MDS Task Force on Mild Cognitive Impairment in Parkinson's Disease: Critical Review of PD-MCI

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ABSTRACT: There is controversy regarding the definition and characteristics of mild cognitive impairment in Parkinson's disease. The Movement Disorder Society commissioned a Task Force to critically evaluate the literature and determine the frequency and characteristics of Parkinson's disease–mild cognitive impairment and its association with dementia. A comprehensive PubMed literature review was conducted using systematic inclusion and exclusion criteria. A mean of 26.7% (range, 18.9%–38.2%) of nondemented patients with Parkinson's disease have mild cognitive impairment. The frequency of Parkinson's disease–mild cognitive impairment increases with age, disease duration, and disease severity. Impairments occur in a range of cognitive domains, but single domain impairment is more common than multiple domain impairment, and within single domain impairment, nonamnestic is more common than amnestic impairment. A high proportion of patients with Parkinson's disease–mild cognitive impairment progress to dementia in a relatively short period of time. The primary conclusions of the Task Force are that: (1) Parkinson's disease–mild cognitive impairment is common, (2) there is significant heterogeneity within Parkinson's disease–mild cognitive impairment in the number and types of cognitive domain impairments, (3) Parkinson's disease–mild cognitive impairment appears to place patients at risk of progressing to dementia, and (4) formal diagnostic criteria for Parkinson's disease–mild cognitive impairment are needed. © 2011 Movement Disorder Society

Key Words: mild cognitive impairment; Parkinson's disease; systematic review

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Cognitive impairment is common in Parkinson's disease (PD), with long-term longitudinal studies reporting that most PD patients develop dementia (PDD).[1–3] The impact of PDD is substantial, with major consequences for functioning,[4–6] nursing home admission,[7] psychiatric morbidity,[8] caregiver burden,[9,10] and mortality.[11,12]

Mild cognitive impairment in PD (PD-MCI), defined as cognitive decline that is not normal for age but with essentially normal functional activities, also appears to be common, even at the time of PD diagnosis and prior to initiation of dopaminergic therapy.[13] Although the term *MCI* applied to PD is not without controversy,[14,15] it is more frequently used and more widely accepted than alternative terms. Identifying PD-MCI is important clinically, as these patients appear to be at increased risk for developing PDD.[16] The biological validity of PD-MCI is supported by preliminary structural[17] and functional[18,19] neuroimaging, electroencephalography,[20,21] and genetic,[22,23] cerebrospinal fluid,[24–26] and autopsy studies[27] showing an association between a range of neuropathophysiological variables and either cognitive impairment or cognitive decline in nondemented PD patients. From a scientific standpoint, studying PD-MCI offers insight into the neural substrate of the earliest stage of cognitive decline in PD, which may lead to early intervention and may guide drug development focused on preventing or delaying the onset of PDD.

Despite what is known about PD-MCI, the heterogeneity of cognitive deficits from the initial stages of the disease and the relative scarcity of longitudinal studies have made it difficult to definitively determine the following: (1) whether there are different and reproducible subtypes of PD-MCI, (2) what proportion of PD-MCI patients progress to PDD, (3) whether the term *MCI* can be defined and operationalized in PD to determine those patients at imminent risk of PDD, and (4) whether this risk differs on the basis of MCI subtype.

Given the critical importance of having uniform criteria for PD-MCI both for the identification and management of PD patients and for future therapeutic trials, the Movement Disorder Society (MDS) commissioned a task force to: (1) critically evaluate the literature, (2) more accurately determine the frequency and characteristics of PD-MCI and its conversion rate to PDD, and (3) propose formal diagnostic criteria for PD-MCI. The present article deals with the first 2 of these issues because they are necessary to address prior to proposing new criteria. Criteria and guidelines for the definition and ascertainment of MCI in PD based on the present "state of the art" will be addressed in a future article.

