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Obsessive-Compulsive Disorder in Patients with Mild Cognitive Impairment: A Comparative Study with Healthy Older Adults

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ABSTRACT

Background: Mild cognitive impairment is considered a prodromal state and a risk factor for dementia. To the best of our knowledge, no previous studies have examined the relationship between obsessive-compulsive disorder and mild cognitive impairment. One of the risk factors for the development of mild cognitive impairment may be obsessive-compulsive disorder. In this study, we hypothesized that the patients with mild cognitive impairment had a significantly higher rate of obsessive-compulsive disorder than healthy elders, and some types of preexisting obsessive-compulsive symptoms may be associated with mild cognitive impairment.

Methods: A total of 66 subjects (mild cognitive impairment = 35; healthy elderly = 31) were assessed for severity of cognitive impairment using the Mini-Mental State Examination, Clinical Dementia Rating Scale, and Addenbrooke's Cognitive Examination III tests. Lifetime diagnosis of obsessive-compulsive disorder was assessed through Structured Clinical Interview of the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition Axis I disorders. The severity of the obsessive-compulsive disorder and the content of previous obsessive-compulsive symptoms were measured by Yale–Brown Obsessive-Compulsive Scale.

Results: Mild cognitive impairment patients had more previous depressive episodes and a lifetime diagnosis of obsessive-compulsive disorder when compared with healthy subjects, $P = .023$. Educational level was significantly lower in mild cognitive impairment patients than in healthy elders, $P = .037$. The contamination obsessions and cleaning and checking compulsions were significantly higher in the patients with mild cognitive impairment than in healthy subjects, $P = .044$. Hamilton Anxiety Rating Scale and Hamilton Depression Rating Scale scores were significantly higher in patients with mild cognitive impairment, $P = .009$ and $P = .045$ respectively. Lower educational level, previous obsessive-compulsive disorder, Hamilton Anxiety Rating Scale and Hamilton Depression Rating Scale scores, and checking compulsions significantly predicted the patients with mild cognitive impairment, $P = .044$.

Conclusion: Our findings may demonstrate that lower educational level, previous obsessive-compulsive disorder, checking compulsions, and current anxiety and depression severity appeared significantly associated with mild cognitive impairment. We suggest that previous obsessive-compulsive disorder and checking obsessive-compulsive symptoms may be related to earlier stages of memory dysfunction.

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INTRODUCTION

Mild cognitive impairment (MCI) is considered to represent a cognitive impairment between normal cognitive aging and dementia. The prevalence of MCI in the elderly ranges from 3% to 20%.[1] Mild cognitive impairment is characterized by mild cognitive decline, progressive neuronal loss, the formation of neurofibrillary tangles, the deposition of Aβ within the brain, and no significant disability. Based on the type or domain of cognitive deficit, 4 MCI subtypes have been proposed: amnestic MCI single domain, amnestic MCI multiple domain, non-amnestic MCI single domain, and non-amnestic MCI multiple domain.[2]

It has been shown that many modifiable factors such as the presence of neuropsychiatric symptoms[3] can play a role in the development of MCI.

Mild cognitive impairment patients have a 35%-75% prevalence of various neuropsychiatric symptoms including anxiety, depression, apathy, and irritability.[4] There is growing evidence indicating a link between depression, MCI, and Alzheimer's disease (AD). Some studies have shown that MCI patients with depression are more likely to develop AD than those without depression.[5,6] Therefore, it

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is supposed that depression is associated with a higher rate of progression from MCI to dementia.[7]

Obsessive-compulsive disorder (OCD) is a psychiatric disorder characterized by uncontrollable, reoccurring thoughts (obsessions) and/or behaviors (compulsions).[8] In AD and OCD patients, impairments in executive functions may have a secondary influence on other functions, including memory. Neuroimaging studies of OCD have highlighted dysfunctions in the frontal-subcortical circuit involving the orbitofrontal cortex, anterior cingulate, striatum, and thalamus.[9] The role of serotonin, dopamine, and glutamate in OCD is well known.[10] Moreover, central cholinergic systems might also be involved in the pathophysiology of OCD.[11] Since the glutamatergic system plays an important role in memory and information processing, changes in this system contribute to neuropsychopathology in AD.[12] Imaging studies have indicated that 5-hydroxy-tryptamine 2A receptor loss[13] and an imbalance between the cholinergic and serotonergic systems may explain the cognitive impairment associated with AD.[14]

Some studies have reported that obsessive-compulsive (OC) symptoms most frequently precede the clinical diagnosis of frontotemporal dementia.[15] An elderly woman with cognitive impairment and some behavioral disorders also had a past history of severe OCD.[16] In a recent study, the authors found that the mean number of lifetime compulsions predicted the diagnosis of AD.[17] They also reported that preexisting hoarding and controlling obsessions and compulsions are associated with the occurrence of AD.

