Mild parkinsonian signs: the interface between ageing and Parkinson's disease

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Abstract
Mild Parkinsonian Signs (MPS) describe a spectrum that exists between the expected motor decline of normal ageing and a more serious motor deterioration resulting from Parkinson's disease (PD) and neurodegeneration. Although MPS are a feature of the prodromal stage of PD, their formal definition is unclear and still relies somewhat on conventional clinical criteria for PD. This review will summarise the early motor features of PD and methods of assessment, from conventional clinical scales to advances in quantitative measures. Finally, the boundaries of motor decline as part of normal ageing and pathological neurodegeneration will be discussed.

Introduction

Mild Parkinsonian Signs (MPS) describe the motor spectrum that spans from normal ageing to the early stages of Parkinson's disease (PD).[1] A variety of other terms have been used to describe these features, such as subthreshold parkinsonism and subtle motor/parkinsonian signs. PD is generally a slowly progressive degenerative disease and because it is diagnosed on the basis of established and typical motor features, subtle motor manifestations may be apparent years before the diagnosis.[2] However, many MPS are not specific to PD and may not progress in the same manner; substantial overlap with normal ageing is to be expected.[3]

The phase before a diagnosis of PD has often been referred to as the 'pre-motor' phase, but the truth is that motor features in the pre-diagnostic phase have received surprisingly little attention compared to non-motor features.4 As such, it is difficult to say whether there is a definite 'pre-motor' phase, when objective motor dysfunction has been observed in many prodromal settings.[5-8] Although several studies have objectively documented motor markers of neurodegeneration in PD (see Table 1), there is still controversy about when they exactly start and how reliably they can be detected.

Defining MPS

MPS in the elderly population without PD cluster into four domains: bradykinesia, tremor rigidity, and gait and posture.[9,10] They are known to be present at early stages of PD (see Figure). We will focus on these domains one by one.

Bradykinesia

Bradykinesia is the only clinical sign that is required to be present in every patient with PD according to the Queen Square Brain Bank Criteria.[11] It is described as the 'slowness of movement initiation with progressive reduction in speed and amplitude (sequence effect) of repetitive actions'.[12] It is interpreted by patients as clumsiness or weakness when performing fine and repetitive movements. Compensatory mechanisms help to maintain stable dopaminergic transmission and motor function at early stages of PD.[13] However, these compensatory mechanisms can fail when more challenging tasks are performed with associated 'unmasking' of subtle motor deficits.[4]

Changes in handwriting are thought to be an early sign of PD,[14] with micrographia (gradual reduction in letter size) being an example of 'real-world' bradykinesia.[15] In some studies, micrographia has been documented up to four years before diagnosis.[16] Recently, the term 'dysgraphia' has been introduced. It goes further than micrographia and includes other kinetic variables apart from the script size, such as velocity, fluency, and sentence slope which may help to detect even earlier changes in handwriting.[14]

Similar to handwriting, speech is an automated task that requires a high level of motor coordination. Abnormalities may appear at early stages of PD; hypophonia, poor articulation, and hesitation are some of the manifestations of vocal hypokinesia.[17] The Oxford Discovery Parkinson's Cohort (OPDC) included smartphone-based voice analysis as part of a motor battery. Speech and tremor were found to be the most discriminatory markers between patients with PD, patients with REM-sleep behaviour disorder (RBD) and controls.[18] In a separate case-control study, footage of video recordings from interviews and press conferences on television were used to extract acoustic measurements and demonstrated changes in voice frequency up to five years prior to diagnosis of PD.[19] A reduction in spontaneous (involuntary) eye-blinking and

Table 1. Summary of remarkable but non-exhaustive list of epidemiological studies proving the existence of motor prodromes

