Psychological Distress and Risk for Dementia

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The concept of mild cognitive impairment (MCI) primarily emphasizes changes in individuals' mental abilities, but it has recently been suggested that neuropsychiatric symptoms should also be considered important factors in age-related neurodegeneration. Psychological distress, defined as a reaction of an individual to external and internal stresses, is characterized by a mixture of psychological symptoms. It also may be considered a neuropsychiatric symptom encompassing depression, anxiety, and apathy. This paper reviews and summarizes recent evidence and relevant issues regarding the presence of psychological distress in healthy older adults and MCI patients and its relationship to risk for developing dementia. Results presented in this review show that psychological distress and depressive, anxious, and apathetic symptoms can be present in MCI and may predict progression to dementia. This article also provides suggestions for future research.

Introduction

Estimates indicate that 24 million individuals in the world currently suffer from dementia, and this number is expected to double every 20 years [1]. In the United States, 4.5 million individuals were afflicted with Alzheimer's disease (AD) in 2000 [2]. Thus, dementia in general and its most common form, AD, clearly have become a major public health issue around the world as aging increases in Western and Eastern countries [3].

The fifth annual Mild Cognitive Impairment (MCI) Symposium, held in April 2007 in Florida, focused on the issue of whether the time has come to revise criteria for AD. International experts agreed that AD can and probably should be diagnosed before the onset of dementia, particularly as new interventions become available [4]. The concept of *mild cognitive impairment* thus is the result of the past 10 to 15 years of research efforts to diagnose the prodromal phase of AD and that of other neurodegenerative dementias. MCI is currently diagnosed using Petersen's criteria: 1) memory complaint, preferably corroborated by an informant; 2) objective memory impairment relative to age- and education-matched healthy individuals; 3) intact general cognitive functioning; 4) absence or few problems with activities of daily living; and 5) no dementia [5]. Petersen [6] later suggested the existence of four MCI subtypes: 1) single-domain amnestic MCI (A-MCI; ie, isolated memory impairment), 2) multiple-domain A-MCI (ie, memory impairment and a deficit in at least one other cognitive domain), 3) single-domain nonamnestic MCI (ie, an isolated nonmemory impairment), and 4) multiple-domain nonamnestic MCI (ie, deficits in multiple nonmemory domains). Although there is no clearly established cutoff score to determine the objective memory impairment, Petersen and colleagues [5] showed that memory performances of individuals with MCI tend to fall 1.5 SDs below the mean for age and education. An annual conversion rate to AD or other dementias of up to 20% has been reported [7], as well as a conversion rate of 48% after 30 months of follow-up in individuals with A-MCI [8]. However, depending on the study and methodology used (eg, clinical vs community samples), the rates generally vary between 12% and 15% [9–12].

Whereas the MCI concept is essentially cognitive in nature, the experts of the Second Canadian Conference on the Development of Antidementia Therapies emphasized that neuropsychiatric symptoms also should be considered pertinent indicators of the installation of a neurodegenerative process in old age [13]. Psychological distress experienced by patients suffering from various mental disorders was neglected for a long time but has regained attention in the past 10 years because of its relevance to compliance, quality of life, and prediction of treatment outcome [14]. Psychological distress is usually defined as a reaction of an individual to external and internal stresses and is characterized by a mixture of psychological symptoms, such as poor self-esteem, hopelessness, helplessness,

dread, confused thinking, sadness, and anxiety, and psychophysiologic symptoms [15]. Psychological distress has stronger relationships with common psychosocial factors and tends to be milder and more transient than depression [16]. However, psychological distress may be considered as a neuropsychiatric symptom that also encompasses depression, anxiety, and apathy symptoms.

The present paper reviews and summarizes the recent evidence and relevant issues regarding the presence—in healthy older adults and patients with MCI—of psychological distress (ie, presence of depressive, anxious, and/or apathetic symptoms) in relation to progression toward dementia. This article also provides suggestions for future research.