To the best of our knowledge, no previous studies have examined the relationship between OCD and MCI. Since MCI is generally considered a prodromal state and a risk factor for dementia, it is possible that dementia-related factors are also associated with MCI. One of the risk factors for the development of MCI may be OCD. Therefore, the primary aim of this study was to compare the rate, severity, and content of prior OCD in patients with MCI and healthy elderly subjects. We hypothesized that patients with MCI have a significantly higher rate of OCD than healthy elderly patients and that some preexisting OC symptoms may be associated with MCI.

MAIN POINTS

- Lifetime diagnosis of obsessive-compulsive disorder is higher in mild cognitive impairment (MCI).
- The contamination obsessions and cleaning and checking compulsions were significantly higher inthe patients with MCI
- The presence of obsessive compulsive symptoms may be a risk factor for the development of MCI.

MATERIAL AND METHODS

The study design was approved by Aydın Adnan Menderes University ethic committees (Approval Number: 2017/1244), and all participants or their caregivers gave informed consent for participation. We screened the patients who consecutively applied to Aydın Adnan Menderes University Neurology Department with the diagnosis of MCI. Subjects were not cognitively deficient enough to meet DSM-IV-Text Revision (TR) criteria[18] for dementia. Control participants included individuals considered cognitively normal by clinical assessment. Exclusion criteria for all participants included dementia, lifetime or current substance use disorder, psychosis, bipolar disorder, head injury, visual or hearing impairments, or neurologic disorders. All subjects had a complete neurological examination, usual blood tests, and brain computed tomography scan or magnetic resonance imaging (MRI). Subjects who did not have a caregiver at the time of assessment were also not included in the study. The caregiver was a relative of the patient who had constant, daily contact with the patient. Since patients with cognitive impairment can give unreliable reports, we applied clinical scales by obtaining information from caregivers who have detailed information about the patient. All but 8 patients were receiving at least 1 antidementia drug at the time of evaluation. All clinical and demographic data were obtained through a semi-structured case report form.

A total of 66 subjects were included in the study sample (MCI = 35; healthy elderly = 31). Patients with MCI were diagnosed by a clinical consensus meeting the amnestic MCI multiple domain diagnostic criteria defined by Petersen.[19]

Lifetime diagnosis of OCD was assessed through Structured Clinical Interview of the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition Axis I disorders (SCID-I).[20] The severity of cognitive impairment was assessed using the Mini-Mental State Examination (MMSE),[21] the Clinical Dementia Rating Scale (CDR),[22] and Addenbrooke's Cognitive Examination III tests (ACE-III).[23] The MMSE is a valid and most common tool for assessing cognitive deficits. The MMSE measures time and place orientation, attention, immediate and delayed memory, and calculation, language, and constructional ability. Possible scores range from 0 to 30; scores below 24 are generally considered indicative of cognitive impairment. The CDR is a semi-structured interview that assesses impairment in the areas of memory, orientation, judgment and problem-solving, community affairs, home and hobbies, and personal care. Five-point ratings are used to evaluate each area: 0 means "none," 0.5 means "questionable," 1 means "mild," 2 means "moderate," and 3 means "severe." Addenbrooke's Cognitive Examination III test is a screening test consisting of tests of attention, orientation, memory, language, visual perceptual, and visuospatial skills. The highest possible score on the ACE-III is 100 points, and lower scores indicate

worse cognitive functioning. Subjects had an MMSE ≥ 24 with a concern for a deficit in cognition compared to their previous level. Their cognitive performance was lower than expected based on the patient's age and educational background (CDR scores were 0.5 or 1). As assessed by the patient and a relative, there was little or no disturbance in daily activities.

