Mild cognitive impairment in Parkinson’s disease

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Abstract

The concept of mild cognitive impairment (MCI) in the general population has received increased attention over recent years, and is associated with risk of progression to Alzheimer’s disease. Within Parkinson’s disease (PD), MCI (PD-MCI) is also now recognised to be relatively common, with certain subtypes predicting progression to Parkinson’s disease dementia (PDD). Recently, criteria to better characterise PD-MCI and its subtypes have been produced by the Movement Disorder Society. In contrast to the population as a whole, where amnestic MCI is the most common subtype, non-amnestic PD-MCI dominates, with prominent executive and attention dysfunction. Although the pathophysiology of PD-MCI is poorly understood and encompasses both PD and non-PD pathology, it is most likely the result of a complex interaction between neurotransmitter dysfunction, synaptic pathology, protein aggregation and neuronal damage. Determining the factors that influence the progression of these pathologies in PD and the individuals at risk of ultimately developing PDD is critical for targeted intervention and drug discovery studies. Further work is required, however, to determine the significance of PD-MCI and also to validate the diagnostic criteria. This would be best delivered in the form of longitudinal studies in homogenous cohorts of PD participants, to allow prognostication and generalisation among the PD population. At the present time, no drug therapies are available for PD-MCI. Management includes screening for the disorder, excluding treatable causes of cognitive decline and cautious use of dopamine agonists and medications such as anticholinergics.

Keywords: Parkinson’s disease, mild cognitive impairment, dementia, amyloid, older people

Introduction

Mild cognitive impairment (MCI) is defined as a transitional state between normality and dementia, with subjective or objective cognitive impairment and little or no impairment in daily functioning [1]. The last 15 years has seen a large rise in the literature on MCI in the general population, with data from epidemiological studies demonstrating that 10–15% per year progress to dementia, largely of the Alzheimer’s-type [2]. MCI may represent the earliest clinical spectrum of dementia, and therefore has been identified as an important opportunity to study the underlying pathogenesis of cognitive impairment, possible biomarkers and neuroprotective therapeutic strategies to prevent subsequent cognitive decline. Furthermore, as the prevalence of MCI increases with age, it is an important concept for geriatricians to recognise.

Dementia is a frequent and distressing complication of Parkinson’s disease (PD) with a cumulative incidence approaching 80% in community-based studies [3]. Parkinson’s disease dementia (PDD) and dementia with Lewy bodies (DLB) are both part of a Lewy body (LB) disease spectrum and are separated by the ‘one year rule’, which states that if extrapyramidal motor features have been present for 12 months or more before the onset of dementia, the diagnosis should be PDD; otherwise it is that of DLB. The development of PDD predicts increased mortality [4], caregiver strain [5], institutionalisation and healthcare costs [6]. The concept of MCI in Parkinson’s disease (PD-MCI) has received increasing attention recently, with opposing views as to whether it is part of the PDD continuum or a fluid process of changing impairment. Although not analogous to the field of Alzheimer’s disease (AD), where the significance of MCI is perhaps better understood, it is now recognised that PD-MCI may represent a pre-dementia state and is associated with increased healthcare costs [6], poorer self-reported quality of life [7, 8], greater falls risk [9] plus...
subtle impairments in instrumental activities of daily living [8, 10]. A recent study demonstrated that the level of global disability, as measured by the Unified Parkinson’s Disease Rating Scale (UPDRS) Part II and the Schwab and England ADL scale, increased in a stepwise manner from those with PD who were cognitively normal, to those with PD-MCI and finally to those with PDD [10]. An earlier study examining PD participants with a range of cognitive abilities demonstrated a strong association between cognitive impairment and impairment in ADLs, even among non-demented patients [8]. This narrative review therefore concentrates on our current understanding of PD-MCI, including the most recent studies, and its importance for geriatricians caring for patients with PD.