Results of Systematic Literature Reviews on MCI and Psychological Distress

The results of two recent systematic literature reviews [17••,18] supported the recommendation of the Second Canadian Conference on the Development of Antidementia Therapies. In the first review, Apostolova and Cummings [17••] analyzed 21 peer-reviewed papers published before December 2006 that included samples of at least 20 patients with MCI and behavioral data. Eight were population-based studies (six cross-sectional, two longitudinal), and 12 used convenience samples from tertiary memory disorders clinics and research databases (five cross-sectional, seven longitudinal). Apostolova and Cummings [17••] found that behavioral abnormalities were reported in 35% to 75% of patients with MCI. The most common problems were depression, apathy, anxiety, and irritability. The authors explained the observed variability in symptom prevalence by the different sampling methods, MCI diagnostic criteria, and behavioral instruments used. According to Apostolova and Cummings [17••], a compelling body of evidence indicated that MCI patients with behavioral features, especially depression and agitation, were more prone to developing AD than patients without these features. However, longitudinal data for apathy, anxiety, psychosis, disinhibition, agitation, euphoria, aberrant motor behavior, and irritability were very scarce and sometimes missing.

The critical review of Beaudreau and O'Hara [18] found that generalized anxiety disorder was the most common *DSM-IV-TR* anxiety disorder in older individuals, with a lifetime prevalence of 10.2%. However, about 20% of older adults reported subsyndromal anxiety symptoms. Interestingly, cross-sectional investigations generally support the hypothesis that the presence or severity of anxiety is associated with lower cognitive performance in older adults (with effect sizes in the moderate range). Only a few longitudinal studies investigated anxiety as a predictor of cognitive decline in older individuals, and the evidence was controversial, possibly due to investigational differences of how anxiety was measured. The ability to predict cognitive decline from baseline anxiety thus may have been attenuated by measuring neurotic traits rather than clinically significant anxiety [18].

The results of these two literature reviews were consistent with the recent cross-sectional and prevalence data from an ongoing population-based prospective cohort study conducted at the Mayo Clinic Study of Aging on a sample of 1969 individuals without dementia [19]. Neuropsychiatric data were available for 319 of 329 patients with MCI (97.0%) and for 1590 of 1640 healthy older adults (97.0%). The main outcome measure was the Neuropsychiatric Inventory Questionnaire score [20], which is a shorter version of the Neuropsychiatric Inventory [21]. Multivariate logistic regression analyses were conducted after adjusting for age, sex, and educational status. By considering the odds ratio and frequency of a symptom, the most distinguishing features between the two groups were apathy, agitation, anxiety, irritability, and depression. The odds ratio was highest for delusion; however, delusion was rare in participants with MCI and those with normal cognition. The population-attributable risk for delusion was only 2.62%, compared with 14.60% for apathy. Nonpsychotic symptoms affected approximately 50% of patients with MCI and 25% of individuals with normal cognition.

Historical Cohorts and Longitudinal Studies: Neuropsychiatric Symptoms and Risk for Dementia

Wilson and colleagues [22•] were the only researchers to study the risk of developing MCI in older individuals presenting with chronic psychological distress. The sample was recruited from two cohort studies (the Religious Order Study and the Rush Memory and Aging Project) using uniform annual clinical evaluations and including a detailed cognitive testing and clinical classification of MCI. Follow-up data were available for 1256 individuals without cognitive impairment and dementia. At baseline, the participants completed a six-item measure of neuroticism from the 12-item neuroticism scale of the NEO Five Factor Inventory [23], an indicator of the tendency to experience psychological distress. During up to 12 years of follow-up, 482 individuals (38%) developed MCI. The risk of MCI increased by about 2% for each one-unit increase on the distress scale (RR, 1.02; 95% CI, 1.01–1.04), with the association slightly stronger in men than women. Overall, a distress-prone person was about 40% more likely to develop MCI than someone not prone to distress. Adjustment for depressive symptoms at baseline did not change results substantially. Depressive symptoms were also related to risk of MCI, but not after controlling for distress score. In mixed-effects models, higher distress score was associated with lower level of function in multiple cognitive domains at baseline and more rapid cognitive decline, especially in episodic memory. Thus, the authors concluded

that in older persons without manifest cognitive impairment, higher level of chronic psychological distress was associated with increased incidence of MCI [22•].

