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Mild cognitive impairment in Parkinson's disease: How much testing is needed for correct diagnosis?

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ABSTRACT

Cognitive deficits are one of the most common non-motor symptoms of Parkinson's disease (PD). Mild cognitive impairment (MCI) affects about 27% of non-demented PD patients. The high prevalence of PD-MCI and PD with dementia (PD-D) as well as increasing life expectancy in PD creates the need for valid serial cognitive assessment in every PD clinic. In this paper we discuss the PD-MCI criteria and testing recommendations (Movement Disorder Society Task Force Guidelines) in the context of referral for neuropsychological assessment in clinical practice. The methodology suggested in the PD-MCI diagnosis guidelines is compared against PD-D testing recommendations. The requirement for at least 10 cognitive tests to allow PD-MCI subtype to be determined is questioned, as a direct correspondence between low scores on a particular test and a domain-specific deficit cannot be assumed. As a variety of factors may underlie an impaired test score, the same test score may be affected by different deficits in different patients (e.g. a low verbal fluency score may be due to executive or language decline). A pathway approach to PD-MCI diagnosis is presented, inline with PD-D diagnostic guidelines. In cases where thorough screening results and clinical history are consistent with each other and presentation seems typical for PD-MCI, level I diagnosis could be established without neuropsychological assessment. However, when screening results diverge from the clinical history or the presentation is atypical, neuropsychological assessment should precede the diagnostic formulation.

Mild cognitive impairment in PD

Non-motor manifestations, such as cognitive and emotional symptoms, are increasingly recognized as important in the management of people with Parkinson's disease (PD). Eighty to ninety percent of Parkinson's disease (PD) patients will develop dementia in the disease course [1–3]. The average time from motor onset to dementia in PD is 10 years [3]. Dementia is preceded by mild cognitive impairment (MCI) [4]. MCI is diagnosed in about 27% of non-demented PD patients [5], sometimes even in de novo PD patients [6–8]. Preliminary data suggest that the annual conversion rate of Parkinson's disease with mild cognitive impairment (PD-MCI) to Parkinson's disease with dementia (PD-D) is about 9% in early PD and within 1–3 year follow-up the patients may either remain cognitively stable, progress to dementia, or revert to normal cognition [9]. Deterioration of cognitive function from baseline is associated with reduced health-related quality of life [10]. Cognitive decline is faster in individuals with earlier postural instability and gait disorder (PIGD) [8,11,12]. Similarly, multiple-domain non-amnestic PD-MCI subtype is associated with more pronounced PIGD than other subtypes [13].

The high prevalence of cognitive impairment in PD, unclear prognosis in the case of PD-MCI diagnosis and the increasing life expectancy [14] creates the need for serial cognitive assessment in every PD clinic. The PD-MCI diagnostic criteria [15] promote the awareness of cognitive deficits in PD patients among movement disorders specialists and in the healthcare system. Hopefully, they will lead to improved access to cognitive assessment and rehabilitation for PD patients.

This paper discusses the PD-MCI criteria and testing recommendations from a neuropsychological perspective. It addresses a number of questions, including whether the PD-MCI concept is useful (as a diagnosis and in terms of planning treatment), and how to incorporate level I and level II diagnostic criteria into clinical practice. Finally, the extent to which PD-MCI [15] and PD-D [16] criteria and assessment recommendations [15,17] are consistent with each other is examined.

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Is the concept of PD-MCI clinically useful?

The clinical utility of the PD-MCI concept has been recently discussed by Burn and Barker [18], Jellinger [19], Korczyn [20], Copeland and Schiess [21] as well as Yarnall et al. [22]. MCI was introduced to the PD literature following its use in relation to Alzheimer's disease [18]. It can be argued that introducing MCI to medical nomenclature in the case of AD may have facilitated earlier disease diagnosis [23]. Given the lack of widely available definitive biomarkers of early phase AD, diagnosis of MCI provides a means of identifying people with an elevated risk of conversion. However, in PD patients, the diagnosis of a neurodegenerative disease is already established and therefore the MCI label will not facilitate diagnosis of PD. From the medical practitioner's point of view, diagnosis of dementia in PD currently has more treatment implications than diagnosis of PD-MCI given that PD-D is a contraindication for deep brain stimulation and there is no pharmacological treatment recommended for PD-MCI. On the other hand, a PD-MCI diagnosis could be used to facilitate access to non-pharmacological interventions. A recent review of non-pharmacological interventions in older people with MCI suggested a possible benefit from such interventions in the domains of memory and executive functions [24]. Hindle et al. [25] have also recently reviewed non-pharmacological interventions for cognitive deficits in PD. Studies addressing the efficacy of such treatments in PD are scarce and not methodologically convincing, but as some results are positive, more rigorous studies are needed and it seems reasonable to expect that in the future identification of cognitive impairment will lead to prescription of interventions to treat or manage the impairments.