Materials and Methods

Literature Search and Selection of Articles

A comprehensive review of the literature through September 1, 2010, was conducted through Medline
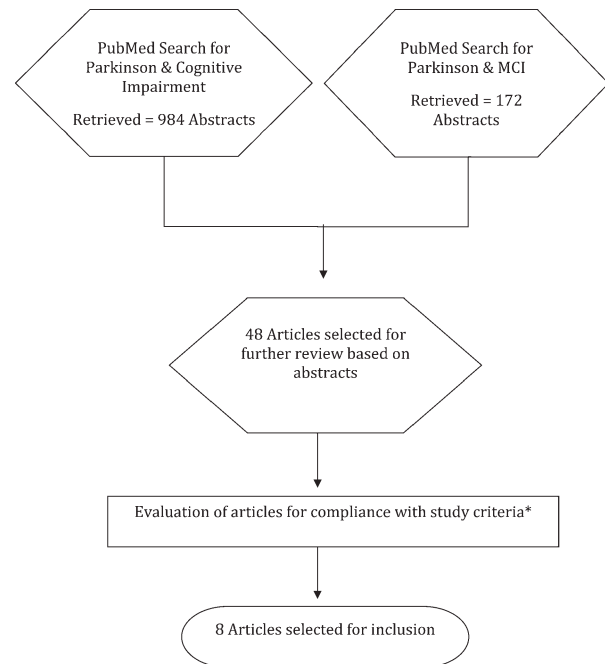

FIG. 1. Search results (*study criteria: see text).

(PubMed) using combined free search terms that included "Parkinson," "cognitive impairment," and "mild cognitive impairment." The search was limited to empirical English-language articles. The search retrieved 984 articles using the key terms "Parkinson and cognitive impairment" and 172 articles using "Parkinson and mild cognitive impairment," with most of the latter articles already retrieved in the first search (Fig. 1).

Abstracts (or articles when abstracts lacked information on inclusion and exclusion criteria) were further scrutinized to include only those reports that fit study inclusion criteria: (1) a minimum of 100 nondemented PD patients in cross-sectional studies or 50 patients in prospective studies; (2) the presence of quantitative neuropsychological information covering at least 3 of 5 cognitive domains: memory, executive, attention/working memory, visuospatial, and language; and (3) comparison of PD with a local control group or use of normative values. Exclusion criteria were: (1) lack of definition of impaired cognition or dementia in review articles, guidelines, meta-analyses, and clinical therapeutic trials (unless the trial was negative); and (2) cognitive studies in demented or surgically treated PD patients and in patients with other neurological diseases and articles focused on depression, REM sleep behavior disorder, olfactory dysfunction, impulse control disorders, or psychosis without relevant cognitive data. Articles with abstracts that did not explicitly disclose all inclusion/exclusion criteria were included for further review.

Forty-eight articles met study inclusion criteria based on the review. The 48 articles were reviewed by 5 pairs

of task force members (approximately 10 articles per pair) who independently extracted key data from the identified articles.[1,3,12,13,16,28–70] The most common reasons for exclusion were lack of definition of impaired cognition or failure to explicitly exclude patients with dementia,[1,3,29,30,33,42,44–46,48,49,51,55–57,59,62,64,66,67] sample size not meeting inclusion criteria,[31,32,35,37,52,58,60,71,72] and evaluation of less than 3 domains of cognition.[3,12,61,63,65,69]

Data Extraction and Quality Assessment

The task force members rated the articles using a structured form that included: (1) type of study (random, door to door; multiple sources; hospital based); (2) number of PD patients and percentage of patients with MCI; (3) demographics; (4) diagnostic criteria for PD, MCI, and PDD; (5) neuropsychological tests utilized; (6) number of cognitive domains tested; and (7) the presence of a normal control group or use of tests with normative values. For our final analysis, we selected articles that had clearly defined cognitive and PD diagnostic criteria, studied at least 3 cognitive domains with standard versions of published neuropsychological tests, either included a control group matched by age and education evaluated with the same protocol or utilized test normative values to define MCI, and did not include the same study population as another study (except for prospective studies).

Results

A total of 8 articles met all the inclusion/exclusion criteria. The studies included a total of 776 PD patients from 6 cross-sectional studies and 198 from 2 prospective studies (Table 1) and varied widely regarding design, population, and criteria and methods for defining MCI and dementia.