Interestingly, the same authors tested the hypothesis—this time only on the participants from the Religious Order Study—that depressive symptoms increased during the prodromal phase of AD [24]. For up to 13 years, 917 older Catholic nuns, priests, and monks without dementia at study onset completed annual clinical evaluations that included administration of the 10-item Center for Epidemiologic Studies Depression Scale and clinical classification of MCI and AD. At baseline, participants reported a mean (SD) of 1.0 (1.5) depressive symptoms. Those who developed AD (n = 190) showed no increase in depressive symptoms before the diagnosis was made, a finding not modified by age, sex, education, memory complaints, vascular burden, or personality. No systematic change was observed in depressive symptoms after the AD diagnosis, although symptoms tended to decrease in women relative to men and in those with a higher premorbid level of openness and a lower premorbid level of agreeableness. Among individuals without cognitive impairment at baseline, depressive symptoms did not increase in those who subsequently developed MCI. Wilson et al. [24] concluded that there was no evidence of an increase in depressive symptoms during the prodromal phase of AD. However, the sample was very mildly depressed at baseline per the Center for Epidemiologic Studies Depression Scale scores, and the participants were all highly educated (mean, 17.8 ± 3.3 years of education in participants with incident AD vs 18.2 ± 3.4 years of education in unaffected participants). Perhaps the participants' education level played a protective role against the development of depression, as recent data from the Nord-Trondelag Health Study (1995–1997) showed that higher educational levels seem to have a protective effect against anxiety and depression that accumulates throughout life, whereas low educational levels were significantly associated with anxiety and depression [25].

Stepaniuk et al. [26] cross-sectionally and longitudinally investigated the relationship between cognitive status and neuropsychiatric impairments in nondemented older adults using data from the Canadian Study of Health and Aging (CSHA). These longitudinal data were collected three times (CSHA-1, CSHA-2, and CSHA-3) at 5-year intervals. Individuals were classified as with (n = 240) and without (n = 386) cognitive impairment at CSHA-2. Loss of interest, changes in personality and mood, and depression were reported by a knowledgeable informant more frequently for those with cognitive impairment than those without cognitive impairment. After controlling for initial cognitive status, loss of interest and depression contributed significantly to the prediction of MCI, dementia, and AD over time. These findings suggest that these neuropsychiatric symptoms play significant roles throughout the course of cognitive decline [26].

The data of Stepaniuk et al. [26] were corroborated by the results obtained in the Italian prospective, population-based, longitudinal cohort study conducted by Ravaglia and colleagues [27]. Baseline data were available for 595 adults who were 65 years of age and older with no cognitive impairment (NCI) and 72 patients with prevalent MCI. The NCI group underwent a 4-year follow-up for incident MCI. Baseline depressive symptoms were measured using the 30-item Geriatric Depression Scale (GDS). These symptoms were more frequent in patients with prevalent MCI (44.4%) than in NCI participants (18.3%). The association was independent of MCI subtype, antidepressant use, and sociodemographic and vascular risk factors. In NCI individuals, baseline depressive symptoms were also associated with increased risk of MCI at follow-up, but only for participants on antidepressant drugs at baseline (incident cases, 72.7%), compared with those without depressive symptoms and not on antidepressant therapy (incident cases, 24.0%).