Study	Design	Follow-up	Sample size	Age (years)	Motor assessment	Findings
Rotterdam [56]	Nested case-control	23 years	1090 (PD) 109(AMC)	78±7(SD)	Clinical interviews Medical record General impression	Motor progression (<8 years before diagnosis): slowness > tremor > rigidity > postural abnormalities > falls
Bruneck cohort [57]	Longitudinal cohort	5 years	284(MPS+) 109(MPS-)	66.5±7.8 (SD)	UPDRS-III	MPS were associated to SN-hyperechogenicity (OR: 2.0), hyposmia (OR: 1.6), but not with VRF
TREND cohort [58]	Cross-sectional	NA	698	64	UPDRS-III Motor symptoms questionnaire*	Positive relationship between motor score and number of non-motor markers (depression, anxiety and probable RBD)
PREDICT-PD [7]	Cross-sectional	NA	74(HR) 111(LR)	HR:72.2 (69.0- 75.5)	MDS-UPDRS-III, Global impression**	HR: significant higher motor scores than LR HR: more likely to fulfil MPS criteria Risk estimates predicted motor scores
THIN database [25]	Longitudinal Case-control	17 years	8166 (PD) 46755 (AMC)	75(68–81)	Medical records	Tremor: the most common motor marker (RR:7.6 at 10 years, RR: 13.7 at 5 years before diagnosis) Balance impairment and rigidity appeared 2-5 years before diagnosis
PARS cohort [59]	Longitudinal cohort	8 years	185 (hyposmic)	66.6 (SD 5.7)	UPDRS-III	Higher motor score (2.7 vs 1.3) and rate of phenoconversion to PD in subjects with abnormal dopamine transporter scan

TREND: Tübinger evaluation of Risk factors for Early detection of NeuroDegeneration, THIN: The UK Health Improvement Network,
PARS: Parkinson Associated Risk Syndrome, NA: not-applicable, AMC: age-matched controls, MPS: mild parkinsonian signs, HR: higher risk (above the 15th centile of risk estimates), LR: lower risk (below the 85th centile), SD: standard deviation, OR: odds ratio, RR: relative risk, VRF: vascular risk factors,
RBD: REM-sleep behaviour disorder,
* Motor questionnaire: sialorrhea, hypophonia, micrographia, slowing of fine hand movements, arm swing reduction, dysarthria, and rest tremor,
**Global impression scale: 0—normal, 1—unspecific minor abnormality, 2—subtle signs associated with PD, 3—possible early PD, 4—probable PD

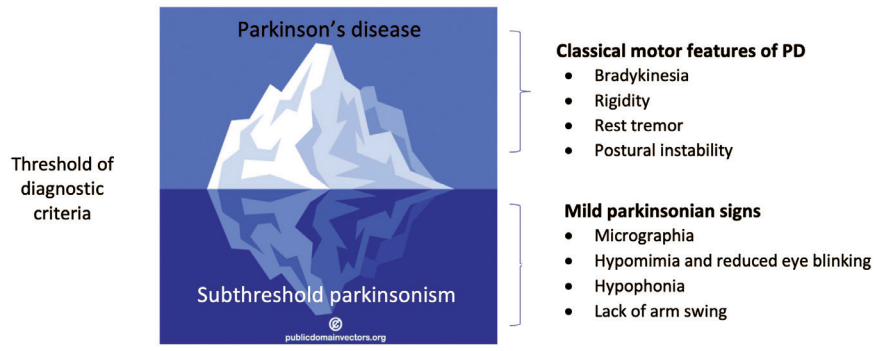

Figure. The iceberg of motor domain during the neurodegeneration process. Post-diagnostic phase: easily noticeable features on the top of the iceberg. Pre-diagnostic phase: subthreshold parkinsonism with hidden motor features on the bottom of the iceberg.

lack of normal facial responsiveness are characteristic features of hypomimia, which are often described as early motor signs of PD.[20] Unlike spontaneous blinking, rapid voluntary blinking, has been poorly studied in PD, but a recent study suggested that it might be an early marker.[21]

Tremor

A self-limiting, stress-induced bout of tremor can be the first symptom of PD.[22] In the absence of tremor at rest, the outstretching of hands and a short intermission followed by a re-emergent postural tremor, may also be evident at the early stages of PD.[23] Numerous studies support the idea that tremor in general is an early feature of PD. For example, a longitudinal study conducted in central Spain showed that after three-years of follow-up, people with 'essential tremor' had four times more likelihood of being diagnosed with PD than those without tremor.[24] Similar results were found in another longitudinal study, with isolated action and rest tremor associated with a doubling of the risk of PD.[5] In analyses using data from the UK Health Improvement Network (THIN) database, 8166 PD patients were compared with 46455 healthy controls, and revealed that tremor was the most common and earliest motor marker reported in primary care with a subsequent diagnosis of PD up to ten years later.[25] Essential tremor, which increases in prevalence and severity with age, might account for some of the tremor which precedes a diagnosis of PD. Epidemiological studies support this idea and find that essential tremor can be associated with PD, mild cognitive impairment (MCI) and dementia.[26]