Cross-sectional Studies

Table 2 shows the neuropsychological tests and domains explored, MCI criteria used, and MCI subtypes found in each study. Overall, the studies demonstrate that PD-MCI is common in PD patients without dementia (mean cross-sectional prevalence, 26.7%; range, 18.9%–38.2%), its frequency increases with age and duration of PD, single-domain impairment is more common than multiple-domain impairment, and in the case of single-domain impairment, nonamnestic MCI is more common than amnestic MCI.

Aarsland et al[28] evaluated a community-based incident cohort of 196 nondemented, drug-naive PD patients[73] and 201 healthy controls (HCs). The neuropsychological battery measured global cognition with the Mini–Mental State Examination (MMSE) and evaluated 3 cognitive domains with additional neuro-

psychological testing. The authors calculated z scores for the PD patients based on control data. They categorized MCI cases as 1 of 4 subtypes (Table 2). Compared with HCs, PD patients were impaired on all neuropsychological tests, and 18.9% met criteria for MCI (Table 1), with a risk ratio (RR) of 2.1 compared with controls. Older PD patients ($\geq$65 years) had a higher RR (2.6) of having MCI than younger cases (<65 years; RR, 1.5).

Foltynie et al[34] assessed cognitive function in an incident cohort of 159 PD patients.[74] Thirteen of the patients (8%)[74] scored < 24 on the MMSE and were considered to have dementia, even though dementia at diagnosis was an exclusion criterion. Of the remaining 146 cases, 142 were included in the study, and more than one third were considered cognitively impaired, defined as scoring $\geq$1 SD below the normative mean in a pattern recognition task (temporal lobe impairment), the Tower of London task (frontostriatal impairment), or both tests (global impairment). The term *MCI* was not used in this study.

Hoops et al[40] compared the discriminant validity of the Montreal Cognitive Assessment (MoCA) and MMSE at diagnosing MCI in PD, using a neuropsychological test battery as a gold standard. Among a convenience sample of 132 PD cases at a movement disorders clinic,[73] 12.9% had PDD and 20% had MCI based on a test battery that evaluated 4 cognitive domains.

Mamikonyan et al[47] explored the cognitive performance of 106 PD patients (a convenience sample at a movement disorders clinic), who had intact global cognition based on their age- and education-adjusted MMSE score. Thirty-one patients (29.2%) were classified as having MCI, defined as scoring $\geq$1.5 SDs below the normative data in at least 1 of the 3 domains assessed. The authors concluded that cognitive impairment is frequent in PD patients with normal cognition based on MMSE score and that memory deficits are common at the stage of PD-MCI.

Muslimovic et al[13] studied 115 PD patients without "global cognitive deterioration," defined as an MMSE score <24 and 70 elderly HCs in one of the most detailed investigations of cognition in nondemented PD patients. A comprehensive battery of 28 neuropsychological tests was administered, and PD patients were significantly impaired on 20 of these. Twenty-seven patients (23.5%) were cognitively impaired, defined as scoring $\geq$2 SDs below the normative mean on $\geq$3 cognitive tests, compared with 4% of HCs. The domains most commonly impaired were attention/executive function, psychomotor speed, and memory.

Pai et al[53] studied cognitive abilities in 102 nondemented PD patients recruited from a behavioral clinic. They used the Chinese version of the Cognitive Ability Screening Instrument, a comprehensive screening instrument with normative data that includes

TABLE 1. Demographics of studies that met systematic review study inclusion criteria

