Prognosis of Mild Cognitive Impairment in Early Parkinson Disease

The Norwegian ParkWest Study

Kenn Freddy Pedersen, MD, PhD; Jan Petter Larsen, MD, PhD; Ole-Bjorn Tysnes, MD, PhD; Guido Alves, MD, PhD

Importance: Mild cognitive impairment (MCI) is common in Parkinson disease (PD), but the prognostic value of MCI in early PD is unknown.

Objective: To examine the course of MCI and its progression to dementia in an incident PD cohort.

Design: Prospective longitudinal cohort study.

Setting: The Norwegian ParkWest study, an ongoing population-based study of the incidence, neurobiology, and prognosis of PD in western and southern Norway.

Participants: A population-based cohort of 182 patients with incident PD monitored for 3 years.

Main Outcomes and Measures: Serial neuropsychological tests of attention, executive function, verbal memory, and visuospatial skills were administered at baseline, 1 year, and 3 years. Patients were classified as having MCI and received a diagnosis of dementia according to published consensus criteria.

Results: Significantly more patients with MCI than without MCI at baseline (10 of 37 [27.0%] vs 1 of 145 [0.7%]; relative risk, 39.2 [95% CI, 5.2-296.5]; \( P < .001 \)) progressed to dementia during follow-up. Of those with MCI at baseline, 8 of 37 (21.6%) had MCI that reverted to normal cognition during follow-up. Mild cognitive impairment at the 1-year visit was associated with a similar progression rate to dementia (10 of 36 patients [27.8%]) and reversion rate to normal cognition (7 of 36 [19.4%]). However, among the 22 patients with persistent MCI at baseline and the 1-year visit, 10 (45.5%) developed dementia and only 2 (9.1%) had MCI that reverted to normal cognition by the end of study.

Conclusions and Relevance: Mild cognitive impairment at PD diagnosis predicts a highly increased risk for early dementia. Repeated neuropsychological testing increases the prognostic accuracy of MCI with respect to early dementia development in PD.

A detailed description of the multiple case finding strategies and the diagnostic procedures has been published. The initial study cohort was recruited between November 1, 2004, and August 31, 2006, and comprised 212 patients with incident PD, of whom 196 were drug-naive, nondepressed and nondemented, and eligible for follow-up. After baseline, therapy with dopaminergic medication was started, and the patients came to clinical visits at 6-month intervals, with standardized motor, neuropsychiatric, and cognitive assessments conducted at study entry and after a mean (SD) time of 1.0 (0.1) and 3.0 (0.2) years of follow-up. During follow-up, diagnosis changed or became uncertain in 14 participants. The remaining 182 patients met the National Institute of Neurological Disorders and Stroke and the UK PD Society Brain Bank diagnostic criteria for PD at their final visit. None fulfilled the diagnostic criteria of dementia with Lewy bodies, AD, or other dementia syndromes. All patients were white.

The study was approved by the Regional Committee for Medical Research Ethics, Western Norway. Signed written informed consent was obtained from all participants.

CLINICAL ASSESSMENT

All patients were interviewed and examined by trained members of the ParkWest study group. A semistructured interview was performed to obtain information on clinical history and demographic variables at baseline, 1 year, and 3 years of follow-up. At each visit, the severity of parkinsonism was assessed by the Unified Parkinson’s Disease Rating Scale and the Hoehn and Yahr scale. Severity of depressive symptoms was assessed by the Montgomery-Asberg Depression Rating Scale, which has been validated and recommended for use in patients with PD, with a score above 17 indicating major depression with high specificity.

NEUROPSYCHOLOGICAL ASSESSMENT

Patients underwent a standardized program of cognitive tests at baseline and follow-up visits after 1 and 3 years. Global cognitive functioning was measured using the Mini-Mental State Examination, and a neuropsychological test battery minimally affected by motor performance was administered by trained study nurses who, at reassessments, were unaware of the patients’ previous MCI status, to assess cognitive domains known to be affected in PD. Attention was examined using the word-reading and color-naming parts of the Stroop test. Executive functions were assessed with the Semantic Verbal Fluency Test and the interference condition of the Stroop test. Verbal memory was examined using the California Verbal Learning Test II (CVLT-II), from which total immediate recall (sum of trials 1-5), short-delay, and long-delay free recall scores were included. Visuospatial abilities were assessed with the Silhouettes and Cube subtest from the Visual Object and Space Perception battery.

