Original Article

Analysis of neuropathological comorbid conditions in elderly patients with mild cognitive impairment in a tertiary care center in South India

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Abstract

Introduction: Mild cognitive impairment (MCI) is a transitional stage in the continuum of cognitive decline. Multiple risk factors may be involved apart from neuropathological states such as Alzheimer's disease, Parkinson's disease, and vascular dementia. There is scant data in the literature pertaining to our study population in Kerala, South India that provide associations between suggested risk factors and MCI. Most of the elderly present to family and primary care physicians with complaints of some form of memory impairment. **Objectives:** To find out the significant neuropathological comorbid conditions present in elderly patients with MCI. To assess for other risk factors in the same population- including laboratory parameters, comorbidities, and psychosocial parameters. **Methods:** This retrospective record-based study included a sample of 93 patients with MCI as quantified by the Mini-Mental Status Examination (MMSE). These subjects were compared with controls ($n = 97$) without MCI, with respect to neuropathological diagnoses, laboratory parameters and psychosocial parameters. **Results:** The findings of our study were that female gender, higher depression scores, a greater number of medications taken, benzodiazepine use, higher alkaline phosphatase levels, positive fall history, loss of a spouse, and lower levels of education were associated with MCI. MCI is negatively associated with positive alcohol history. The most commonly seen proven neuropathological diagnosis was Parkinson's disease. **Conclusion:** The risk factors that were found in our study should be highlighted in the elderly and preventive measures should be taken to prevent the downward progression through the cognitive continuum. Prospective studies looking into mild cognitive impairment with better screening tools and proper assessment of neuropathological comorbid conditions can further elucidate the findings related to this study.

Keywords: Continuum of cognitive decline, mild cognitive impairment, mini-mental status examination, neuropathological comorbid conditions, risk factor analysis

Introduction

According to the ICD-10 diagnosis code G31.84, Mild Cognitive Impairment (MCI) is defined as a broad term that encompasses changes in cognition in patients with normal brain characteristics and a variety of neuropathological states.[1] Most importantly, MCI includes the changes in cognition, which may be seen either due to or co-occurently in Alzheimer's disease, vascular dementia, Parkinson's disease, Lewy body disease, Huntington's disease, traumatic brain injury, and a variety of infections such as HIV and prion disease.[1] Concerning functional status, MCI is defined by cognitive impediments beyond those expected for the patient's age and educational status but are not significant

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enough to disrupt activities of daily living or affect global cognitive function.[2] Perhaps a definitive perception of MCI can be understood from the principle of a cognitive continuum- MCI is a transitional stage where cognitive decline is greater than the expected cognitive decline of normal aging, but not as severe as a diagnosis of dementia.[2,3]

It is also beneficial to understand that MCI does not only imply memory deficits. It is classified as amnestic MCI and non-amnestic MCI. The former involves memory impairment, and the latter affects non-memory cognitive domains such as language, executive function, or visuospatial skills. Amnestic MCI is more associated with an outcome of Alzheimer's disease. In contrast, non-amnestic MCI is associated with other conditions such as vascular dementia and Parkinson's disease.[4,5]

The major dilemma regarding MCI is its multifactorial etiology. Recognized risk factors include diabetes mellitus, systemic hypertension, depression, anxiety, and polypharmacy.[3,6,7] Benzodiazepine use in the elderly is associated with altered cognition, and prolonged consumption is described as a risk factor for MCI.[8] History of traumatic brain injury is also associated with an increased risk of an MCI diagnosis.[9]

MCI is expected to be on the rise as the population worldwide continues to age and healthcare facilities improve, with many elderly patients presenting with complaints of some form of memory impairment. India is expected to have a 300% increase in dementia prevalence from a 40-year-period spanning 2001–2040.[10] The state of Kerala, where the study is being conducted, is the fastest ageing among all Indian states.[11] Moreover, it is projected that by 2050, 35% of Kerala's population will be older than 60 years.[12] The importance of dementia as a public health problem, especially in our study population, cannot be overstated. The overall progression of mild cognitive impairment to dementia is debatable, with an overall annual progression of 12% in the general population and about 20% in populations at higher risk.[13] Studies in Kerala show a prevalence of MCI as high as 26% in the geriatric population aged 60 and above.[3] The likelihood of progression from MCI to any form of dementia has been suggested to occur at a rate three to five times higher than those with normal cognition.[13]

In spite of the leaps and bounds made by physicians in recent years in the field of medicine, it is a shocking yet true fact that MCI is still a diagnosis often missed by perhaps the most experienced of primary care providers or family physicians. Its incidentally cryptic nature of presentation and lack of awareness of the condition in many cases, is often the cause behind its late detection, by which point it would have been too far gone.