Artero and colleagues [28] investigated the risk factors for MCI and progression to dementia in a prospective, community-based study involving 6892 participants without dementia who were 65 years of age and older at baseline. Participants were recruited in three French cities. Cognitive performance, clinical diagnosis of dementia, and clinical and environmental risk factors were assessed at baseline and at 2-year and 4-year follow-ups. Forty-two percent of the population was classified as having MCI at baseline. After adjustment for confounders with logistic regression models, men and women classified as having MCI were more likely to have depressive symptoms and to be taking anticholinergic drugs. Men were also more likely to present with a higher body mass index, diabetes, and stroke, whereas women were more likely to have poor subjective health, to be disabled, to be socially isolated, and to suffer from insomnia. The principal adjusted risk factors for men for progression from MCI to dementia were (in descending order) ApoE4 allele, stroke, low education level, loss of instrumental activities of daily living, and age. In women, progression was best predicted by loss of instrumental activities of daily living, ApoE4 allele, low education level, subclinical depression, use of anticholinergic drugs, and age. Therefore, the authors concluded that men and women have different risk profiles for MCI and progression to dementia and suggested that intervention programs should focus particularly on risk of stroke in men and on depressive symptomatology and use of anticholinergic medication in women.

Palmer and colleagues [29] examined the occurrence of neuropsychiatric symptoms and the relationship to future development of AD in individuals with and without MCI. For 3 years, these authors observed 185 individuals with NCI and 47 with MCI (single-domain amnestic and multiple-domain amnestic), 75 to 95 years old, from the population-based Kungsholmen Project (Sweden). Three

types of neuropsychiatric symptoms were evaluated at baseline: mood-related depressive symptoms, motivation-related depressive symptoms, and anxiety-related symptoms. AD was diagnosed according to the *DSM-III-R* criteria at 3-year follow-up. The psychiatric symptoms occurred more frequently in individuals with MCI (36.2% mood, 36.2% motivation, and 46.8% anxiety symptoms) than in cognitively intact older adults (18.4% mood, 13.0% motivation, 24.9% anxiety). Of the individuals presenting with MCI and anxiety symptoms, 83.3% developed AD over follow-up, compared with 6.1% of cognitively intact individuals and 40.9% who had MCI without anxiety. Among individuals with MCI, the 3-year risk of progressing to AD almost doubled with each anxiety symptom. Conversely, among cognitively intact individuals, only depressive mood symptoms were related to AD development. The predictive validity of MCI for identifying future AD cases improved in the presence of anxiety symptoms. However, depressive symptoms did not show a statistically significant prediction for AD among individuals with MCI because they were highly prevalent in patients with MCI who remained dementia free (31.3%) and patients with MCI who developed AD (37.5%). The authors speculated that in the first group of patients, MCI was related to an underlying psychiatric disorder, and in the second group, MCI and depression were associated with neurodegeneration [29].

Other authors did not find a relationship between depressive symptoms and progression to dementia [30•,31,32]. Panza and colleagues [30•,31] studied the possible effect of depressive symptoms, measured with the GDS, on the rate of progression to dementia in MCI patients after a 3.5-year follow-up and the interaction between depressive symptoms and vascular risk factors for conversion to dementia. A total of 2963 individuals from a sample of 5632, 65 to 84 years old, were assessed at the first (1992–1993) and second survey (1995–1996) of the Italian Longitudinal Study on Aging, a prospective cohort study. Among the 2963 participants, 139 prevalent MCI patients were diagnosed at the first survey. At the 3.5-year follow-up, 105 new cases of MCI were diagnosed [31], and 14 MCI patients progressed to dementia. However, Panza et al. [30•,31] found no significant relationship between depressive symptoms and rate of progression to dementia. No sociodemographic variables or vascular risk factors modified the association between depressive symptoms and conversion to dementia. The authors concluded that their findings did not support a role for sociodemographic variables or vascular risk factors in the association of depressive symptoms with conversion to dementia [30•,31].

Rozzini and colleagues [32] analyzed the relationship among depressive symptoms, loneliness, and the conversion to dementia in MCI outpatients recruited from January 2004 through January 2006. Depressive symptoms and loneliness were assessed using the GDS. Two years after baseline, 42 patients had converted to dementia: 28 to AD, four to AD and cerebrovascular disease, five to dementia with Lewy bodies, and five to frontotemporal dementia. A logistic regression analysis revealed that the Alzheimer's Disease Assessment Scale-Cognitive Subscale baseline score and loneliness, but not depressive symptoms, were independently associated with the conversion of MCI to dementia [32].