DIAGNOSIS OF MCI

A diagnosis of MCI in patients with PD was made according to recently proposed consensus criteria. In the present study, patients were required to meet the following criteria: (1) objective cognitive deficits as defined by at least 2 neuropsychological test scores falling 1.5 SDs or more below the mean value of appropriate norms, (2) subjective cognitive problems reported by patients or family members as defined by a score greater than 3.0 on the Informant Questionnaire on Cognitive Decline in the Elderly, or a score of 1 or more on item 1 (intellectual impairment) of the Unified Parkinson’s Disease Rating Scale part I (mentation, behavior, and mood section), (3) no functional impairment in basic activities of living caused by cognitive dysfunction (see the Diagnosis of Dementia subsection), and (4) not demented. Published normative data for all neuropsychological tests were applied, correcting for age, as well as sex and educational level, if possible. Because neuropsychological testing did not include measures of language function, subclassification of PD-MCI was not performed (level 1 criteria).

DIAGNOSIS OF DEMENTIA

A diagnosis of possible or probable PDD was made by consensus between 2 of the authors (K.F.P. and G.A.) according to published criteria on the basis of all available information, including neuropsychological testing, evidence of temporal cognitive decline as assessed by neuropsychological test scores and Mini-Mental State Examination scores, and a standardized interview to assess functional impairment caused by cognitive dysfunction (including information about impaired occupational functioning leading to disability benefit or the new appearance of problems with self-administration of medication and/or car driving but not associated with motor impairment). Presence of apathy, hallucinations, or delusions was considered supportive but not mandatory for the diagnosis of PDD. Exclusion criteria for PDD included features suggesting other comorbid conditions or diseases as the cause of mental impairment, such as acute confusion due to systemic diseases or drug intoxication, major depression, and abrupt deterioration or stepwise progression of cognitive deficits indicating cerebrovascular disease.

FOLLOW-UP

The flow of patients through the study period is summarized in the Figure. Of the 182 patients who met the criteria for PD at diagnostic reevaluation, we could account for dementia status in all by the study’s end, including 8 who withdrew consent from study participation (none with PDD after 3 years of routine clinical follow-up). In addition, 8 patients died during follow-up. Of these, 7 had not developed dementia, whereas 1 patient developed PDD 2 years after diagnosis, 6 months before death.

STATISTICAL ANALYSIS

Dementia incidence was estimated as the number of cases with dementia divided by the total number of person-years at risk during follow-up. Person-years at risk were estimated as the total follow-up time until dementia, death, or study end for those who remained nondemented. For cases of incident dementia, the time of dementia onset was assumed to be the midpoint of the interval between assessments at which dementia was diagnosed. Proportions and relative risks (RRs) with 95% CIs were calculated. Group differences in demographic, clinical, and neuropsychological variables were analyzed with the independent-sample unpaired t test, Mann-Whitney test, x² test, and Fisher exact test where appropriate. The paired Wilcoxon signed rank test was used to compare differences in neuropsychological variables over time (baseline and follow-up surveys) and to calculate effect sizes. The effect size, r, was considered small if 0.1, medium for 0.3, and large when 0.5 or greater. Analyses were performed using commercial software (PASW, version 18.0; SPSS/IBM). Two-tailed analysis was conducted, with P < .05 considered significant.
RESULTS

BASELINE CHARACTERISTICS

Of the 182 patients with incident PD included in this 3-year follow-up study, 37 patients (20.3%) met the criteria of MCI at baseline, whereas 145 patients (79.7%) did not (Table 1). Patients with MCI at baseline were older and had less education, longer disease duration, more severe parkinsonism, and lower Mini-Mental State Examination scores than did those without MCI. There were no significant differences regarding sex, severity of depressive symptoms, or drug use.