Epidemiology of PD-MCI

The prevalence of PD-MCI varies widely depending on the study population (community- or hospital-based, incident or prevalent cases, age and disease severity, use of controls), the neuropsychological tools used and the definition of MCI applied (Table 1). Not surprisingly, studies of incident, drug-naive patients have demonstrated the lowest prevalence of PD-MCI (14.8% [11] and 18.9% [12]), with longer disease duration such as the work from Janvin et al. [13] or retrospective studies [14] producing higher figures (52.8% for both). However, the presence of PD-MCI was 57% in a longitudinal study of patients with a shorter disease duration (3.5 years) [15]. In an attempt to overcome methodological variation, Aarsland et al. [16] performed a meta-analysis of over 1,000 patients encompassing eight centres in Europe and the USA. A mean of 25.8% (95% CI: 23.5–28.2) were classified as PD-MCI, based on age- and education-corrected z scores of <1.5 SD below normative values in one or more cognitive domains, although significant variations were seen across the separate centres studied.

Prior to 2012, there were no consensus criteria for the diagnosis of PD-MCI. Of the 14 studies in Table 1, nine used neuropsychological test scores of <1.5 SD below control values or normative means, three used a cut-off of 1 SD (all three studies by the same group), one used 2 SD and the last used no strict cut-off. This explains in part the variation in frequencies of MCI reported. As per the definition, 16 and 2.5% of subjects will fall <1 and 2 SD of the mean, respectively, of a normally distributed test, and hence a less stringent cut-off could lead to a higher likelihood of false positive MCI cases. This was succinctly demonstrated by researchers in New Zealand, who evaluated 143 PD participants and 50 matched controls on 20 neuropsychological measures [25]. The prevalence of PD-MCI was 14% when a cut-off of two test scores within one domain <2 SDs below normative values was used, but increased to 89% when one score <1 SD was used. The authors recommended that two scores <1.5 SD either within a single domain or in two separate domains should be used as criteria for PD-MCI [25]. Variations are also attributable to whether subjective cognitive impairment was included as part of the diagnostic criteria; there is however, evidence that this may not be a reliable discriminator of MCI, with subjective memory complaints commonly reported in those who are cognitively normal (PD-CN) and under-reported in those with impairments [20]. Including cognitive complaint as part of a definition of MCI greatly increases the number classified with the disorder [26]. In addition, the differences in frequencies of MCI may be due to the number of neuropsychological tests used by study participants, with larger numbers of tests increasing the probability of false-positives. This can be avoided to some extent by defining MCI using impairment in more than one test, or standardising impairments within tests within separate cognitive domains.

Risk factors and course

The heterogeneity of PD-MCI suggests that cognitive correlates may not be generalizable to the whole population. Nevertheless, increased age [15, 16, 18, 19, 21, 23, 24], motor disease severity [16, 18, 19, 23], non-tremor-dominant motor phenotype [11, 14, 15, 19] and lower educational levels [18, 22, 24] all seem to be robustly associated with MCI risk. Other possible associations include the presence of depression [16, 19], male gender [16] and anti-anxiety medication use [23]. In addition, one recent study examined the predictors of separate MCI subtypes in PD [27]. In keeping with previous studies, non-amnestic single-domain MCI (naMCI-sd) was the most common subtype in 128 PD-MCI participants, but within the non-amnestic multiple-domain (naMCI-md) participants, significantly greater scores on axial functioning/gait subset of the UPDRS motor score were observed, compared with the amnestic single-domain (aMCI-sd) subtype [27]. The authors postulated that non-dopaminergic deficits may link these specific motor and cognitive phenotypes. Evidence in older adults without PD has demonstrated that gait dysfunction and falls [28, 29] are both risk factors for future cognitive decline, hence it is likely that this may also be true in PD, although small vessel disease may also contribute.