By including the early assessment of MMSE scores in regular checkups by family physicians, and at rural setups where it would otherwise not be considered as an important aspect of evaluation, it can go a long way in making a marked difference in the lives of many. If left undetected, it can have grave implications on not just the longevity of the individual and his/her health from a clinical standpoint, but can also affect the lives of their caregivers.

Materials and Methods

This was a retrospective record-based study conducted in the Department of Geriatrics at Amrita Institute of Medical Sciences and Research Centre, Kochi – a tertiary care center in Kerala, South India. Ethical clearance to undertake the study was obtained from the Institutional Review Board of Amrita Institute of Medical Sciences and Research Centre, Kochi.

The Mini-Mental Status Examination (MMSE) is a commonly used clinical assessment in geriatric practice used for quantifying the level of cognition across all major domains in elderly patients. Measured with a maximum possible score of 30, a score of 18-23 inclusive of the scores on either side of the range suggests MCI.[14] MMSE has been used as the diagnostic screening test in our study.

Patients aged 60 and above who had attended the outpatient clinic or had been admitted as inpatients in the department, with MMSE scores of 18-23, were included in the study and classified as patients with MCI.

The study period was between the years 2015-2020. Over 4000 records were searched for the required MMSE characteristics. Patients with established delirium and who did not have complete records were excluded from the study.

Based on the proportion of Alzheimer's disease (58.4%), vascular dementia (24.4%) and Lewy body disease (17.2%), which were observed in an earlier publication by Chen *et al*.[6] and with 95% confidence and 10-unit absolute error the sample size was calculated to be $n = 93$. Hence 93 subjects were taken serially who fit the criteria for mild cognitive impairment from the given study period.

To obtain statistical association to analyze the primary and secondary variables, including risk factors and laboratory parameters, a control group of patients without mild cognitive impairment, defined by an MMSE score greater than 23, was collected at random with $n = 97$.

Study variables

Major variables

Sociodemographic variables

Age and gender of all patients were taken. Patients aged 60 and above were included in the study.

Neuropathological comorbid conditions

Based on the patient history, the opinion of a neurologist, and MRI reports available in the electronic medical records, some patients were categorized as having a comorbid neuropathological condition – namely, Alzheimer's disease, Parkinson's disease, vascular dementia, Lewy body disease or traumatic brain injury.

Mild cognitive impairment

Mild cognitive impairment was quantified according to the MMSE screening tool, which has been in place for the last few decades. A score of 18 to 23 was taken and was assigned as mild cognitive impairment.[14] Another group of patients who had MMSE scores from 24 to 30, i.e., little to no cognitive decline, served as the control group for the study.

Secondary variables

Depression

Depression was calculated according to the Geriatrics Depression Scale (GDS) out of a possible 30 points. A score greater than 9 is associated with depression.[15]

Comorbidities and laboratory parameters

Data regarding the presence or absence of type 2 diabetes mellitus, systemic hypertension, coronary artery disease were collected from patient history. Data from liver and renal function tests were collected to assess the respective organs. Vitamin D levels, mean corpuscular volume and hemoglobin (anemia panel), thyroid function test and serum electrolyte levels were also added in the analysis to provide a comprehensive study into the metabolic functioning of the patients.