MCI STATUS AND RISK OF DEMENTIA

Ten of 37 patients (27.0%) with MCI vs only 1 of 145 patients (0.7%) without MCI at baseline developed incident dementia within 3 years of follow-up, all meeting the criteria of probable PDD. Hence, the sensitivity was 90.9% and the specificity was 84.2% for MCI at baseline to detect patients with dementia development during the first 3 years after PD was diagnosed. The corresponding positive predictive value was 27.0% and the negative predictive value was 99.3%.

The RR for dementia in patients with MCI vs non-MCI at baseline was 39.2 (95% CI, 5.2-296.5; \( P < .001 \)). The incidence rate of dementia per 1000 person-years of observation was 2.3 (95% CI, 0.1-12.8) in patients without MCI at baseline, 98.9 (95% CI, 47.4-181.9) in patients with MCI at baseline, and 20.5 (95% CI, 10.2-36.7) overall.

At the 1-year follow-up, MCI status was available in 178 patients, with 36 patients (20.2%) classified as MCI and 142 patients (79.8%) as non-MCI (Table 2). Mild cognitive impairment at 1 year was equally predictive of incident dementia during follow-up as MCI at PD diagnosis (27.8% vs 27.0%), and the reversion rate to normal cognition at the final visit was also similar (19.4% for MCI at the 1-year visit compared with 21.6% for MCI at baseline). However, the combination of MCI status at baseline and 1 year of follow-up demonstrated that, among patients with MCI on both occasions, 45.5% converted to dementia and only 9.1% reverted to normal cognition. Thus, the sensitivity was 90.9% and the specificity was 92.8%, whereas the positive predictive value was

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<th>Table 1. Baseline Demographic and Clinical Characteristics of Incident Parkinson Disease Patients With and Without Mild Cognitive Impairment</th>
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<td><strong>Characteristic</strong></td>
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Abbreviations: MADRS, Montgomery-Åsberg Depression Rating Scale; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination; PD, Parkinson disease; UPDRS, Unified Parkinson’s Disease Rating Scale.

*For PD-no MCI vs PD-MCI.

**Independent-sample t test.

†Fisher exact test.
45.5% and the negative predictive value was 99.4% for persistent MCI at 1 year to detect incident dementia within 3 years of PD diagnosis.

**PREDICTORS OF MCI CONVERSION TO DEMENTIA**

Patients with MCI that converted to dementia were older and showed more deficits on measures of attention (Stroop color) and verbal memory (CVLT-II total immediate and total delayed free recall) at baseline than MCI nonconverters but did not differ significantly in other demographic, clinical, or neuropsychological variables (Table 3 and Table 4). There were no significant differences in the use of levodopa, dopamine agonists, or entacapone between MCI converters and nonconverters at their final visit. None of the MCI converters were receiving monoamine oxidase inhibitors (Table 5).

**REVERSAL OF MCI**

Eight patients with MCI at baseline reverted to normal cognition at the end of follow-up. Among these, 6 patients had less than 2 impaired neuropsychological tests, and 2 failed to meet both objective and subjective cognitive criteria of MCI at follow-up. Patients with MCI that reverted to normal cognition during follow-up were significantly younger ($P = .003$) and had shorter disease duration ($P = .03$), less severe parkinsonism ($P = .04$), and better test performance on the Stroop word ($P = .002$), Stroop color ($P = .001$), semantic fluency ($P = .02$), and CVLT-II total immediate recall ($P = .045$) at baseline than...
did MCI converters. Please refer to eTables 1 and 2 (http://www.jamaneuro.com) for more details. The MCI reverters also showed significant improvement in Stroop interference and CVLT-II total immediate recall scores between baseline and 3-year follow-up (median, 20.0 vs 25.0, \( P = .01 \); and median, 23.5 vs 33.0, \( P = .03 \)), with large effect sizes \((r = 0.63\) and 0.56, respectively) but exhibited no significant differences in other neuropsychological variables over time (data not shown). Neither MCI reverters nor patients with stable MCI were using cholinesterase inhibitors at their final visit compared with 20% of the MCI converters.

**COMMENT**

This prospective population-based study of an incident PD cohort demonstrates that MCI within the first year of PD diagnosis signals a highly increased risk for early incident dementia. More than 25% of patients with MCI at diagnosis of PD developed dementia within 3 years of follow-up compared with less than 1% of patients without MCI at PD diagnosis. Among patients with MCI at baseline and 1 year of follow-up, almost half progressed to dementia. These findings support the validity of the MCI concept in patients with early PD.