To date, only three studies have published data on longitudinal outcomes in PD-MCI. Janvin et al. studied 72 non-demented PD participants with a mean age at baseline of 71 years and a disease duration of between 10 and 12 years, of whom 59 completed assessments 4 years later [13]. The presence of MCI at baseline assessment was significantly associated with cognitive decline at follow-up, with 62% of those with PD-MCI versus 20% of those who were cognitively normal developing dementia. After controlling for age, sex, disease stage and education in a logistic regression model, MCI at baseline was strongly associated with development of dementia (OR, 5.1; 95% CI, 1.51–16.24). The only subtype that was associated with later dementia was naMCI-sd (OR, 8.3; 95% CI, 1.8–37.5); however, the small numbers within the subgroups means that definitive conclusions cannot be drawn.
**Table 1. Demographic and clinical features of studies in PD-MCI**

<table>
<thead>
<tr>
<th>Reference</th>
<th>PD</th>
<th>Controls</th>
<th>Mean age PD</th>
<th>Disease duration (years)</th>
<th>Type of study</th>
<th>Country of origin</th>
<th>MCI definition</th>
<th>Cognitive domains assessed</th>
<th>%MCI</th>
<th>Cognitive profile</th>
<th>Other comments</th>
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</table>
| [17]      | 102| 0        | 68          | NA                      | Cross-sectional; hospital clinic; prevalent cases | Taiwan         | <1.5 SD below age- and educationally-matched groups; Cognitive Ability Screening Instrument (CASI) used (max score 100) | Remote memory, recent memory, attention, mental manipulation, orientation, abstract thinking, language, drawing and verbal fluency | 38.2 | Recent memory, verbal fluency, abstract thinking and orientation all impaired to a high degree | (1) Higher educational level did not protect against cognitive decline  
(2) CASI has not been validated in PD |
| [18]      | 159| 0        | 70.6        | NA (incident)            | Cross-sectional; community; incident | UK              | <1 SD below normative values for PRM and TOL             | Temporal lobe plus frontostriatal impairment tested with PRM and TOL, respectively; MMSE also assessed | 30.1* | 9.6% frontostriatal impairment; 8.2% temporal lobe deficit; 11% global deficits*  
(1) *1. Note 159 patients but 13 had MMSE<24; in total 36% therefore had some cognitive impairment  
(2) 2. Patients with global or frontal impairments were significantly older, had higher UPDRS motor scores, and lower premorbid IQs than CN |