The Yale-Brown Obsessive-Compulsive Scale (Y-BCOS)[24] was administered to the participants to determine the severity of present OCs. The types of a lifetime and current OCs were determined using the Y-BOCS symptom checklist. Participants and their caregivers were asked to report whether OC symptoms first appeared before or around the onset of cognitive impairment symptoms. The severity of current depression and anxiety was assessed with the Hamilton Depression Rating Scale (HDRS)[25] and the Hamilton Anxiety Rating Scale (HARS).[26]

Statistical Analysis

Groups were compared using Pearson's Chi-square or Fisher's exact tests for categorical variables. The Kolmogorov-Smirnov test was used to analyze the normality of continuous data. The differences between the 2 groups in continuous variables were examined with the Mann-Whitney *U*-test. We performed 2 multinominal logistic regression analyses to determine whether the diagnosis of OCD and some types of OC symptoms are associated with MCI, even controlling for educational level, HDRS scores, and previous depressive episodes. Possible independent predictors were selected through comparison analyses. Results are reported as relative odds ratios with 95% CIs. The significance level was established as $\alpha = 0.05$.

RESULTS

As indicated in Table 1, there were no significant differences between patients with MCI and healthy controls with respect to age, gender, marital status, and comorbid medical disorders. Mild cognitive impairment patients had more previous depressive episodes ($P = .010$) and a lifetime diagnosis of OCD ($P = .003$) when compared with healthy subjects. Educational level was significantly lower in MCI patients than in healthy elders ($P = .007$). Hamilton Depression Rating Scale ($P = .021$), HARS ($P < .001$), and total ($P < .001$) and obsession ($P < .001$) and compulsion ($P = .001$) subscale scores of Y-BOCS were significantly higher in patients with MCI compared to healthy subjects. We also found that cleaning ($P = .030$) and checking compulsions ($P = .003$) were significantly higher in the patients with MCI than in healthy subjects.

In order to examine whether previous OCD, previous depression, age, education, or family history were associated with MCI, we performed binary logistic regression analysis with the enter method (Table 2). The final model for MCI was able to explain 53.0% of the variance. The model was found to fit the data adequately ($P = .472$) and was able to predict the outcome between MCI and healthy subjects ($P = .001$). Overall, the model was able to correctly predict 71.2% of all cases. We found that lower educational level ($P = .035$) and previous OCD ($P = .011$) were significantly associated with MCI.

DISCUSSION

Neuropsychiatric symptoms in MCI subjects are considered a prodromal presentation of the underlying neurodegenerative process or a causal factor for subsequent dementia. To our knowledge, no studies have previously examined the risk of OCD in the development of MCI. Only a few studies and case reports have claimed that the primary diagnosis of OCD may be a risk factor for AD. In this study, we examined the presence and content of previous OCD in MCI patients compared to healthy elderly subjects. Our results indicated that MCI patients had more severe current OC and depression, had a higher previous history of depression and OCD, and had a lower education level than healthy individuals. In addition, the rate of OC symptoms, particularly cleaning and checking compulsions that existed before the onset of cognitive impairment, was higher in MCI patients than in the lifetime OC symptoms in the healthy elderly. Lower educational level and previous OCD were significantly associated with MCI even after controlling for previous depression, family history of dementia, and age.

It is still unclear whether education is a risk factor for MCI. In this study, we found that the educational level of MCI patients was significantly lower than that of healthy subjects and significantly predicted the MCI diagnosis after controlling for the rate of previous depression. Our finding is consistent with some previous studies reporting that healthy older adults with higher levels of education are less likely to develop MCI than those with lower or no education.[27]

In the current study, our results demonstrated that the patients with MCI were more anxious than healthy subjects during the assessment. The severity of current anxiety was significantly associated with MCI diagnosis. Since we did not assess the past and current diagnoses of any anxiety disorders, we could not determine the influence of anxiety on patients with MCI. Anxiety has been studied less than depression, and there is a complex relationship between anxiety and cognitive impairment. Previous investigations indicate that older adults with cognitive impairment display more anxiety symptoms compared with controls and that higher anxiety is related to poorer cognitive performance.[28] Past or current anxiety is considered a prodromal risk factor for cognitive impairment and dementia.[29,30] Biringer et al[31] noted that high anxiety levels only with depressive symptoms are related to cognitive impairment. Some studies found that high anxiety levels were negatively associated with cognitive performance.[32]