Authors	Sample size (n)			Age (y)		Education (y)		Disease duration (y)	
	Total	PD-NC	PD-MCI	PD-NC	PD-MCI	PD-NC	PD-MCI	PD-NC	PD-MCI
Cross-sectional studies									
Aarsland et al (2009)[28]	196	159 (81.1%)	37 (18.9%)	67.0 ± 9.4[a]	70.2 ± 7.6[a]	10.9 ± 3.2[a]	11.2 ± 3.7[a]	2.3 ± 1.7[a]	2.4 ± 2.1[a]
Foltynie et al (2004)[34]	142 (T = 159)	92 (64.8%)	50 (35.2%)	66.5[b]	73.7[b]	NA	NA	3.1	2.2
Hoops et al (2009)[40]	115 (T = 132)	92 (80.0%)	23 (20.0%)	63.9 ± 9.7	68.1 ± 9.2[c]	16.5 ± 3.1[c]	16.2 ± 3.1	5.5 ± 4.7	8.2 ± 5.9[c]
Mamikonyan et al (2009)[47]	106	75 (70.7%)	31 (29.2%)	64.6 ± 10.3[a,d]		15.6 ± 3.0[a,d]		6.5 ± 5.8[a,d]	
Muslimovic et al (2005)[13]	115	88 (76.5%)	27 (23.5%)	64.9 ± 10.4[a]	70.3 ± 8.1[a]	11.6 ± 2.3	11.7 ± 2.7	1.5 ± 0.9	1.66 ± 0.9
Pai et al (2001)[53]	102	63 (61.8%)	39 (38.2%)	68.0[d]		6.2[d]		NA	NA
Total	776	569 (73.3%)	207 (26.7%)						
Longitudinal studies									
Janvin et al (2006)[16]	72[e,f]	34 (47.2%)[f]	38 (52.8%)[f]	68.1 ± 9.2[a]	73.2[a]	10.2 ± 3.9[a]	8.8[a]	12.2 ± 4.6[a]	11.2[a]
Williams-Gray et al (2007)[68g]	126[f]	41 (32.5%)[g,h]	72 (57.1%)[h]	NA	NA	NA	NA	NA	NA
Total	198	75 (38%)	110 (55.6%)						

n, Participants in study with Parkinson's disease (PD) who met inclusion criteria; PD-NC, PD without MCI; PD-MCI, PD with MCI; NA, data not available; T, total sample size includes demented patients; significant between-group (PD-NC vs PD-MCI) differences at [a]P <.05, [b]P <.001; [c]data include PD-MCI and PDD; [d]data of the whole sample, not specified by group; [e]59 completed follow-up (82%), of whom 24 developed dementia; [f]at baseline; [g]longitudinal study of Foltynie et al[34] sample; [h]at follow-up; [g]13 developed PDD (10.3%).

subscores for 5 cognitive domains. They found that 38.2% fulfilled MCI criteria, defined as ≥1.5 SDs below the mean in at least 1 subtest.

Longitudinal Studies

One of the studies reviewed[68] included the longitudinal assessment of patients on whom baseline data were reported in the cross-sectional studies selected above.[34] Janvin et al[16] conducted a longitudinal study of cognitive function in a community-based sample of 145 PD cases. Cases and controls were assessed at baseline and after 4 years. Patients with an MMSE score < 25 at baseline were considered demented and excluded. Of the 145 original cases, 72 PD nondemented cases were studied and compared with 38 HCs. After 4 years, for those who completed follow-up, dementia developed in 18 of 29 patients with PD-MCI at baseline (62.0%), compared with 6 of 30 PD patients with normal cognition at baseline (20.0%). This sample consisted of established PD patients, explaining the higher overall conversion rate to PDD over the same period used in the CamPaign study (see below). The proportion converting to PDD was numerically higher among those with single-domain nonamnestic MCI (69%) compared with amnestic MCI (40%), and in a logistic regression analysis this MCI subtype at baseline predicted PDD development. The authors concluded that PD-MCI is a risk factor for developing PDD.

Williams-Gray et al[68] reassessed 126 nondemented PD patients between 3 and 5 years after their baseline evaluation and found that 10% developed PDD over this period. In this first wave of follow-up, older age, non-tremor-dominant phenotype, higher Unified Parkinson's Disease Rating Scale motor scores, and below-average performance on tests of semantic fluency, pentagon copying, spatial recognition memory, and Tower of London were associated with a more rapid rate of decline on the MMSE and progression to PDD. The authors concluded that posterior cortical cognitive deficits increased the risk for the development of PDD, whereas frontostriatal cognitive deficits did not.

