Published in final edited form as:

J Alzheimers Dis. 2010 ; 22(3): 1005–1013. doi:10.3233/JAD-2010-101230.

Mild cognitive impairment is associated with mild parkinsonian signs in a door-to-door study of an elderly Arab population

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Abstract

Mild Cognitive Impairment (MCI) and healthy aging have been shown to be associated with Mild Parkinsonian Signs (MPS). We performed a door-to-door observational and follow-up study amongst consenting residents of Wadi Ara Arab villages in northern Israel aged 65 years ($n = 687$) to examine whether MPS represent a risk factor for MCI and/or conversion from MCI to Alzheimer's disease (AD). In Phase 1, 223 cognitively normal (CN) and 173 MCI subjects were assessed by interview for medical history, neurological examination, motor part of the Unified Parkinson Disease Rating Scale (mUPDRS) (divided into item-clusters: axial, limb bradykinesia, tremor and rigidity) and cognitive tests. MCI subjects ($n = 111$) were reevaluated in Phase 2 for conversion to AD at least one year after initial assessment. MCI subjects had a higher frequency of axial dysfunction (8.7% vs. 1.3%) and limb bradykinesia (10.4% vs. 1.3%) than CN subjects ($p < 0.001$, both). Stepwise logistic regression analysis estimating the probability of MCI vs. CN revealed higher mUPDRS (OR = 1.19, 95% CI, 1.05 to 1.35, $p = 0.006$) and higher limb bradykinesia scores (OR = 1.75, 95% CI, 1.2 to 2.56, $p = 0.003$) and not age as explanatory variables. Presence of MPS did not predict conversion to AD after adjustment for age and time-interval. These results suggest that axial and bradykinetic parkinsonian signs represent risk factors for MCI but MPS may not predict conversion from MCI to AD.

Keywords

Mild Cognitive Impairment; Mild Parkinsonian Signs; Alzheimer's disease; neuroepidemiology; risk factors; aging

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1. Introduction

Mild Parkinsonian Signs (MPS) include gait and balance disturbances, rigidity, bradykinesia, and tremor. The prevalence of MPS in healthy individuals on clinical examination is more common with increasing age but estimates vary [1]. MPS have also been described in the context cognitive decline [1].

The identification and classification of the prodromal stages of neurodegenerative diseases is key to clinical, neuropathological, disease mechanism, neuroimaging and clinical trial research. MPS may be a biomarker indicative of an increased risk for the development of Alzheimer's disease (AD), Lewy body disease or full-blown Parkinson's disease (PD). The Israeli-Arab population studied herein is remarkable for a high prevalence of dementia, low levels of schooling and high consanguinity rates [2, 3]. Additionally, while the prevalence of PD is similar to that described in Western countries (1.4%), the frequency of action tremor (1.8%) and essential tremor (0.8%) is unusually low [4]. In this study, we examined whether mild parkinsonian signs (MPS) and which MPS item-clusters are associated with mild cognitive impairment (MCI) and/or conversion from MCI to Alzheimer's disease (AD).

2. Methods

2.1 Study population and setting

We performed a door-to-door observational study with follow-up in Wadi Ara (the Ara Valley), an Arab community of 81,400 inhabitants located in northern Israel.

Eligibility criteria—All Wadi Ara residents aged ≥ 65 years on prevalence day (January 1st, 2003) were eligible (n = 2,067, according to the Israel Central Bureau of Statistics). There were no selection criteria.

We ascertained individuals aged ≥ 65 years between January 2003 and December 2007 and subsequently performed follow-up assessments without any selection criteria. The study was approved by the Institutional Ethics Committee of the Sheba Medical Center according to guidelines from the Israel Ministry of Health and was reviewed by the Institutional Review Boards of University Hospitals of Cleveland, the Universities of Case Western Reserve, Boston and Louisville. All participants signed a written consent form in Arabic. In the event of the subject being illiterate, the interviewer read the consent form to the subject, who then signed by fingerprinting with the index finger of his/her dominant hand.

Assessment of Parkinsonian Signs—All subjects underwent neurological examination including the motor part of the UPDRS (mUPDRS) [5]. The mUPDRS score was split into four sub-categories (item-clusters): Tremor (items 20–21), Rigidity (item 22 excluding neck rigidity), Limb Bradykinesia (LB) (items 23–26) and Axial (items 18,19,27–31 and neck rigidity from item 22). We defined MPS as present if the mUPDRS score was ≥ 2. Each item-cluster was defined as being abnormal if the score was ≥ 2 [6].