Table 1. The Comparison of 3 Groups with Regard to Some Sociodemographic and Clinical Variables

	MCI ($n=35$)		Healthy Subjects ($n=31$)		*P*
	n	%	n	%	
Gender					.193
Female	18	51.4	11	35.5	
Male	17	48.6	20	64.5	
Marital status					.324
Married	22	62.9	23	74.2	
Seperated/divorced	13	37.1	8	25.8	
Preexisting obsessions					
Aggressive	5	14.3	1	3.2	.202
Contamination	7	20.0	1	3.2	.058
Hoarding	5	14.3	1	3.2	.202
Symmetry	7	20.0	2	6.5	.156
Religious	3	8.6	-	-	.241
Miscelleneous	6	17.1	2	6.5	.265
Preexisting compulsions					
Cleaning	8	22.9	1	3.2	.030
Checking	11	31.4	1	3.2	.003
Counting	1	2.9	-	0.0	1.000
Ordering	4	11.4	1	3.2	.360
Hoarding	2	5.7	-	0.0	.494
Miscelleneous	-	0.0	2	6.5	.217
Previous OCD	15	42.9	3	9.7	.003
Previous depression	20	57.1	8	25.8	.010
	Median	Min-max	Median	Min-max	*P*
Age	69	47-87	71	60-90	.877
Educational level (years)	5	1-15	11	1-20	.007
Y-BOCS total	15	0-25	0.00	0-22	<.001
Obsession	8	0-13	0.00	0-10	<.001
Compulsion	8	0-13	0.00	0-12	.001
HDRS	8	0-13	4	0-32	.021
HARS	10	0.30	3	0-23	<.001
MMSE	25	15-30	29	27-30	<.001
CDR total	2.500	0-8	0.000	0-2	<.001
Memory	0.500	0-2	0.000	0-1	<.001
Orientation	0.000	0-2	0.000	0-0	<.001
Judgment	0.500	0-2	0.000	0-1	<.001
Community affairs	0.500	0-1	0.000	0-0.5	<.001
Home and hobbies	0.500	0-2	0.000	0-0.5	<.001
Personal care	0.0	0-1	0.000	0-0	.003
ACE-III total	65.0	27-96	85.0	55-98	<.001
Attention	16.00	6-18	18.00	12-18	<.001
Orientation	7.00	0-14	11.00	4-14	<.001
Memory	12.00	2-24	19.00	10-26	<.001
Language	20.00	7-26	26.00	9-27	<.001
Visual skills	13.00	4-16	16.00	10-16	.002

*$P < .05$

Y-BOCS, Yale-Brown Obsessive-Compulsive Scale; HDRS, Hamilton Depression Rating Scale; HARS, Hamilton Anxiety Rating Scale; MMSE, Mini-Mental State Examination; CDR, Clinical Dementia Rating Scale; ACE-III, Addenbrooke's Cognitive Examination III tests; OCD, obsessive-compulsive disorder.

Table 2. Binary Logistic Regression Analysis to Determine Whether Previous Depression, Previous OCD, Educational Level, Family History, or Age Were Associated with MCI (Reference Group: Healthy Subjects)

	Exp(B)	OR (95% CI)	*P*
Educational level	1.155	1.010-1.321	.035
Previous OCD	7.497	1.592-35.293	.011

P-value of binary logistic regression model is .001
OCD, obsessive-compulsive disorder; OR, odds ratio.

Anxiety has also been proposed as a causal factor influencing the neuropathological processes leading to cognitive decline and dementia.[33] We suggest that higher anxiety levels in our patients with MCI may contribute to later cognitive impairment and thus may increase the risk for dementia.

The relationship between depression and cognitive disorders is also complex and controversial. Some authors reported a higher prevalence of depression in MCI patients compared to healthy controls.[34] Previous studies showed that patients with depressive symptoms in MCI patients are associated with an increased risk for the further development of AD.[35] A longitudinal study found that early depressive symptoms in patients with MCI may indicate a preclinical sign of dementia.[36] In our study, similar to previous findings,[37,38] the severity of current depression and frequency of previous depression were significantly higher in patients with MCI compared to healthy subjects. However, previous depressive episodes did not predict MCI diagnosis after controlling for previous OCD and educational level.

