Santos MA, Mandelli ML, Binney RJ, Ogar J, Wilson SM, Henry ML, et al. Features of Patients With Nonfluent/Agrammatic Primary Progressive Aphasia With Underlying Progressive Supranuclear Palsy Pathology or Corticobasal Degeneration. JAMA Neurol. 2016;73(6):733-742
[35] Ananthavarathan P, Patel B, Peeros S, Obrocki R, Malek N. Neurological update: non-motor symptoms in atypical parkinsonian syndromes. J Neurol. 2023;270(9):4558-4578
[36] Dissanayaka NN, Sellbach A, Silburn PA,

O'Sullivan JD, Marsh R, Mellick GD. Factors associated with depression in Parkinson's disease. J Affect Disord 2011;132(1–2):82–88.

[37] Lansdall CJ, Coyle-Gilchrist ITS, Vázquez Rodríguez P, Wilcox A, Wehmann E, Robbins TW, et al. Prognostic importance of apathy in syndromes associated with frontotemporal lobar degeneration. Neurology. 2019;92(14):e1547-e1557

[38] Srulijes K, Mallien G, Bauer S, Dietzel E, Gröger A, Ebersbach G, et al. In vivo comparison of Richardson's syndrome and progressive supranuclear palsy-parkinsonism. J Neural Transm (Vienna). 2011;118(8):1191-1197

[39] McKeith IG, Ferman TJ, Thomas AJ, Blanc F, Boeve BF, Fujishiro H, et al. Research criteria for the diagnosis of prodromal dementia with Lewy bodies. Neurology. 2020 Apr 28;94(17):743-755

[40] Horsager J, Knudsen K, Sommerauer M. Clinical and imaging evidence of brain-first and body-first Parkinson's disease. ***Neurobiol Dis***. 2022;164:105626.

[41] Jellinger KA. Is Braak staging valid for all types of Parkinson's disease?. ***J Neural Transm (Vienna)***. 2019;126(4):423-431.

[42] Kashihara K, Imamura T, Shinya T. Cardiac 123I-MIBG uptake is reduced more markedly in patients with REM sleep behavior disorder than in those with early stage Parkinson's disease. ***Parkinsonism Relat Disord***. 2010;16(4):252-255

[43] Hamada K , Hirayama M , Watanabe H , Kobayashi R , Ito H , Ieda T, et al. Onset age and severity of motor impairment are associated with reduction of myocardial 123I-MIBG uptake in Parkinson's disease***. J Neurol Neurosurg Psychiatry*** 2003;74:423–426

[44] Katzenschlagger R, Evans A. Impulse dyscontrol and dopamine dysregulation syndrome. In: Chaudhuri KR, Tolosa E, Schapira AHV, Poewe W, eds. Non-motor Symptoms of Parkinson's Disease. 2nd ed. Oxford, UK: Oxford University Press 2014;420- 435

[45] Titova N, Chaudhuri KR. Personalized medicine in Parkinson's disease: Time to be precise. ***Mov Disord***. 2017;32(8):1147-1154