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<th>Mean age PD (years)</th>
<th>Disease duration (years)</th>
<th>Type of study</th>
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<th>Cognitive profile</th>
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</table>
| [19]      | 115 70      | 66.2                | 1.6                      | Cross-sectional; hospital clinic; early PD | Netherlands | $<2$ SD below mean score of matched controls in $\geq 3$ neuropsychological tests | Psychomotor speed, attention, language, memory, executive functions, and visuospatial/constructive (28 tests administered) | 23.5 (4.3 control group) | Attention, executive and memory function most impaired of controls | (1) Age at disease onset independent predictor of cognitive ↓  
(2) Impaired were older, male, had later disease onset, ↓ disease severity, ↑ depression scores, and more severe axial and speech symptoms |
| [13]      | 72 38       | 71.0                | 10.6                     | Longitudinal; community; prevalent cases | Norway | $\leq 1.5$ SD below mean score of controls in 1, 2 or 3 neuropsychological tests; DRS and MMSE also used | Short-time visual memory (BVRT), visuospatial (JLO) and attention/executive (SWT) domains | 52.8 | naMCI-sd 44.7%, multiple domains slightly impaired 39.7%, amnestic 15.8% | (1) 62% MCI demented at 4 years of 20% cognitively normal (OR 4.8; 95% CI 1.58–14.8)  
(2) Single-domain non-amnestic MCI only associated with development dementia (OR 8.3; 95% CI 1.8–37.5) |
<p>| [20]      | 86 0        | CN 5,4; MCI 74.6; PDD 79.9 | CN 5-4; MCI 9.2; PDD 16.8 | Cross-sectional; prevalent cases | USA | $\leq 1.5$ SD below age corrected mean score consistently in 1 of 5 cognitive domains, plus subjective memory complaint | Frontal/executive (Stroop, TMT A and B), amnestic (RA/WLT), visuospatial (CDT, JLO), attention (WAIS III forward and backwards) and language (COWA, category fluency) | 20.9 (25.3 non-demented PDs) | sdMCI-frontal/executive 39%; naMCI-med 22%; aMCI-sd 22%; aMCI-md 11% sdMCI-language 6% | Language dysfunction rarely seen; domains of visuospatial and attention did not reach threshold of dysfunction in the PD-MCI group |</p>
<table>
<thead>
<tr>
<th>Study</th>
<th>Sample Size</th>
<th>Age</th>
<th>Gender</th>
<th>Intervention</th>
<th>Region</th>
<th>Cognitive Test(s)</th>
<th>Participants</th>
<th>Predictors of Cognitive Decline</th>
</tr>
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<tbody>
<tr>
<td>[15]</td>
<td>126</td>
<td>0</td>
<td>NA</td>
<td>NA (3.5 years' for whole cohort)</td>
<td>UK</td>
<td>Frontal (TOL, SRM, phonemic fluency), temporal (PRM, semantic fluency) and parietal function (pentagon copying)</td>
<td>57</td>
<td>Predictors of cognitive decline independent of age were non-tremor-dominant phenotype, impaired semantic fluency and impaired pentagon copying</td>
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<td></td>
<td></td>
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<td></td>
<td>Longitudinal, community</td>
<td></td>
<td></td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>[21]</td>
<td>141</td>
<td>0</td>
<td>CN, MCI</td>
<td>Cross-sectional</td>
<td>Korea</td>
<td>Attention (forward digit span), language (BNT), visuospatial (RCPT); memory (SVLT) and executive function (phonemic word association test)</td>
<td>40.4</td>
<td>aMCI-sd 25.9; sd language 12.3%; sd visuospatial 10.5%; sd executive 3.5%; md 47.4%</td>
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<td></td>
<td></td>
<td></td>
<td>57; MCI 64</td>
<td></td>
<td></td>
<td></td>
<td>40.4</td>
<td>Age was significant predictor of all subtypes of MCI, domain most influenced by age was executive function</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Cross-sectional</td>
<td>Korea</td>
<td>&lt;1.5 SD below the mean score for the age- and education-matched control group in ≥1 of 5 cognitive domains tested</td>
<td>40.4</td>
<td>Age was significant predictor of all subtypes of MCI, domain most influenced by age was executive function</td>
</tr>
<tr>
<td>[22]</td>
<td>86</td>
<td>30</td>
<td>68.1</td>
<td>Cross-sectional; newly diagnosed; drug naive</td>
<td>Sweden</td>
<td>Episodic memory; working memory; visuospatial function; verbal fluency; naming and executive function</td>
<td>30</td>
<td>30% had deficits in ≥1 domain, 16% deficits in ≥2 domains</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Cross-sectional</td>
<td>Sweden</td>
<td>&lt;1.5 SD below control means (matched for age/sex/educational level if possible) for &gt;50% of single test results within a domain</td>