Rigidity

Cogwheel rigidity is a distinctive feature of PD.[23] In the study undertaken using the THIN database (see above), rigidity and shoulder pain were features that were apparent two years before PD diagnosis.[25] Moreover, rigidity and changes in posture were the most prevalent signs in a group of elderly people with MPS studied by Louis and colleagues, with 24% of subjects presenting with isolated rigidity.[27] These results may explain the weighting of rigidity in MPS criteria defined by the same authors, with five out of ten items being related

to rigidity. However, rigidity is not always easy to detect. It may manifest through non-specific symptoms such as shoulder pain, stiffness, and postural abnormalities when resting or walking. To date there is a lack of tools to objectively assess rigidity beyond traditional clinical examination.

Posture and Gait

The prevalence of gait abnormalities increases with age, but some patterns have been shown to be more PD-specific.[28] On examination, a classic early parkinsonism posture when walking includes reduced arm swing, with a flexed elbow and a hand held in a flexed-adducted position. Kinnier Wilson was one of the first authors to introduce the concept of motor symptoms preceding clinical diagnosis. He described that when seated or standing, patients may maintain the same position without making the normal adjustments which one sees in healthy people (Kinnier Wilson, Neurology; Volume II, 1940). Using wearable technology for objective gait analysis, Mirelman and colleagues found that arm swing asymmetry and loss of limb coordination appeared to be less associated with ageing and more likely to occur in early PD.[29]

Postural instability, so long considered the fourth cardinal sign in the Queen Square Brain Bank Criteria, was excluded from the Movement Disorders Society Criteria for PD that were published in 2015.[30] This was mainly because early postural instability should make clinicians consider the possibility of an atypical parkinsonian disorder.

It is not surprising that gait patterns, as an automated and rhythmic task, may yield clear indications of MPS. These include the emergence of step-to-step variability, arm swing asymmetry and reduced truncal rotation.[31] At the early stages of PD, when compensatory mechanisms may be present, dual-tasking during walking is a strategy to make MPS more prominent.[32,33] Walking during simple and challenging conditions was evaluated in a cohort of 696 healthy controls followed up between 2009 and 2016. It was found that step-to-step time variability and gait asymmetry were the best parameters preceding PD diagnosis up to four years.[33] These results were in line with a longitudinal study in RBD patients using UPDRS and the Timed Up and Go test showing that gait abnormalities were present between 4-6 years prior to the diagnosis of an overt parkinsonian disorder.[34]

The contribution of cerebrovascular disease to MPS in the ageing population has been studied. For example, brain autopsies were examined from 418 donors in the Religious Order Study cohort who had been evaluated during life for parkinsonian signs.[35] Macroscopic infarcts were associated with higher global parkinsonian scores. In particular, subcortical infarcts (macroscopic infarcts and multiple microinfarcts) were related to gait impairment. These associations did not change after adjusting for the presence of dementia.

The motor continuum from natural ageing to neurodegeneration

Parkinsonian signs are common in the elderly. The prevalence of MPS in population-based studies ranges from 30 to 40% in elderly people which is much higher than the prevalence of PD.[27] For example, in one study in a community setting, MPS were found in more than one third of individuals over the age of 65 years.[28] This suggests that MPS cannot be exclusively considered part of the prodromal spectrum of PD and they may evolve into other conditions with a common denominator of nigrostriatal dysfunction. Numerous studies, which were summarised in a review published by Louis et al, have demonstrated that there is an appreciable increase in the incidence of Alzheimer's disease (AD) in people with MPS.[3] In one study, a third of patients with AD were found to have parkinsonism, which in turn was associated with the presence of neurofibrillary tangles in the substantia nigra.[36] On the other hand, MPS may barely progress over time. This observation was made in one longitudinal cohort where one quarter of individuals with MPS remained stable.[37] Based on the multiple trajectories that MPS can have, it seems reasonable to focus our attention on distinguishing which individuals with MPS will continue to age normally and which may be in the early stages of PD or dementia.