Discussion

The results of our systematic literature search and review are that: (1) an average of 26.7% (range, 18.9%–38.2%) of nondemented PD patients have PD-MCI, (2) cognitive deficits can be detected in some patients even at the time of PD diagnosis, (3) the frequency of MCI increases with age and with duration and severity of PD, (4) impairments can occur in a range of cognitive domains, (5) nonamnestic single-domain MCI is more common than amnestic single-domain MCI, and (6) PD-MCI appears to be a risk factor for the development of PDD.

TABLE 2. Assessments, PD-MCI criteria, and cognitive profiles

Author (year)	Domains (tests) assessed	Depression scale	MCI definition	Subjective impairment required	Cognitive profile found
Aarsland et al (2009)[28]	*Verbal memory* (California Verbal Learning Test II, total immediate recall, short-delay and long-delay free recall) *Visuospatial ability* (VOSP Silhouette and Cube subtests) *Attention, executive function* (animal names, MMSE Serial 7s, Stroop Color-Word Test)	MADRS	≥1.5 SDs below the z score in at least 1 of 3 domains	No	Total MCI: 18.9% 86.5% SD 62.2% nonamnestic MCI-SD 24.3% amnestic MCI-SD 13.5% MD 2.7% non-amnestic MCI-MD 10.8% amnestic MCI-MD
Foltynie et al (2004)[34]	*Executive function* (animal fluency and FAS fluency; modified Tower of London task) *Spatial memory* (CANTAB Spatial Recognition Subtest) *Pattern recognition memory* (CANTAB Pattern Recognition Memory Subtest)	No depression scale	≥1 SD below the normative data in ≥1 test	No	Total MCI: 35.2% 58.0% SD 34.0% frontostriatal deficits-SD 24% temporal lobe deficits-SD 42.0% frontostriatal and temporal deficits-MD
Hoops et al (2009)[40]	*Memory* (Hopkins Verbal Learning Test, at least 1 of 2 measures impaired) *Executive function* (Tower of London) *Attention* (backward digit span) *Visuospatial* (cube copying)	GDS-15	≥1.5 SDs below normative data on tests on at least 2 cognitive domains[112]	Yes and preserved independent activities of daily living	Total MCI: 20.0% MCI subtypes not described
Mamikonyan et al (2009)[47]	*Memory* (Hopkins Verbal Learning Test–Revised, abnormal if impaired in 2 of 3 components: immediate free recall total score, retention percentage, and recognition) *Executive function* (Stroop Color-Word Test; Tower of London; semantic verbal fluency, abnormal if impairment in 2 of 3 tests) *Attention* (Digit Span)	Inventory of Depression Symptomatology	≥1.5 SDs below normative data in ≥1 domain	No	Total MCI: 29.2% 61.3% SD 29% attention–SD 19.3% amnestic–SD 13% executive–SD 38.7% MD
Muslimovic et al (2005)[13]	*Executive function* (Trails A and B, Stroop Color-Word Test, Tower of London-Drexel test, modified Wisconsin Card Sorting Test, WAIS-R digit symbol test, Control Word Association Test, category fluency, WAIS-III similarities)	Hospital Anxiety and Depression Scale	≥2 SD below normative data on ≥3 neuropsychological tests	No	Total impaired: 23.5%

(Continued)

TABLE 2. (Continued)

Author (year)	Domains (tests) assessed	Depression scale	MCI definition	Subjective impairment required	Cognitive profile found
	Memory (Auditory Verbal Learning Test, Rivermead Behavioral Memory Test, Logical Memory Test, Wechsler Memory Scale III, Visual Association Test) *Attention* (WAIS-R digits forward and backward) *Language* (Boston Naming Test) *Visuospatial and constructive function* (Judgment of Line Orientation, Groningen Intelligence Test–spatial subtest, Clock Drawing Test)				MCI subtypes not described (reported overall percentage of impaired tests)
Pai et al (2001)[53]	*Memory* (Cognitive Ability Screening Instrument, CASI subtest) *Executive Function* (CASI subtest) *Attention* (CASI subtest) *Language* (CASI subtest) *Visuospatial* (CASI subtest)	No depression scale	≥1.5 SDs below mean in ≥1 subtest	No	Total MCI: 38.2% MCI subtypes not described (reported overall percentage of impaired tests)
Prospective Janvin et al (2006)[16]	*Short-term visual memory* (Benton Visual Retention Test) *Visuospatial abilities* (Judgment of Line Orientation test) *Executive function* (Stroop Color-Word Test)	BDI	≥1.5 SDs below control group in ≥1 test		Total MCI: 52.8%[a] 60.5% SD[a] 44.7% nonamnestic–SD[a] (26.3% executive–SD; 18.4% visuospatial–SD) 15.8% amnestic–SD[a] 39.5% MD[a]
Williams-Gray et al (2007)[68]	*Executive* (animal fluency and FAS fluency, Tower of London) *Pattern recognition memory* (CANTAB Pattern Recognition Memory Subtest) *Visuospatial* (copy of MMSE pentagon) *Spatial Memory* (CANTAB Spatial Recognition Memory subtests)	BDI	≥1 SD below control group on ≥1 test	No	Total MCI: 57.1% MCI[b] frontostriatal-SD ("predominant")