<td>30</td>
<td>(1) Education was the only independent significant predictor of severe cognitive impairment (2) Included 5 patients in ‘PD’ group with normal DaT</td>
</tr>
<tr>
<td>[23]</td>
<td>106</td>
<td>0</td>
<td>64.6</td>
<td>Cross-sectional</td>
<td>USA</td>
<td>Memory (HVLT-R – 3 components), executive function (Stroop, semantic fluency) and attention (digit span)</td>
<td>29.2</td>
<td>17.9% sd (attention 8.5, memory 5.7, executive 3.8%); 11.3% md</td>
</tr>
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<td></td>
<td></td>
<td></td>
<td>6.5</td>
<td>Cross-sectional</td>
<td>USA</td>
<td>≤1.5 SD below normative means on ≥2 tests (for memory and attention) or a single test (attention)</td>
<td>29.2</td>
<td>Predictors of MCI were ↑ age, ↑ Hoehn and Yahr stage, ↑ UPDRS motor score, anti-anxiety medication use and a trend towards ↑ ESS score</td>
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<tr>
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<th>Disease duration (years)</th>
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<th>Cognitive profile</th>
<th>Other comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>[12]</td>
<td>196 171 67.7</td>
<td>2.3</td>
<td>Cross-sectional; drug naive</td>
<td>Norway</td>
<td>&lt;1.5 SD below mean for corrected z score for at least one of the cognitive domains</td>
<td>Verbal memory (CVLT-II); visuospatial (Y.8P silhouettes); attentional/executive (serial 7s, Stroop, semantic fluency)</td>
<td>18.9</td>
<td>62.2% of MCI group had naMCI-sd; 24.3% aMCI-sd; 10.8% aMCI-md and 2.7% naMCI-md</td>
<td>(1) The largest effect size was found for verbal memory (2) No clinical or demographic differences found between those with PD-MCI cf PD-CN</td>
</tr>
<tr>
<td>[14]</td>
<td>72 0 CN 63.7; MCI 66.0</td>
<td>CN 5.8; MCI 8.7</td>
<td>Retro-spective record review</td>
<td>USA</td>
<td>Deficits in ≥2 tests within a domain; plus subjective and objective cognitive impairment (strict cut-offs not used)</td>
<td>Visuospatial (JLO, pentagons); language (BNT, phonemic and semantic fluency); attention (digit forwards, TMT A); executive (TMT B, WORLD backwards) and memory (CERAD word list or HVLT-R)</td>
<td>52.8</td>
<td>naMCI-sd 36.8%, aMCI-sd 23.7%, aMCI-md 23.7% and naMCI-md 15.8% (memory &gt; executive &gt; visuospatial &gt; language &gt; attention deficits)</td>
<td>Those with MCI had ↑ duration of PD and ↑ PIGD subscale scores</td>
</tr>
<tr>
<td>[16]</td>
<td>1,346 0 NA</td>
<td>NA</td>
<td>Meta-analysis 8 centres</td>
<td>Italy</td>
<td>&lt;1.5 SD below mean for corrected z score on ≥1 cognitive domain</td>
<td>Attention/executive; visuospatial; memory (variety of tests used)</td>
<td>25.8</td>
<td>11.3% naMCI-sd; 8.9% aMCI-sd; 4.8% aMCI-md and 1.3% naMCI-md. Memory (13.3%)&gt;visuospatial (11%)&gt;attention/executive dysfunction 10.1%</td>
<td>MCI associated with ↑ age at assessment and at disease onset, male gender, depression, more severe motor symptoms, and advanced disease stage</td>
</tr>
<tr>
<td>[11]</td>
<td>121 100 66.6</td>
<td>1.2</td>
<td>Cross-sectional; early drug naive</td>
<td>Italy</td>
<td>&lt;1.5 SD scores in ≥2 tests</td>
<td>Memory (B, HVLT, Rey Figure Recall); language (BNT, semantic and phonemic fluency); executive (Stroop, FAB, TMT A and B, digit span, Corsi test, MCST, CPM 47); praxis (Rey figure copy) and visuospatial function (JLO)</td>
<td>14.8 (control group 7)</td>
<td>5% naMCI-md; 4.1% naMCI-sd; 4.1% aMCI-md and 1.7% aMCI-sd</td>
<td>(1) Bradykinesia, axial impairment and absence of tremor associated with ↑ risk of MCI (2) PIGD patients had higher proportion of MCI than TD (23.2 ± 6.3%)</td>
</tr>
</tbody>
</table>
The CamPaIGN cohort has also explored the evolution of cognitive dysfunction [15, 18, 30]. Although MCI was not studied specifically, over a mean of 5.2 years, 17% of incident PD cases developed PDD, with increasing age, impairments in semantic fluency and visuospatial function and MAPT H1/H1 genotype all significantly associated with a more rapid cognitive decline [15, 30]. COMT genotype and impairments in frontally based tasks were not associated with deteriorating cognition, lending support to the hypothesis that more posteriorly based cognitive deficits increase the risk of subsequent decline due to a more posterior deposition of Lewy bodies, combined with the ageing process plus cholinergic dysfunction. Most recently, follow-up of MCI cases from the ParkWest Study [12] demonstrated that a diagnosis of MCI versus non-MCI at baseline visit had a relative risk for dementia of 39.2 at 3 years [31].