The boundaries between normal ageing, MPS and pathological nigrostriatal degeneration are difficult to determine. Clinical examination may reveal clues to define these boundaries; a non-progressive course, symmetric distribution, and slowness with a lack of decrement, are all motor features of ageing.[3] Axial signs can predominate in older people with MPS and are usually less responsive to L-dopa in patients with PD.[38] Several studies have specifically assessed the relative risk of MPS for subsequent diagnosis of PD and, in one example, MPS at baseline had a relative risk of 5.5 (2.4–12.6) for incident PD over 10 years of follow-up.[39]

Minn Aye and colleagues recently evaluated the presence of MPS in an elderly community.[40] They found that one quarter of the group had subtle movement abnormalities and this proportion increased with age, with three out of ten people older than 75 showing some degree of motor dysfunction. After adjusting for age and gender, cognitive dysfunction and symptoms of RBD were found to be associated with MPS, which suggests that in a proportion there may be an underlying neurodegenerative process.[40]

Although MPS are prevalent in elderly people, the underlying neuropathology remains unclear. The loss of pigmented neurons in the substantia nigra (SN) pars compacta together with the presence of Lewy bodies (LB) are the hallmarks of PD. However, post-mortem studies have shown that Lewy body pathology is not exclusive to PD and have been found incidentally in 2-61% of healthy brain donors.[41] Fearnley and Lees found that individuals with incidental LB had an intermediate SN neuronal loss between PD cases and controls, and postulated that they might represent a preclinical stage of PD.[42] On the other hand, MPS can be found in elderly people with SN neuronal loss and without LB. Ross and collaborators examined the brains of participants in the Honolulu Heart Program/Honolulu-Asia Ageing Study (HHP/HAAS). They estimated the density of neurons in the SN in PD cases, individuals with incidental LB, and elderly people without either condition.[43] They found that brains from older individuals without LB but who had MPS were associated with lower neuron density in the dorsomedial and dorsolateral quadrants of SN, in contrast to ventrolateral portion of SN which is seen in PD and incidental LB.

Analogy with 'Mild Cognitive Impairment'

The concept of MCI was created to identify individuals who might be in the prodromal stages of AD and other types of dementia. The identification of MPS provides similar opportunities for early detection, but also pitfalls. MCI and MPS can occur simultaneously in the same person, increasing the chance of developing a neurodegenerative disorder. As with MCI, clinical subtypes of MPS could indicate a variety of different underlying parkinsonian disorders.[44] Unlike MCI, clinical scales including patient's subjective impression about their functional impairment are more difficult to use in PD due to lack of awareness of motor disability usually seen in PD patients.[45] MPS and MCI also share in common associations with chronic cerebrovascular disease. The role that cardiovascular risk factors play in brain health is unquestionable.[46] What is noteworthy, however, is increasing evidence of a direct relationship between cardiovascular risk factors and AD.[47] The study of the interplay between cardiovascular disease and the pathology of common neurodegenerative diseases is an important area, given that some of these interactions are potentially modifiable.

Methods of assessing motor dysfunction

One particular challenge is the development of tests to detect subtle motor abnormalities, because the heterogeneity of the motor phenotype makes it difficult to standardise methods of analysis.[4] There is no protocol of motor assessment that is well adapted to early stages of PD. Standardised approaches, adapting current clinical scales and creating objective tools, are required to set the boundaries between prodromal and established PD.[48]

Clinical scales

The Movement Disorders Society (MDS)-Unified Parkinson's Disease Rating Scale (UPDRS) is a standard means of assessment in PD.[49] The motor part (part III) is a semi-quantitative scale based on integer scoring on simple motor tasks addressed to evaluate the cardinal signs of PD. Of note, it was designed for established PD, so it is not expected to be sensitive to detect MPS at the early stages.[4]

The two most widely accepted criteria for defining subthreshold parkinsonism were published by Louis and colleagues, and Berg and colleagues on behalf an MDS Task Force.[27,49]

The former was based on binary scoring (present or absent) of ten items assessing facial expression, speech, tremor at rest, rigidity, posture and axial bradykinesia, but not limb bradykinesia (which is necessary for PD diagnosis). MPS were defined when any of the following conditions were met: rating ≥ 1 for one rigidity item (neck, right and left arm and leg) AND axial bradykinesia AND at least 1 of the four remaining items.[50] Of note, the Louis definition did not include appendicular bradykinesia. Since limb bradykinesia almost certainly belongs to the spectrum of MPS and, in fact may be essential to detect early forms of neurodegenerative parkinsonism, several groups have gone back to integrate the full MDS-UPDRS into the Louis criteria for identifying MPS.[7,51,52] The MDS Task Force definition requires exceeding a cut-off of 6 on the MDS-UPDRS part III, without the inclusion of kinetic and postural tremor, to be defined as subthreshold parkinsonism.[49]

There exists a modified bradykinesia scale which separately scores three kinetic parameters (frequency, rhythm, and amplitude) for each repetitive movement evaluated in the MDS-UPDRS-III (finger tapping, prono-supination and opening-closing hand).[53] However even with these modifications, there are additional important features such as manual dexterity, posture and gait under challenging conditions that are not captured.