BDI, Beck Depression Inventory; MADRS, Montgomery and Asberg Depression Rating Scale; GDS, Geriatric Depression Scale; VOSP, Visual Object and Spatial Perception Battery; MMSE, Mini–Mental Status Exam; WAIS-R, Weschler Adult Intelligence Scale–Revised; WMS, Wechsler Memory Scale; WCST, Wisconsin Card Sorting Test; COWAT, Controlled Oral Word Association Test; CANTAB, Cambridge Neuropsychological Test Automated Battery; FAS fluency, test of fluency for words starting with F, A, and S; [a]at baseline; [b]at follow-up. Subjects with MCI were categorized as single domain only (cognitive impairment in a single domain, SD), multiple domain (cognitive impairment in 2 or more cognitive domains, MD), and overall impairment (sum of patients who had either single- or multiple-domain cognitive impairment).

Prevalence and Correlates

The majority of PD patients will develop dementia.[3,20] The point prevalence of PDD is approximately 30%,[75] and the cumulative prevalence is at least 75% for PD patients surviving more than 10 years.[2,3] As MCI precedes PDD, the cumulative prevalence of PD-MCI must be at least as high as that of PDD. Consequently, our finding that approximately 27% of PD patients meet criteria for PD-MCI at any given time is not surprising. Our results are similar to those recently reported by Aarsland et al,[76] who used a common methodology for the definition of MCI on pooled data of more than 1000 nondemented PD patients from multiple centers and found that 25.8% (23.5%–28.2%) had MCI.

The lowest proportion of patients with MCI was found in a study of patients at early PD stages,[13] and the highest proportion in studies including cases with more advanced disease severity and duration.[16,68,76] The variation in MCI frequency in the articles reviewed also reflects differences in methodology (eg, study settings and populations, recruitment methods, MCI diagnostic criteria, number of cognitive domains assessed, number of tests used for each domain, and how impairment on a test was defined). That cognitive deficits in PD are detectible in some patients even at the time of clinical diagnosis highlights complexities in differentiating PD from dementia with Lewy bodies.

The correlates of PD-MCI have not been studied extensively. Of the studies included in this review, there was evidence that increasing age,[34,47] more severe PD,[34,47] late onset of disease,[13] and lower educational level[53] were associated with PD-MCI.

Profile of Cognitive Impairment

Although the cognitive deficits in PD have traditionally been classified as being "subcortical" in nature[77] (ie, relatively greater impairments in executive abilities, information-processing speed, and working memory compared with episodic memory storage and language), our review has shown that a range of cognitive domains are impaired in PD patients without dementia. Other research in PD has demonstrated deficits in executive (ie, impaired planning and working memory),[78] visuospatial,[79] attentional,[80] memory,[81] and even language[82–85] abilities.

In all of the studies reviewed here, single-domain MCI was more common than multiple-domain MCI, and nonamnestic MCI was more common than amnestic MCI in patients with impairment in a single domain. Debate exists about the extent to which the mild memory and language deficits in PD are secondary to executive and working memory problems. In addition, as prospective studies using formal definitions for MCI subtypes are almost nonexistent, the

usefulness and predictive value of this PD-MCI classification structure is currently hypothetical.