Pathogenesis

The exact underlying pathophysiology of PD-MCI remains the subject of debate, largely due to the scarcity of neuropathological data. Structural and functional imaging, neurophysiological techniques and cerebrospinal fluid (CSF) analysis provides some *in vivo* evidence of the mechanisms underlying MCI. Only one neuropathological study in well-characterised PD-MCI in which participants were followed prospectively has been reported [32]. Eight cases were examined, of whom four were classified as amnestic and four as non-amnestic MCI. The neuropathology was heterogeneous, with five cases exhibiting limbic or neocortical LB pathology and the remainder predominantly consisting of brainstem LB pathology. Diffuse amyloid plaques were seen in the majority of cases [33], with two of the amnestic MCI subgroup meeting neuropathological criteria for AD. Cerebrovascular pathology was frequently seen. In correspondence relating to this study, Kurt Jellinger reported on a further eight cases of MCI, where four cases were defined as aMCI-sd, three were nMCI-sd and one MCI multiple domains [34]. Again the neuropathology was heterogeneous, with most patients having limbic or neocortical LB deposition, and some displaying Alzheimer-type pathology. These studies provide evidence that the neuropathology underlying PD-MCI may be similar to, but less advanced than, that found in PDD.

Changes seen in structural and functional imaging provide further evidence of the possible underlying pathogenesis of PD-MCI. Extensive grey matter loss on structural magnetic resonance imaging is a consistent finding in PDD [35]; in MCI, a more selective loss has been observed [35, 36]. Atrophy was noted in frontal [35, 36], prefrontal [36, 37], temporal [35], hippocampal [35, 37], amygdala [35], parietal [37] and occipital [36, 37] regions, and may be attributable to neuronal and synaptic loss from LB and/or AD-type pathology. However, a study in *de novo* incident PD cases did not demonstrate significant grey matter loss, perhaps due to the shorter disease duration, arguing for functional
neurotransmitter loss rather than structural grey matter loss as a pathological basis for MCI [38]. Functional imaging using 18F-fluorodeoxyglucose positron emission tomography (PET) has demonstrated metabolic abnormalities associated with PD-MCI, with metabolic reductions demonstrated in frontal and parietal association areas plus relative increases in the cerebellar vermis and dentate nuclei [39]. This pattern predicted performance in memory and visuospatial domains, with a more recent PET study by the same authors revealing a difference in parietal and prefrontal metabolism in those with multiple-domain MCI compared with PD-CN participants [40]. Other studies have demonstrated cerebral hypometabolism in posterior cortical regions in participants with PD-MCI compared with those with PD and normal cognition [41]. Taken together, neurotransmitter deficits in PD-MCI may explain the PET findings, with dopaminergic dysfunction accounting for frontotemporal hypometabolism and subcortical cholinergic loss leading to posterior changes. Although these imaging findings suggest a causal link, they may be secondary contributors, with other markers (such as those measuring neurotransmitter changes or neuropathology) more sensitive to the upstream process.