Technology-based tools

Quantitative motor assessments together with sophisticated software analysis have been created to address the limitations of conventional clinical scales mentioned above. Although technology-based tools allow objective detection of subtle motor abnormalities, clinical expertise remains equally important to avoid results misinterpretation.[54]

The range of technology available has grown exponentially in the last decade. The kinds of devices range from body sensors to smartphone applications but have also been expanded from controlled conditions measured in the laboratory to real life monitoring in the home-environment.

An important question is whether the existing scales ought to be the gold standard of assessment for MPS or whether there is a need to create new signatures of early motor dysfunction in PD, with an increasing reliance on objective measures.[55]

Conclusions

MPS are an important aspect of the prodromal phase of PD. There are many unanswered questions about where the boundary lies between the ageing process and nigrostriatal degeneration, their progression to early PD or dementia, and the time over which MPS emerge and the best means to quantify early motor dysfunction. The creation of a motor battery that combines a variety of motor assessments under challenging conditions, incorporating technology and clinical acumen, is needed and should be evaluated on a large scale in population-based studies involving elderly people.

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The British Society of Pharmacy Sleep Services launched

12th July 2021 saw the launch of the British Society of Pharmacy Sleep Services (BSPSS) https://bspss.org/ The Society will support through education, community pharmacists' knowledge and understanding of various sleep disorders, to ensure that patients receive timely and appropriate advice and are signposted to other healthcare professionals where necessary.

The BSPSS is undertaking research https://bspss.org/ examining community pharmacists' current knowledge and awareness of various sleep-related problems; to identify critical knowledge gaps and guide subsequent development of future training materials. The Society invites all community pharmacists to complete the Quiz.

The Community Pharmacists' role in sleep problems

President of the BSPSS, Community Pharmacist Gareth Evans, says: "The BSPSS will promote the role of community pharmacy as a trusted source of advice and information for patients with sleep problems, in order to create a patient-centric network of pharmacy-based sleep services. Community pharmacists are the healthcare professionals on the high street and a highly accessible source of advice on a wide range of health issues."

Nevertheless, he believes that community pharmacists are an under-utilised resource for patients with sleep problems. He continues "with the appropriate training, community pharmacists can triage patients seeking advice on a wide range of sleep-related problems including insomnia, snoring, sleep apnoea and even narcolepsy."

The BSPSS will establish a network of sleep-trained pharmacists who liaise with local sleep services and perhaps in the future, refer patients directly into these services.

About the British Society of Pharmacy Sleep Services

The Board of the BSPSS are pharmacy and sleep medicine professionals, who come together to enhance sleep education for community pharmacists. The BSPSS will provide up to date sleep and circadian research, and information to pharmacists around the world, to improve patient access to valid, evidence-based sleep information at their first healthcare interaction.

Novartis receives EU approval for Kesimpta® (ofatumumab), self-administered, targeted B-cell therapy for adult patients with relapsing MS

Novartis announced on March 30th 2021 that the European Commission has approved Kesimpta® (ofatumumab) for the treatment of relapsing forms of Multiple sclerosis (RMS) in adults with active disease defined by clinical or imaging features. Kesimpta is a targeted, precisely dosed and delivered B-cell therapy that has shown superior efficacy with a similar safety profile compared with teriflunomide, a first-line treatment in MS. Kesimpta is the first B-cell therapy that can be self-administered once-monthly at home via the Sensoready® autoinjector pen and can be a first-choice treatment option for patients with RMS.

"Slowing the worsening of disability is one of the main goals when managing RMS and evidence shows that early initiation of a high-efficacy treatment can improve long-term outcomes. Additionally, as RMS progresses, it can substantially increase overall healthcare costs as a result of increased disability," said Haseeb Ahmad, Global Head of Value & Access, Novartis Pharmaceuticals. "Kesimpta's powerful efficacy and favourable safety profile has the potential to become a first-choice treatment to help improve the quality of life of people living with MS, as well as having broader value in potentially reducing medical costs associated with infusion therapies."

View the full press release at https://acnr.co.uk/2021/04/ofatumumab/