MCI Patients With Depressive Symptoms: Clinical Characteristics of the Converters to AD

Not all patients with MCI presenting with depression develop AD. Houde and colleagues [33] reported that the simple presence or absence of depression at referral did not predict progression from MCI to AD in 60 patients with A-MCI who were observed annually for an average of 4.3 years. However, positive answers to specific GDS questions that referred to "melancholic" affect and the persistence of depression over 2 to 3 years significantly predicted cognitive deterioration that eventually led to AD.

Robert and colleagues [34••] examined the influence of the apathy dimensions, such as emotional blunting, lack of initiative, and lack of interest, on the risk of developing AD in patients with A-MCI presenting with depressive symptoms. This longitudinal study involved 14 French memory clinics; apathy was measured in 214 MCI patients using the Apathy Inventory [35], the French validated version of the apathy scale of Marin and colleagues [36]. The principal end point was the conversion to AD during the 3-year follow-up. After 3 years, 59 patients (27.6%) had developed AD. The risk of conversion to AD was significantly higher for patients with lack of interest. Using Cox analyses and controlling for age, gender, and education, the difference between survival curves was significant for lack of interest. The authors therefore concluded that lack of interest, a mild behavioral sign, could be an indicator of potential decline in MCI patients. This finding needs to be replicated in larger samples [34••].

Psychological Distress/Mood Symptoms Versus MCI and Dementia: Differential Cognitive Profiles?

Older depressed, nondemented patients often present with deficits in attention, episodic memory, confrontation naming, verbal fluency, visuospatial ability, processing speed, and executive functions. Although these cognitive impairments are also observed in patients with AD, cognitive alterations in early AD are usually more severe than those in patients with depression in nearly every cognitive domain. Memory problems in depression are frequently related to attention and/or executive function deficits, whereas in AD, patients present with severe encoding difficulties [37,38•].

In addition, depending on the subtype of MCI, patients presenting with this condition do so with only one (eg, memory or nonmemory) impairment or several cognitive impairments in different cognitive domains [5,6]. On the other hand, young and older patients with various mood disorders (eg, anxiety, depression, and bipolar I and II disorders) often present with cognitive performances 2 SDs below the mean on two or more cognitive domains [39]. However, surprisingly, very few authors have investigated the differential cognitive profiles of patients with MCI with and without psychological distress or mood symptoms and of patients with only mood symptoms. Only three cross-sectional studies have investigated this issue to date [40–42].

In the first study, Federico et al. [40] compared the performance of 76 patients with AD, 46 patients with A-MCI, and 36 patients with anxiety/depression (but without A-MCI) on three different episodic memory tests: three-word immediate and delayed recall of the Mini-Mental State Examination, 10-picture reminding test, and the free recall/cued recall 16-item memory test of Van der Linden et al. [43]. The patients with AD and A-MCI differed from the depressed/anxious participants on all subcomponents of the memory tests. Only the three-word immediate and delayed recall of the Mini-Mental State Examination and the immediate recall (encoding) of the free and cued recall reminding test (16-item) did not differ between AD and MCI. Scores of total and free recalls significantly distinguished the three groups of patients: the AD patients had the worst performance, followed by the MCI patients, and then by the depressed/anxious participants.

In the second study, Hudon et al. [41] examined executive functions and verbal episodic memory in 33 healthy older adults, 18 older adults with A-MCI plus subclinical depressive symptoms (A-MCI/D+ group), and 26 older adults with A-MCI but no depressive symptoms (A-MCI group). Patients with A-MCI/D+ showed a poorer controlled inhibition capacity than A-MCI and control groups on the Stroop-Victoria task [44]. In addition, these patients recalled fewer words than control participants on immediate free, delayed free, and delayed total recall paradigms of episodic memory, as measured by the free recall/cued recall 16-item memory test [43]. The performance on immediate free recall suggested a self-retrieval deficit, but the performance on delayed total recall also revealed an encoding impairment. The A-MCI group exhibited normal performance on the executive task but nonetheless showed pervasive memory impairment. A memory deficit was registered on the free and total recall paradigms on immediate and delayed tasks, suggesting the existence of encoding and self-retrieval disturbances. This study showed differences between the pattern of cognitive impairment in A-MCI/D+ and A-MCI subgroups, particularly at the level of executive capacities.