Other potential mechanisms that may underpin the pathophysiology of MCI in PD include cholinergic dysfunction and abnormal processing of the amyloid precursor protein. Cholinergic loss is an established feature of PDD [42] and may contribute to PD-MCI: evidence from a PET study demonstrating a reduction in nicotinic acetylcholine (ACh) receptors in the midbrain, pons and cerebellum in PD subjects with MCI support this hypothesis [43]. In addition, short latency afferent inhibition (SAI) is abnormal in PD-MCI [44] and is an independent predictor of slower gait speed [45]. SAI is a non-invasive neurophysiological technique that relies on cholinergic excitability in the cerebral cortex, and hence can be used as a proxy measure of cholinergic activity. This theory of a cholinergic basis to MCI has biological plausibility in terms of the Braak hypothesis; at Braak Stage 3, where the motor disease may become apparent, there is already destruction of the basal forebrain cholinergic nuclei and consequent ACh loss. Lastly, abnormal amyloid-β deposition and fibrilization due to altered amyloid precursor processing may contribute to PD-MCI. Reduced CSF levels of Aβ42, a marker of amyloid deposition and aggregation, were found in those with PD and who were cognitively impaired but not demented [46]. Reduced CSF Aβ42, 40 and 38 levels also correlated with memory function in early de novo PD participants [47]. However, detection of amyloid-β deposition using PET imaging with Pittsburgh Compound B (PiB) in PD-MCI has been less convincing. In a small cross-sectional study (PiB retention did not differ between groups with PD and normal cognition, PD-MCI or PDD [48], although in more recent longitudinal work, amyloid burden at baseline predicted cognitive decline during the follow-up [49].

In summary, the pathogenesis of PD-MCI is heterogeneous and may differ between individuals and between subtypes. LB deposition, amyloid deposition and neurotransmitter deficits are all likely to contribute, although to a lesser degree than those changes seen in PDD. Further in vivo and post-mortem studies will facilitate future work.

**Definition of PD-MCI**

Owing to the increasing research in PD-MCI and a lack of standardization in defining the disorder, the Movement Disorder Society (MDS) commissioned a Task Force to evaluate the literature and propose criteria [50] for the diagnosis of PD-MCI. The criteria are shown in Table 2. They require the diagnosis of PD, subjective or objective cognitive decline and the demonstration of cognitive deficits that do not interfere with functional independence. As discussed earlier, there is evidence that MCI may impact subtly upon function [8, 10]. This raises something of a paradox; although impaired function is not necessarily perceived by the patient as being attributable to cognitive impairment, more objective evidence might suggest otherwise [8, 10]. The Task Force defined both a level I category, for an abbreviated assessment, and a more comprehensive level II assessment for more diagnostic certainty and for use in a research setting. Strict cut-offs were not defined, with impairment in performance in neuropsychological tests of 1 to 2 SDs. Although commendable and timely, some care is required in the use of the new criteria. Firstly, there is a lack of clarity on some aspects of the criteria, such as whether cognitive impairment is defined on 1 or 2 SDs below ‘normative’ values. Secondly, there may be a lack of stability in the diagnosis of MCI, with a proportion of subjects actually returning to normal cognition at follow-up due to medication effects, learning effects or normal fluctuations in cognition. The definition of MCI should therefore reflect stability over repeated baseline assessments. Thirdly, these criteria require validation in future longitudinal studies to determine whether they are of prognostic significance. Finally, there is an underlying question of whether ‘PD-MCI’ is actually a valid and useful diagnosis, in view of the considerable heterogeneity and possible differing mechanisms underlying the pathophysiology.

**Treatment**

To date, there have been no randomised controlled trials in PD-MCI. A small study of Atomoxetine, a selective norepinephrine reuptake inhibitor, produced an improvement in global cognition in non-demented PD patients, although cognition was only a secondary outcome measure [51]. Trials of cholinesterase inhibitors in PD-MCI and mild dementia, such as the MUSTARD-PD study (www.clinicaltrials.gov: NCT01014858), are ongoing and should inform future practice. Cholinesterase inhibitors may also be useful in other aspects of care in non-demented PD cases, with a recent study suggesting that falls may be reduced by half in PD fallers taking donepezil [52]. Finally, non-pharmacological interventions, such as cognitive intervention programmes [53] or physical exercise, should be investigated further.
Mild cognitive impairment in Parkinson’s disease

uncertain but that in some cases it may be progressive is justified if the patient wishes to know; this may prompt further discussion about future advanced care planning.