We used Gelb's criteria for PD diagnosis [7].

Cognitive Instruments—Arabic translations of the Mini-Mental State Examination (MMSE; maximum score = 30) and the Brookdale Cognitive Screening Test (BCST; maximum score = 24) were used. The BCST was developed at the Brookdale Institute of Gerontology, Jerusalem, Israel, for use in populations with poor literacy and includes items on orientation, language, memory, attention, naming, abstraction, concept formation, attention, praxis, calculation, right-left orientation and visuo-spatial orientation [8].

The Arabic versions of the MMSE and BCST have been validated, and norms have been published [3]. A highly significant correlation between MMSE and BCST scores in normal subjects has previously been reported by our group ($r = 0.852$; $p < 0.0001$). This correlation was of the same magnitude for men ($r = 0.8223$) and women ($r = 0.854$; $p < 0.0001$ for both) [3].

Cognitive Classification

Cognitively Normal (CN): A subject was defined as CN if there were no complaints relating to memory or any other cognitive domain, no evidence of such disturbance according to the informant history or neurological examination, and no evidence of impairment in activities of daily living (ADLs) due to cognitive disturbances [3].

Mild Cognitive Impairment: Subjects were classified as MCI if they had impaired cognitive function on examination, with a Clinical Dementia Rating Scale score of 0.5 [9] and an informant record of cognitive decline, but were fully independent in their activities of daily living [9, 10].

Alzheimer's disease (AD): Dementia was diagnosed according to DSM-IV, [11] ICD-10 criteria [12] and AD by NINCDS-ADRDA criteria for probable or possible AD [13].

Vascular dementia (VaD): VaD was diagnosed according to the International Classification of Diseases, 10th revision (ICD-10) criteria. A history consistent with cerebrovascular disease, pyramidal signs and previous cerebral imaging were actively sought to substantiate a diagnosis of VaD.

Not classifiable: The category “not classifiable” included subjects with complex medical conditions or advanced systemic disease in whom it could not be determined whether the cognitive impairment was due to the underlying medical condition or the neurodegenerative disease.

Since MMSE and BCST scores are strongly dependent on education in both sexes in this population, we did not use cut-off scores for cognitive classification [3]. Three neurologists (MM, RS and RI) reviewed the results of the field examination of each subject in a bi-monthly conference and generated a consensus diagnosis.

2.2 Study design

Phase 1: MPS in MCI versus CN subjects—In Phase 1 of the study, we cognitively classified all subjects that agreed to participate as CN, MCI or dementia and excluded all subjects with dementia.

Among CN and MCI subjects we excluded those with confounding reasons that could influence the mUPDRS score, e.g. PD, drug-induced tremor, previous stroke or other comorbidities (medical, neurological or orthopedic).

Phase 2: Re-examination of MCI subjects for conversion to AD—In Phase 2, all subjects diagnosed as MCI were re-examined after 1 year using the cognitive classifications described above without using any selection criteria. Causes for exclusion (as in Phase 1) were reviewed to account for newly developed confounding comorbidities (e.g. end-stage renal failure or stroke).

2.3 Statistical analysis

Statistical analyses were performed using SAS (Statistical Analysis Software). In Phase 1, we estimated the probability of MCI vs. CN using logistic regression models. The first stepwise logistic regression model estimated the probability of MCI vs. CN as a function of age, total mUPDRS score and its interaction with age. The second used age, mUPDRS item-cluster scores and their interactions with age.

In Phase 2, MCI subjects were re-examined after 1 year to determine conversion to AD. We estimated the probability of conversion to AD vs. remaining as MCI by two stepwise logistic regression models: firstly as a function of age, time interval between the first and second examination, total mUPDRS score and the two-way interactions of these variables and secondly as a function of age, time interval between examinations, each mUPDRS item-cluster score and the two-way interactions of these variables.

Subjects with missing data for any of the explanatory variables were excluded.

3. Results

Of 687 approached subjects, 26 (3.8%) declined examination, 166 were excluded after being classified as suffering from dementia (AD = 89, VaD = 43, other = 34). Eighty-one subjects were excluded because of PD (n = 15), parkinsonism (n = 2), drug induced tremor (n = 7), previous stroke (n = 28) or other medical, neurological or orthopedic comorbidities (n = 29) that would influence the mUPDRS score. Eighteen additional subjects were excluded due to incomplete data. In total 396 subjects (CN = 223, MCI = 173) were included in the study (Figure 1).