In the third study, Rozzini et al. [42] assessed whether MCI patients with anxiety symptoms showed different neuropsychological profiles in comparison with patients with MCI but without anxiety symptoms. Fifty-seven outpatients with MCI were consecutively recruited. All patients were assessed using a complete neuropsychological battery to detect cognitive impairments and the Italian version of the Geriatric Anxiety Inventory (GAI) to detect the presence of anxiety symptoms. Patients with GAI ≥ 10 showed more behavioral and psychological disturbances than patients with GAI less than 10; in particular, they showed more agitation, anxiety, depression, and sleep disorders. Moreover, patients with GAI ≥ 10 were more compromised on instrumental activities of daily living and on executive functions evaluated with the Trail Making Test-B. A linear regression analysis was completed to estimate the coefficients of the linear equation involving neuropsychological, psychobehavioral, and functional characteristics: the executive functions (Trail Making Test-B) were the only variables independently related to the presence of anxiety disturbances. Rozzini et al. [42] hypothesized that the strict interaction between anxiety symptoms and executive functions could depend on specific pathologic features at the level of caudate nucleus characterizing early phases of dementia.

The results of these three studies clearly demonstrate a need for comparison of MCI with and without depressive and/or anxious symptoms. In MCI patients with these mood symptoms, executive functions seem especially vulnerable. More cross-sectional and longitudinal studies would help to clarify whether A-MCI/D+ should be considered as subclinical late-life depression or if it corresponds to Petersen's conception of A-MCI evolving toward AD. These data would impact on the development of treatment that is better adapted to these patient populations.

Conclusions

MCI, dementia, and psychological distress or late-life mood disorders/symptoms are currently viewed as three distinct syndromes that are diagnosed using different sets of clinical criteria [5,6,45]. However, the present literature review has underlined important similarities among the three. First of all, psychological distress, depressive, anxious, and apathetic symptoms can be present in MCI and predict progression to dementia. Future research will need to address the issue of the differential cognitive profiles between MCI with and without neuropsychiatric symptoms and between MCI with neuropsychiatric symptoms and late-life neuropsychiatric symptoms without MCI. The cognitive and clinical profiles of MCI with and without neuropsychiatric symptoms converting or not to dementia will be investigated using longitudinal study designs and standardized neuropsychological and

mood measures. Investigating the neurobiologic variables underlying the relationship between mood symptoms and dementia would also inform us on the pathophysiologic mechanisms of dementia and mood disorders. Regarding depression and dementia, hypotheses involving vascular changes in the frontostriatal circuits and hypercortisolemia were formulated to account for depression and cognitive decline in MCI and atypical AD patients [38•,46]. The National Institute of Mental Health Panel Experts [47••] recently underlined that the most consistent findings in this regard were structural measures (eg, regional atrophy and mediotemporal atrophy), positron emission tomography functional measures, and several promising cerebrospinal fluid measures. ApoE genotype is the most consistent genetic marker, but others are being examined. According to these experts, future research will need to reconcile the divergent paths of research regarding the underlying pathologic features seen on neuroimaging [47••].

Disclosures

No potential conflicts of interest relevant to this article were reported.

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This was the report of the National Institute of Mental Health conference on "Perspectives on Depression, Mild Cognitive Impairment, and Cognitive Decline." During the meeting, experts considered how the varied perspectives might be better integrated to examine the associations among depression, MCI, and cognitive decline and to illuminate the common or distinct mechanisms involved in these associations. The paper contains an exhaustive and critical literature review on this important topic.