Conclusion

In conclusion, PD-MCI is a common heterogeneous disorder, and may represent the earliest opportunity to halt the underlying pathogenic process of PDD. The pathogenesis of PD-MCI may differ between individuals and between subtypes. LB deposition, amyloid deposition and neurotransmitter deficits are all likely to contribute, although to a lesser degree than those changes seen in PDD. Further in vivo and post-mortem studies will facilitate future work. Criteria for the diagnosis of PD-MCI require validation in the longitudinal follow-up to determine relevance and utility to clinical practice. Finally, our understanding of the significance of PD-MCI should be improved by prospective studies in early disease, allowing future early targeted therapeutic intervention and disease modification.

Key points

- MCI in Parkinson’s disease (PD-MCI) is increasingly recognised and is a heterogeneous condition.
- In contrast to the general population, where amnestic MCI is the most common subtype, non-amnestic subtypes dominate.
- Some PD-MCI subtypes are associated with an increased risk of progression to PD dementia (PDD).
- The underlying pathophysiology is likely to include neurochemical dysfunction, synaptic loss and protein aggregation.
- Practical management of PD-MCI includes exclusion of reversible causes and discussion with the patient and their family.

Conflicts of interest

None declared.

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Practical management of PD-MCI

Geriatricians are likely to be managing increasing numbers of patients with PD-MCI in the future. Most will not have immediate access to full-neuropsychological assessment in a clinic setting, and it is the authors’ opinion that the MoCA is the most useful screening tool, with published screening cut-offs for both MCI and PDD [54], and the advantage of an administration time of just 10 min. Further investigations are generally not required, although a routine dementia screen for reversible causes (such as B12 and thyroid function tests) is warranted. Dopamine agonists for motor control and anticholinergic drugs for non-motor symptoms should be used with caution, or not at all. An explanation to the patient and their family that the prognosis of PD-MCI is

Table 2. Diagnostic criteria for PD-MCI

<table>
<thead>
<tr>
<th>Inclusion criteria</th>
<th>Level I (abbreviated assessment)</th>
<th>Level II (comprehensive assessment)</th>
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<tr>
<td>Diagnosis of PD</td>
<td>Impairment on a scale of global cognitive abilities validated for use in PD (MoCA, SCOPA-COG, PD CRS, MDRS)6 or Impairment on at least two tests, when a limited battery of neuropsychological tests is performed</td>
<td>Neuropsychological testing that includes two tests within each of the five cognitive domains (attention and working memory, executive, language, memory and visuospatial) Impairment on ≥2 neuropsychological tests (either two impaired tests in one cognitive domain or one impaired test in two different cognitive domains) Impairment on neuropsychological tests may be demonstrated by: Performance 1–2 SDs below appropriate norms or Significant decline demonstrated on serial cognitive testing or Significant decline from estimated premorbid levels Subtype classification for PD-MCI (optional, requires two tests for each of the five cognitive domains assessed) PD-MCI single-domain—abnormalities on two tests within a single cognitive domain (specify the domain), with other domains unimpaired or PD-MCI multiple-domain—abnormalities on at least one test in two or more cognitive domains (specify the domains)</td>
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<tr>
<td>Cognitive decline, in context of established PD, reported by patient/carer/treating physician</td>
<td></td>
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<tr>
<td>Cognitive deficits not severe enough to interfere with functional independence, although subtle impairments may be present</td>
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</table>

6MoCA Montreal Cognitive Assessment; SCOPA-COG Scales for Outcomes of Parkinson’s disease Cognition; PD CRS PD Cognitive Rating Scale; MDRS Mattis Dementia Rating Scale.
Supplementary data

Supplementary data mentioned in the text are available to subscribers in *Age and Ageing* online.

References

The very long list of references supporting this review has meant that only the most important are listed here and are represented by bold type throughout the text. The full list of references is available as Supplementary data in *Age and Ageing* online, Appendix 1.


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576