It is still a controversial issue whether a previous diagnosis of OCD may constitute an independent risk factor for later cognitive impairment. Since many previous studies reported impairment in immediate,[39] verbal, nonverbal,[40] and spatial working memory[41] in patients with OCD, our findings that MCI patients had higher rates of OCD before the onset of cognitive impairment become noteworthy. In a recent study that compared 39 patients with AD and 30 age- and gender-matched control subjects,[17] lifetime and current OCs and OCD were significantly more prevalent than in the control group. The authors suggested that OCs might be considerable risk factors for the development of dementia.

In the current study, we found that MCI patients had significantly more previous OCD diagnoses than healthy subjects. Functional MRI studies showed hippocampal and parahippocampal dysfunction in the medial temporal lobe in MCI and OCD.[42-45] In both, implicit memory performance is impaired.[42,46,47] Although we would not have measured retrospectively the possible memory deficits in MCI patients having OC symptoms, we proposed that the preexisting OCD in our patients might be related to MCI through the common pathophysiological mechanisms.

The issue of the relationship between OC symptom type and memory deficits is still under investigation.

In this study, our results demonstrated that MCI patients had significantly more cleaning and checking compulsions than healthy older subjects. Rather than OC symptoms, Y-BOCS total appeared associated with MCI. Therefore, we suggest that the severity of OCD may be related to cognitive dysfunctions in patients with MCI. Since OCD is related to some doubts about whether or not something was not correctly done, memory deficits may be supposed to play a substantial role in the etiology and maintenance of this illness.[48] A previous study found that AD patients had more lifetime and current hoarding, and checking OC symptoms compared to control subjects. The authors reported that lifetime compulsive symptoms may be associated with the development of AD.[17] Tallis et al[49] indicated that impairments in nonverbal memory are related to doubting symptoms. Some studies in OCD patients showed that checkers displayed more deficits in some memory functions compared to noncheckers.[50] More recent research found episodic memory deficits in OCD patients with subclinical checking symptoms.[51] In a functional MRI study in OCD,[52] patients with washing symptoms showed significantly greater activation in bilateral ventromedial prefrontal regions and right caudate nucleus than controls. In patients with checking symptoms, the putamen, globus pallidus, thalamus, and dorsal cortical areas were among the more active regions. Hoarding symptoms were mostly associated with the left precentral gyrus and the right orbitofrontal cortex. Accordingly, Van den Heuvel et al[53] found significant differences in white matter and gray matter volumes for each of the dimensions of symmetry/ordering, contamination/ washing, and harm/checking.

Several limitations of this study should be noted. It is important to declare the predictive limitation of this cross-sectional study since we simultaneously assessed the patients' MCI. Although the medial temporal lobe seems to be involved in both disorders, there is a lack of clear relationship between the development of these disorders. Further longitudinal clinical, genetic, and neuroimaging investigations are required to determine if lifetime OCD and some types of OC symptoms would predispose to the development of later cognitive impairment. The effect of personality is reported previously; however, another limitation of this study is that personality is not evaluated. Small sample size is the other limitation which reduces the power of study. Most notably, retrospective evaluation of depression and OCD may be biased by the patients and their caregivers. Moreover, we could not assess the number of lifetime depressive episodes, and the ages at onset of depression and OCD. We should also emphasize that we did not evaluate the type and duration of previous antidepressant treatments. So, the drug use might have influenced the scores of CDR, ACE-III, and MMSE.

In conclusion, our findings may demonstrate that the patients with MCI had more severe current OCD and depression and had more contamination obsessions and cleaning and checking compulsions when compared with healthy subjects. In particular, lower educational level, previous OCD, and checking compulsions appeared significantly associated with MCI even after controlling for previous depression and other OC symptoms. Although it is not clear whether OCD is a risk factor or an early manifestation for later cognitive impairment, our findings may demonstrate that previous OCD and checking OC symptoms may be related to earlier stages of memory dysfunction. Clinicians should assess the cognition of individuals with OC symptoms and should monitor those with OC symptoms for evidence of cognitive impairment from MCI to AD.

Ethics Committee Approval: Ethical committee approval was received from the Ethics Committee of Aydın Adnan Menderes University (Approval Number: 2017/1244).

Informed Consent: Informed consent was obtained from all participants or their caregivers in this study.

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