3.1 Phase 1

The mean ages of CN subjects (72.2 ± 5.5 years) and MCI subjects (72.5 ± 5.7 years) were not significantly different ($p > 0.1$) (Table 1). The mean mUPDRS score was significantly higher for MCI subjects (0.82 ± 2.3) than for CN (0.30 ± 1.3 , $p = 0.004$). MCI subjects had a higher frequency of axial dysfunction (8.7% vs. 1.3%, $p = 0.0005$) and LB than CN subjects (10.4% vs. 1.3%, $p = 0.0006$). Tremor scores did not differ significantly between the two cognitive groups. There were no subjects with abnormal rigidity scores classified as MCI or CN. We retrospectively verified the files of subjects with abnormal rigidity scores. Reasons for exclusion were: newly diagnosed PD (n = 1), orthopedic comorbidity (n = 1) or previous stroke (n = 2).

The first stepwise logistic regression model which estimated the probability of MCI vs. CN as a function of age, total motor UPDRS score (mUPDRS) and its interaction with age, revealed mUPDRS as the only significant explanatory variable (OR = 1.19, 95% CI, 1.05 to 1.35, $p = 0.006$). Hence, higher mUPDRS scores predicted greater probability of being an MCI subject. Age was not found to be significant. The value of the Akaike's Information Criterion (AIC) for this model was 539.51. The AIC is a measure of goodness of fit of the estimated model which takes into account the number of variables in the model. A relatively lower value AIC represents a better model.

The second logistic regression model which estimated the probability of MCI vs. CN as a function of age, each mUPDRS item-cluster score and their interactions with age, revealed LB as the only significant explanatory variable (OR = 1.75, 95% CI, 1.2 to 2.560, $p = 0.003$). The AIC of 532.14 indicated that the second model was better than the previous one.

3.2 Phase 2

Of 173 subjects with an initial diagnosis of MCI, 111 underwent a second cognitive assessment (Figure 1), 9 died before undergoing a second cognitive assessment, 4 subjects were excluded having developed end-stage renal failure ($n = 2$), stroke ($n = 1$) and an orthopedic complication ($n = 1$), 47 had a time interval between cognitive assessments of 1 year and 2 were lost to follow-up.

The time interval between cognitive assessments for the 111 subjects who underwent a second cognitive assessment was 47 ± 18 months. Twenty-four out of 111 MCI subjects (21.6%) converted to AD, giving an annual conversion rate of 6.0%. Subjects with MPS at baseline had a similar annual AD conversion rate versus those with no MPS at baseline (6.2% vs. 5.9%, $p > 0.1$) (Table 2).

Stepwise logistic regression estimating the probability of MCI subjects converting to AD versus remaining MCI as a function of age, time interval between cognitive examinations, mUPDRS and their mutual interactions revealed age (OR = 1.10, 95% CI, 1.01 to 1.20, $p = 0.03$) and time interval (OR = 1.002, 95% CI, 1.001 to 1.003, $p = 0.005$) as the only explanatory variables. The model was weak in part due to the imbalance in the size of the two groups.

4. Discussion

We found that subjects with MCI have more extrapyramidal signs than age-matched cognitively normal controls. Axial dysfunction and limb bradykinesia were significantly associated with MCI and were the most frequent MPS item clusters, while tremor scores did not differ between MCI and CN subjects. Although several researchers have focused on the relationship of MPS in the elderly with incident dementia,[1] few studies have addressed the issue of MPS in MCI subjects (Table 3). We found that the MPS sub-items with the strongest association with MCI were limb bradykinesia and axial dysfunction. Boyle et al. found MCI patients exhibited more axial signs, rigidity and bradykinesia than CN individuals, but no association with tremor [14]. Louis et al. showed that functional and performance-based scores were correlated more strongly with axial and rigidity scores than with tremor [15]. A larger systematic study of 2230 participants of whom 608 had MCI reported no significant association between axial dysfunction and MCI [6]. The probability of MCI was found to be higher in subjects with MPS, especially with rigidity rather than tremor or axial dysfunction. Our observation that tremor is not associated with MCI is consistent with the findings of Louis et al. and Boyle et al.[6, 14].