Epidemiology of Progression from PD-MCI to Dementia

The few longitudinal studies of nondemented PD patients have found that 20%–60% develop PDD over a period of 2–5 years,[22,46,76,86–89] and even newly diagnosed PD patients on average experience significant decline in a range of cognitive domains over a several-year period.[49,90] The finding that PD-MCI patients are at higher risk for developing dementia is consistent with a clinicopathologic study reporting cognitive impairment in the earliest stages of clinically manifested PD, possibly related to changes in brain stem monoaminergic nuclei or early involvement of forebrain cholinergic nuclei.[91]

Preliminary research suggests that the majority of PD-MCI cases convert to PDD over a several-year period.[16,22,68] The 2 longitudinal studies included in this review differed in terms of design and methodology. Williams-Gray et al[68] followed an incident cohort of nondemented PD patients in 2 waves but did not specifically examine progression from a state of "mild impairment" to PDD. The focus of this research to date has been to determine which demographic (increasing age), neuropsychological (semantic verbal fluency and visuospatial deficits), and genetic (*MAPT* H1/H1 tau genotype) factors predicted conversion to PDD in the second wave of follow-up.[22] The other study used a cross-sectional sample of survivors from a prevalence sample.[16] In this study, Janvin et al found that 62% of PD-MCI patients converted to PDD over a 4-year period, compared with 20% of PD patients with normal cognition. The frequency of conversion to PDD over a 4-year period was: multiple domain MCI, 63%; single, nonmemory domain MCI, 69%; single-domain, amnestic MCI, 40%; and normal cognition, 20%.

Regarding other risk factors, in one of the longitudinal studies reviewed, increasing severity of depression was associated with an increased risk of conversion from PD-MCI to PDD.[16] In other research not covered in this article, demographic and clinical correlates or risk factors for PDD development have included older age, male sex, lower educational level, longer duration of PD, and greater motor impairment.[22,64,83,86,90,92,93]

Clinical Impact

PD-MCI appears to be a clinically significant syndrome, as even mild cognitive deficits or self-rated cognitive deficits in early PD are associated with functional impairment[5,94] and worse quality of life (QoL).[95,96] Thus, identification and intervention at the earliest stage of PD-MCI is a crucial unmet need for the overall care of PD patients. The high frequency of

MCI in PD highlights the need for clinicians to routinely screen for cognitive impairment in PD, as the results, including their prognostic implications, may influence clinical decision making. However, research in this area is preliminary, and additional studies are needed to validate measures that are sensitive to initial changes in independent activities of daily living (IADLs), QoL, and interpersonal relationships that can occur at the stage of PD-MCI.

Complexities in the Assessment of Cognition in PD

Assessment of cognition in PD can be complicated by disease- or medication-related effects, such as bradykinesia, fatigue, sleepiness, and mood disorders, which can adversely affect test results regardless of cognitive abilities. Specifically, motor slowing (ie, bradykinesia) and resting or intentional tremor may lead to impaired performance on any timed test, whereas tremor can interfere with performance on any test requiring motor abilities (eg, use of a pencil to complete a task). However, there has been very little research examining the impact of these factors on cognitive performance specifically.

Another issue is that the definition of MCI forces a dichotomization (present–absent) of a continuous variable (cognitive test performance), and debate continues regarding the appropriate cutoff score and number of tests used to define PD-MCI. Caviness et al[32] reported that 21% of subjects had PD-MCI if an abnormality on multiple tests within a domain was required, but this rose to 42% if an abnormality on only 1 test was required. There is concern that the commonly used definitions of MCI may lack sensitivity to detect early cognitive decline (rather than impairment) in high-functioning persons.[97] Persons functioning at a high level (ie, above average) premorbidly have to experience sizeable declines before scoring at least 1.5 SDs below normative means. Consequently, a considerable proportion of such patients with cognitive decline would be classified as having "normal cognition." Although it can be argued that high premorbid functioning protects against MCI in much the same manner as it does against dementia, this argument ignores that high-functioning persons may be in more demanding work or social settings, in which even small cognitive declines translate into subtle functional impairments. On the other hand, a key feature in diagnosing MCI pertains to a change in cognition. Thus, MCI is not just a value on a cognitive test relative to the mean; rather, it is critical that the person has experienced a change in cognition compared with baseline.