Although long-term studies in PD demonstrate that most patients will eventually develop dementia,\(^{33,34}\) the time of onset of dementia and less severe cognitive deficits is highly variable.\(^{35,36}\) Future interventions are likely to yield the most benefit if initiated early, when cognitive deficits are mild. The construct of MCI in PD has received increased attention during the past 5 years\(^{37}\) but prospective longitudinal studies using formal MCI criteria have not been published, except one study of advanced PD.\(^{38}\) Only recently, a task force of the Movement Disorder Society has proposed specific guidelines and uniform diagnostic criteria for MCI in PD.\(^{39}\) These criteria allow diagnosing PD-MCI based on “comprehensive” (level II) or “abbreviated” (level I) cognitive assessment, with the latter being more suitable for clinical practice as well as for large-scale studies such as ours. Our prospective study demonstrates that MCI, meeting level I criteria, in the first year of PD diagnosis is highly sensitive (91% sensitivity) in detecting patients who will develop early PDD. Equally important, our data show that patients without MCI at PD diagnosis are likely to remain free of dementia for at least 3 years, with a negative predictive value of more than 99%. The low positive predictive value (27%) was not unexpected given the relatively short follow-up period. Whether more extensive neuropsychological testing and follow-up may further improve these figures remains to be clarified.

The pattern of cognitive impairment in PD is heterogeneous, both in cognitive profile,\(^{37}\) pathologic changes,\(^{39,40}\) and genetic contributions.\(^{41}\) In our cohort, impairment in verbal memory and attention was associated with conversion from MCI to PDD. This is consistent with previous studies that have shown frontal/executive and verbal memory deficits to be associated with the development of PDD.\(^{42,43}\) Although others have also found visuospatial dysfunction\(^{44}\) to predict incident dementia in PD. These inconsistencies deserve further investigations but may reflect different definitions of cognitive impairment and PDD, differences in sample characteristics, or biological heterogeneity. In addition, individual differences in cognitive reserve could account for some of these inconsistencies. Educational level is frequently used as a proxy of cognitive reserve, and there is some evidence to suggest that higher educational level may protect against cognitive decline in PD.\(^{45}\) Although patients with MCI in our study had lower educational levels than did those with MCI at baseline, we found no significant differences between MCI reverters and those who did not convert to dementia. However, the small sample size in each MCI subgroup, combined with the short follow-up, does not allow firm conclusions. Studies with larger MCI cohorts, longer follow-up, and more detailed assessment of cognitive reserve are needed to clarify this issue.

The overall incidence of PDD in our study was 20.5 per 1000 person-years of observation but with substantial differences between patients with (98.9) and without (2.3) MCI. Hence, the incidence of PDD was largely driven by participants with PD-MCI. The proportion of patients with and without MCI may vary between studies depending on recruitment strategies and clinical characteristics, such as age, disease severity, and duration of PD. Calculating the incidence of PDD among patients with PD-MCI (separately from patients without PD-MCI) may provide more stable estimates across different populations (ie, clinic vs population-based) and disease stages and thus increase comparability between studies.\(^{46}\)

Among patients with MCI at PD diagnosis, 27% developed incident dementia within 3 years, corresponding to an annual progression rate of MCI to dementia of 9% in early PD. One previous longitudinal study\(^{38}\) of advanced PD reported that 62% of patients with MCI developed dementia during 4 years of follow-up, equivalent to an annual rate of MCI conversion to dementia of 15.5%. These figures are consistent with studies\(^{47}\) in non-PD populations, reporting annual progression rates from MCI to dementia (mainly of Alzheimer disease type) of 6% to 10% in population-based cohorts and 10% to 15% in clinic-based samples.