The PD-MCI concept currently seems most useful in terms of recognizing cognitive deficits in PD that may be distressing for patients and their families and beginning to impact on everyday functioning. This could serve to prompt provision of neuropsychological rehabilitation support and determine choice of medications, prompting avoidance of, for example, anticholinergics.

Are PD-MCI diagnostic criteria consistent and valid?

Litvan et al. [15] devised clinical criteria for PD-MCI level I and level II diagnosis. In the case of PD-D clinical criteria, level I corresponds to diagnosis on the basis of abbreviated assessment (based on the use of brief screening tests), while level II represents diagnosis based on a comprehensive neuropsychological assessment. By contrast, in the case of PD-MCI diagnostic criteria, level I includes not only screening tests, but also a more extensive, albeit still relatively short, neuropsychological assessment (<5 cognitive domains assessed, <2 tests for each of the cognitive domains).

One issue for level I criteria is that they may not be sufficiently sensitive to diagnose PD-MCI given the mild severity of cognitive deficits, or may lack specificity in the context of the potential confounding effects of motor and emotional symptoms (such as depression and anxiety) on cognitive performance. Marras et al. [26] demonstrated that neither the Montreal Cognitive Assessment (MoCA) nor the Scales for Outcomes of Parkinson's disease-Cognition (SCOPA-Cog.), both of which are recommended for level I PD-MCI diagnosis, have satisfactory combined sensitivity and specificity for PD-MCI. McColgan et al. [27] demonstrated much better sensitivity and specificity of the Addenbrooke's Cognitive Examination-Revised for the diagnosis of PD-MCI, a test not recommended in PD-MCI diagnostic criteria.

In relation to level II diagnostic criteria, Burn and Barker [18] highlight some of the ambiguities such as defining the impairment as performance 'approximately 1–2 SDs below normative means'. It remains open to debate if PD-MCI criteria should specify the cut-off in a more stringent way (e.g. 1 SD below expected) and which comparison standard is more important: estimated premorbid level or average performance of a corresponding normative sample. Given that 1 SD below the mean refers to around 16% of the healthy population, the individual background of a patient who scores close to a 1 SD point is important to take into consideration. Using a cut-off of 1.5 or 2 SD may not be as sensitive as was shown in a study comparing 5 different neuropsychological approaches to defining MCI (albeit not in PD context), where the criterion of 1 SD was found to be most informative [28].

PD-MCI level II criteria have been shown to have good intra-rater and inter-rater reliability when a psychometric criterion (score at least 1.5 SD below the demographically corrected mean) is used [29]. However, the proportion of patients diagnosed with PD-MCI using the new level II criteria may largely depend on whether the patient's performance is compared against psychometric or individual-comparison standard (premorbid level) [21]. In the Marras et al.'s study [26] 33% of the patients were diagnosed with PD-MCI according to the psychometric standard, while 79% when decline from estimated premorbid level was considered. This discrepancy highlights the need for further validation of the criteria. If the decline from premorbid level is a better predictor of conversion to dementia than a conservative psychometric standard, it would mean that individual-comparison standards are more valuable than psychometric ones.

How many cognitive tests do we need in order to define PD-MCI subtype?

> "*Batteries do not render diagnostic opinions or behavioral descriptions, clinicians do and without the necessary knowledge, clinicians cannot form reliably valid opinions, no matter what battery they base them on*" (Snow, 1985; see: [30])

Neuropsychological assessment usually follows either a fixed-battery approach or hypothesis-driven approach. The hypothesis-driven approach integrates quantitative and qualitative data and is usually based on semi-flexible test battery [30]. Qualitative data may be sometimes more helpful in the differential diagnosis than test scores, as was demonstrated in the case of dementia with Lewy bodies [31].

The PD-MCI recommendations focus on specific test suggestions, which can be misleading if the multifactorial nature of the tests is not taken into account. Direct test score – dysfunction correspondence cannot be assumed. Unfortunately, neuropsychological tests that address only one cognitive domain and do not engage other domains do not exist. Thus, cognitive scores cannot be treated like laboratory findings in which most indices are mutually independent. Most neuropsychological tests are multifactorial and a variety of deficits may underlie an impaired score [30], e.g. complex executive function tasks usually engage memory and either language or spatial functions, as well as executive functions. Similarly, one deficit (e.g. attention) may affect performance on several measures (see below for test examples). If this is the case, according to the psychometric approach, multiple-domain MCI instead of single-domain MCI could be diagnosed inline with the criteria. Cluster analysis of test performance in MCI usually shows that either language/verbal memory or visuospatial/visual memory scores are closely related [32,33], which implies that in some cases visuospatial perception performance may partially account for visuospatial memory test performance etc. Again, according to the psychometric approach one could identify two deficits instead of one, e.g. the same attentional deficit may affect the patient's performance on a variety of tasks attributed to different domains (e.g. memory or executive), but such a pattern of results should still be interpreted as single-domain PD-MCI and not multiple-domain PD-MCI. Thus,