Additional unresolved issues are whether cognitive decline in PD is linear and whether different profiles of cognitive deficits may have a different evolution and prognosis. Previous studies have noted that time to PDD diagnosis is highly variable[98] and that cognitive changes after relatively long-term follow-up are not too consistent.[97] Although a distinct evolution of different cognitive domains cannot be inferred from a study using only the MMSE, the reanalysis of data from a long-term prevalence study identified a variation in the slope of decline, specifically a rapid cognitive deterioration after a relatively stable period.[99] These data should be examined in light of neuroimaging[18,19] and clinical[52,68] data showing that the transition from MCI to dementia in PD is characterized by the addition of posterior cortical deficits on frontal-subcortical ones.

Biomarkers

None of the reviewed articles examined biomarkers specifically as they pertain to PD-MCI. One of the incident cohorts included in this review underwent a second wave follow-up,[22] and in that research the tau MAPT H1/H1 genotype (but not the COMT genotype) was found to be a risk factor for PDD, a finding recently confirmed.[23] Other genetic polymorphisms (eg, COMT polymorphisms and the BDNF Val66Met genotype[100,101]) have been shown to be associated with impairments in specific cognitive domains or abilities in PD. Several CSF biomarkers for cognitive decline in PD have been proposed.[102] Recent research suggests decreased CSF β-amyloid (Aβ) 1–42 is associated with the early stages of cognitive decline in PD.[24,26] This decrease might be due to specific Aβ plaque pathology, but it may be nonspecific, as Aβ 1–42 has been shown to be decreased in neurodegenerative disorders lacking distinct plaque pathology,[103–105] and in vivo plaque imaging (PET imaging with the Aβ-binding Pittsburgh Compound B) showed no correlation between the plaque load and cognition in PD.[106] Instead, the findings suggested a different mechanism of Aβ processing, perhaps due to synaptic α-synuclein pathology.[107,108] A study using structural neuroimaging, including diffusion tensor imaging, reported white matter abnormalities in nondemented PD patients.[108] In another study[17] that classified patients as PD normal cognition (PD-NC), PD-MCI, or PDD and used 2 different imaging analyses, PD-MCI patients compared with PD-NC either had reduced gray matter in the prefrontal cortex and temporal lobes[17] or were found to have similar regional brain volumes. Using FDG-PET, a PD-related cognitive pattern in nondemented PD patients has been reported, characterized by metabolic reductions in frontal and parietal association areas and relative increases in the cerebellar vermis and dentate nuclei.[109] The pattern predicted memory and visuospatial performance, and in a subsequent study single-domain MCI patients had a PD-related cognitive pattern expression intermediate (but not

statistically significantly different) between normal and multiple-domain MCI patients.[18] Clearly, there is a need for prospective and longitudinal assessment of accessible biomarkers (including CSF, blood, and neuroimaging) and neuropathological examination to further address this issue.

Conclusions and Future Directions

There has been limited research on the epidemiology and prognostic utility of PD-MCI as a clinical syndrome. Nonetheless, the studies selected for review here and other studies of PD-MCI not meeting inclusion criteria yield relatively consistent prevalence estimates of MCI and its subtypes. They also show that single-domain MCI is more common than multiple-domain MCI and that nonamnestic, single-domain MCI is more common than amnestic, single-domain MCI.

The task force has used this critical review of the literature and consensus of experts to formulate PD-MCI diagnostic criteria that will be published separately. Once diagnostic criteria for PD-MCI are proposed, prospective studies enrolling subjects with a wide range of premorbid ability will be needed to examine the predictive value of both MCI overall and MCI subtypes. Intervention trials can target MCI as a clinical syndrome, perhaps stratifying MCI by subtype to determine if particular interventions (pharmacological vs behavioral) have differential acute or long-term effects. Although it is not known if or how a diagnosis of PD-MCI should affect clinical management, at a minimum, these patients should be carefully monitored for ongoing cognitive decline. ∎

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