However, longitudinal studies of MCI in non-PD populations also show that MCI in a considerable proportion of patients remains stable over time or even reverts to normal cognition; in large and well-designed community-based cohorts, reversion rates of 14% to 41% have been reported,\(^{48-50}\) even when MCI was based on comprehensive cognitive test batteries. In our population-based PD cohort, we found that less than 25% of the patients with MCI at PD diagnosis were determined to have normal cognition at 3-year follow-up. However, among patients with persistent MCI during the first year of PD diagnosis, the reversion rate was considerably lower (9.1%), and in almost half, MCI progressed to dementia within the subsequent 2 years of follow-up. Hence, our study demonstrates that repeated neuropsychological testing during the first year of PD diagnosis increases the prognostic value of MCI in early PD, which has implications for clinical practice and future research.

Potential explanations for the observed reversal of PD-MCI in some of our patients include disease-related or...
unrelated comorbidities, measurement errors, learning effects due to repeated neuropsychological testing, or improved cognition after initiation of symptomatic treatment. Although our study does not allow direct conclusions in this respect, we observed a significant improvement in Stroop interference and CVLT-II total immediate recall test performance over time in patients in whom MCI reverted to normal cognition. The former may indicate a cognition-enhancing effect of dopaminergic drugs resulting from increased response inhibition, which is partly mediated by frontostriatal dopamine pathways. Given the progressive nature of PD, dopaminergic drug effects on cognition are likely to be transient. Longer follow-up of our cohort will clarify whether early PD-MCI reverters are prone to reconvert to having MCI that may progress to dementia in a long-term perspective.

Strengths of this study include the (1) population-based incident PD cohort, (2) comprehensive and prospective procedures to diagnose PD and to exclude individuals with alternative diagnoses, (3) repeated neuropsychological assessments, and (4) diagnosis of PD-MCI and PDD according to recently published diagnostic criteria. Our study also has limitations, such as the (1) limited battery of cognitive tests because of the population-based design, (2) relatively few participants with PDD, as expected in early PD, and (3) rather short follow-up period. These limitations, however, do not bias our observation that MCI during the first year after PD diagnosis predicts a highly increased risk for early dementia development in PD. Longitudinal studies with longer follow-up periods are needed to further examine the cognitive trajectories of MCI in PD, their biological correlates, and their effect on dementia risk in a long-term perspective.

Accepted for Publication: December 10, 2012. Published Online: March 25, 2013. doi:10.1001/jamaneurol.2013.2110

Correspondence: Kenn Freddy Pedersen, MD, PhD, The Norwegian Centre for Movement Disorders, Stavanger University Hospital, PO Box 8100, N-4068 Stavanger, Norway (kennfrp@online.no).

Author Contributions: Drs. Pedersen and Alves had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: All authors. Acquisition of data: Pedersen, Tysnes, and Alves. Analysis and interpretation of data: Pedersen, Larsen, and Alves. Drafting of the manuscript: Pedersen and Alves. Critical revision of the manuscript for important intellectual content: All authors. Statistical analysis: Pedersen and Alves. Obtained funding: Larsen, Tysnes. Study supervision: Larsen and Alves.

Conflict of Interest Disclosures: Dr. Pedersen has received speaker honoraria from H. Lundbeck A/S. Dr. Larsen has served on scientific advisory boards for H. Lundbeck A/S and GlaxoSmithKline, has received speaker honoraria from GlaxoSmithKline and Orion Pharma, serves as associate editor of the Journal of Parkinson's Disease, and has received research support from the Western Norway Health Trust, the Norwegian Research Council, and the Norwegian Parkinson Disease Association. Dr. Tysnes has served on scientific advisory boards for H. Lundbeck A/S and GlaxoSmithKline, has received speaker honoraria from GlaxoSmithKline and Orion Pharma, and serves on the editorial board of Acta Neurologica Scandinavica. Dr. Alves has received speaker honoraria from H. Lundbeck A/S and Orion Pharma.

Funding/Support: The Norwegian ParkWest study was supported by grant 911218 from the Western Norway Regional Health Authority, grant 177966 from the Research Council of Norway, and the Norwegian Parkinson Disease Association.

Role of the Sponsors: The sponsors of the study had no role in the study design, data collection, data analysis, data interpretation, or writing of the report.


Additional Contributions: The authors are grateful to all patients for their willingness to participate in this study and thank all personnel involved in planning and conducting the Norwegian ParkWest study.

REFERENCES