We found that 8.8% of our population (cognitively normal and MCI) had MPS. In general it is well established that MPS are more prevalent amongst the elderly. Reported frequencies vary between 15 and 27% [6,15–19]. This heterogeneity may be partly explained by differences in study methodology. In the current study, we excluded subjects with MPS that may be explained by co-morbidities such as previous stroke, end-stage renal failure, severe systemic disease, orthopedic disability or PD. If we had included these subjects (but not those with PD) in the analysis, the proportion of the population with MPS would be 21.2%.

Another cause of heterogeneity lies in the diversity of the definition of MPS. Some studies defined MPS as the presence of any one of the UPDRS rating of 1 or higher [17–20]. Others defined it more rigorously as the presence of 2 parkinsonian signs or a score of 2 for 1 item [15,21]. One logic for using more rigorous criteria is to separate MPS from the signs of normal aging [6]. An important factor that strongly influences the frequency of MPS is age. However, logistic regression analysis revealed no age effect on cognitive status above and beyond the effect of MPS.

The clinical evaluation instruments for the detection of MPS also differ among studies. We used the full motor part of the UPDRS. Some other groups used an abbreviated 10-item UPDRS version [6,17,19,21–23] or a 0–100 nurse-administered UPDRS-derived scale [14,24–27].

Our study carries strengths and weaknesses. The main strength lies in the fact that no selection was involved in the recruitment process and refusal rate was low (3.1%). All subjects who agreed to be examined were included in the study. Weaknesses include the inherent subjectivity of the UPDRS. Another caveat of our results is the sensitivity of the cognitive instruments employed in our door-to-door study design. More extensive cognitive testing may be necessary to diminish potential diagnostic misclassification [28].

Motor features that accompany cognitive decline are important for diagnostic purposes. We did not find that MPS predicted conversion to AD in MCI patients. A prospective study following elderly individuals without dementia at baseline showed that none of the individuals with at least one parkinsonian sign at baseline developed PD. They were significantly more likely to become demented during follow-up [19,20,29]. In a prospective follow up on MPS in a cognitively normal elderly subgroup of participants of the Religious Order Study, progression of extrapyramidal signs (in our study termed MPS), more specifically of gait/posture disturbances (in our study termed axial dysfunction), rigidity and bradykinesia, in descending order, was found to predict cognitive decline [26]. Louis et al. also found that EPS were predictive of dementia [21]. Portet et al. examined the records of individuals without dementia with incident AD during the course of the follow-up and observed an increase in the frequency of all EPS domains with the exception of resting tremor [30]. These findings show that MPS are frequent in AD and that they may appear prior to overt cognitive decline. In our study we did not find a predictive value of MPS for conversion from MCI to AD. However, our sample was not large enough to prove this negative correlation.

The association between MPS and cognitive decline might be due to several possible mechanisms. MPS may be an early manifestation of preclinical neurodegenerative disease. Although one might expect Lewy Body disease to be the most plausible pathology given the temporal juxtaposition of cognitive decline and MPS, many studies demonstrate an association between extrapyramidal deficits and vascular pathology or Alzheimer's disease pathology. Vascular pathology (has been shown to be associated with gait abnormality [31] and increased risk of falling [32]. In an MRI study, MPS was shown to be associated with white matter hyperintensity volume but not total relative hippocampal volume suggesting that vascular pathology has a stronger influence on the presence of MPS than AD pathology [33]. Moreover, there is histopathological evidence linking gait impairment to AD pathology (neurofibrillary tangles) in the substantia nigra [34–36] and the motor cortex [37,38].

MPS and MCI could be considered biomarkers for neurodegeneration. Their co-occurrence may imply that multiple pathologies co-exist and possibly interact. Vascular risk factors may enhance the MPS-cognitive decline interaction. Difficulty in defining and separating the contributing pathologies is very challenging both on the individual clinical level and for research purposes. With the imminent demographic explosion of the elderly population, the number of people living with dementia globally is estimated to double every 20 years and neurodegenerative disease is rapidly becoming one of society's greatest burdens and challenges [39]. The importance in the concept of pre-clinical syndromes lies in the potential of disease modifying agents and risk reduction via life-style interventions.

Acknowledgments

Supported by the NIH RO1 AG017173 and Martin Kellner's Research Fund, American Technion Society.

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Figure 1.

Flow chart for study population.

Abbreviations: AD = Alzheimer's disease, VaD = Vascular Dementia, PD = Parkinson's disease, CN = cognitively normal, ESRF = end-stage renal failure.

Table 1

Mild Parkinsonian Signs (MPS) in Mild Cognitive Impairment (MCI) versus Cognitively Normal (CN) subjects

	CN (n=223)	MCI (n=173)	p-value
Age, years (mean $\pm$ SD)	72.2 $\pm$ 5.5	72.5 $\pm$ 5.7	>0.1
mUPDRS Score (mean $\pm$ SD)	0.3 $\pm$ 1.3	0.8 $\pm$ 2.3	0.004
Resting Tremor Score (mean $\pm$ SD)	0.09 $\pm$ 0.6	0.05 $\pm$ 0.4	>0.1
Limb Bradykinesia Score (mean $\pm$ SD)	0.05 $\pm$ 0.4	0.42 $\pm$ 1.8	0.0004
Axial Score (mean $\pm$ SD)	0.05 $\pm$ 0.09	0.32 $\pm$ 1.03	0.0005
Abnormal Limb Bradykinesia Score	3 (1.3%)	18 (10.4%)	0.00006
Abnormal Axial Score	3 (1.3%)	15 (8.7%)	0.0005
Abnormal Resting Tremor Score	7 (3.1%)	3 (1.7%)	>0.1
Abnormal Postural Tremor Score	11 (4.9%)	3 (1.7%)	0.09
Abnormal Rigidity Score	0	0	NA

Table 2

Mild Parkinsonian Signs in MCI subjects that converted to Alzheimer's disease (AD) versus those that remained MCI

	Remained MCI (n=87)	Converted to AD (n=24)	p-value
Age, years (mean $\pm$ SD)	71.9 $\pm$ 6.1	75.1 $\pm$ 7.9	0.01
Time interval between cognitive examinations (months)	45 $\pm$ 21	59 $\pm$ 21	0.001
mUPDRS Score (mean $\pm$ SD)	1.1 $\pm$ 3.1	1.1 $\pm$ 3.8	>0.1
Tremor Score (mean $\pm$ SD)	0.02 $\pm$ 0.3	0.2 $\pm$ 1.4	>0.1
Limb Bradykinesia Score (mean $\pm$ SD)	0.62 $\pm$ 1.82	0.50 $\pm$ 2.38	>0.1
Axial Score (mean $\pm$ SD)	0.51 $\pm$ 1.51	0.42 $\pm$ 1.49	>0.1

Table 3
Comparison of our study to major studies of Mild Parkinsonian Signs (MPS) in Mild Cognitive Impairment (MCI) patients

Reference	N	Confounders	Percentage Mean age (SD)		Motor scale	Reported relationship of MPS and cognitive function	
			Normal	MCI		MPS sub-items in MCI	MPS sub-items and risk of dementia
Richards et al. 1993 [[19]]	226	Excluded: COPD n=1, rapid dementia n=1	58% 75 (8)	42%	10-item UPDRS [[22]]	Axial, Bradykinesia	Axial (n=4) associated with incident dementia
Louis et al. 2005 [[6]]	2230	Not excluded: stroke or skeletal disease n=8	73% 77 (7)	27% 78 (7)	10-item UPDRS [[22]]	Rigidity	Not reported
Boyle et al. 2005 [[14]]	835	Excluded: dementia and/or PD n=64	72% 80 (7)	28% 83 (7)	modified UPDRS [[24]]	Axial, Bradykinesia, Rigidity	Not reported
Aggarwal et al. 2006 [[27]]	756	Excluded: AD n=60	74% 75 (7)	26% 79 (7)	modified UPDRS [[24]] + Purdue Pegboard	Bradykinesia	Gait, Bradykinesia associated with MCI to AD conversion
Rozzini et al. 2008 [[40]]	150	Not reported	Not reported	72 (8)	7-item UPDRS	Rigidity > Bradykinesia > Tremor [*]	Not reported
Louis et al. 2010 [[23]]	1851	Not excluded: post stroke n=64, arthritis n=146	78% 76 (7)	22%	10-item UPDRS [[22]]	Not reported	Axial, Tremor associated with incident dementia
Current study	495	Excluded: AD, PD, Stroke, systemic orthopedic disease	56% 73 (6)	44% 73 (6)	Motor part of UPDRS [[5]]	A, B	No association with MCI to AD conversion

* Posture and Gait (Axial features) were not measured.

Abbreviations: UPDRS: Unified Parkinson's Disease Rating Scale, PD: Parkinson's disease, AD: Alzheimer's disease