Lifestyle factors

Smoking and alcohol history was taken into account. Educational status and living arrangement were collected. History of falls, which is a crucial variable considering its association with depression and traumatic brain injury, and eventually mild cognitive impairment, was also specifically checked.[9,16]

Polypharmacy and benzodiazepine use

In this study, polypharmacy was defined as more than 5 medicines daily, excluding commonly given vitamin supplements.[7] A specific look into benzodiazepine use in the patients was also carried out as it is associated with cognitive changes if taken daily.[8]

Statistical analysis

Statistical analysis was performed using IBM SPSS version 20.0 software. Numerical variables were represented using mean and standard deviation. Independent sample t-test for normally distributed data and Mann Whitney U test for skewed data were used to study the statistical significance of the difference in the mean values of all continuous variables between cases with MCI and the control group. Chi-square with continuity correction was used to test the statistical significance of the association of all categorical variables between cases and controls. A *P* value of <0.05 was considered to be statistically significant. The incidence of neuropathological comorbid conditions was described in terms of percentages.

Results

93 patients with MCI who fit the inclusion criteria were assessed as the cases from 4000 records of patients from 2015-2020. A control group (n = 97) without MCI collected at random was assigned.

Concerning the sociodemographic variables [Table 1], the case group had more female patients (58.1%), whereas the control group had more male patients (61.9%). The mean age of the case group (76.11 ± 7.147) was higher than the control group (74.46 ± 6.188). Statistically, there was a significant association between gender and MCI (p = 0.006), with the female gender being more associated with MCI. From the independent sample t-test, there was no statistical significance with respect to the age of the patients between the two groups.

25 patients in the case group were reported to have a neuropathological comorbid disorder as a clear-cut diagnosis with thorough investigations [Figure 1]. There were seven cases of medically proven Alzheimer's disease (7.5%), nine cases of Parkinson's disease (9.7%) and eight cases of vascular dementia (8.6%). There was also one case of normal pressure hydrocephalus (1.1%) in the case group. There was only a single case of traumatic brain injury in the control group.

The mean depression score [Table 2] as per the GDS was 7.45 ± 4.35. There was a statistically significant difference between the two groups (p = 0.004), with higher scores being found in the case group. The mean number of drugs taken was found to be 5.15 ± 3.28, and the frequency of polypharmacy was more in the case group (43%) as compared to the control group (29.9%). There was statistical significance with respect to the number of drugs taken (p = 0.003), showing that the intake of medications is more in the cases than in the controls. The frequency of benzodiazepine use was also found to be higher in

Table 1: Sociodemographic variables

Variable	Mild Cognitive Impairment (*n*=93)	Controls- no MCI (*n*=97)	*P*
Age in years (mean±SD)	76.11±7.147	74.46±6.188	0.091
Gender			
Male	39 (41.9%)	60 (61.9%)	0.006
Female	54 (58.1%)	37 (38.1%)	

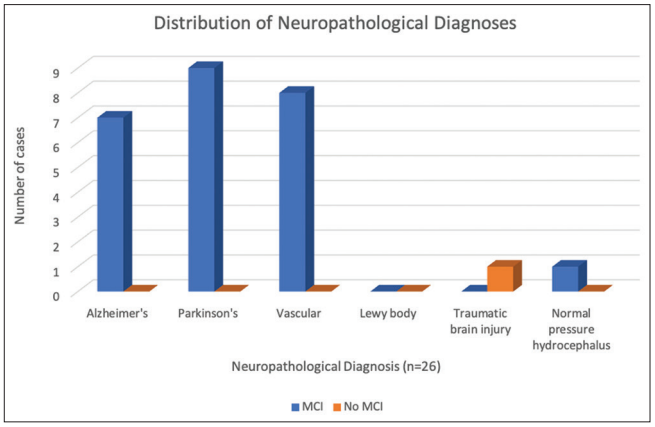

Figure 1: Distribution of Neuropathological Diagnoses

the cases (15.1%) than in the controls (4.1%), with a statistically significant association (p = 0.02).

With respect to the laboratory parameters [Table 2] there were no significant associations except alkaline phosphatase (ALP), where a statistically significant difference was obtained (p = 0.003). Comorbidities such as diabetes, hypertension, coronary artery disease and smoking history did not show a statistical association [Table 3]. Alcohol history was more commonly seen in the control group (35.1%) compared to the MCI group (17.2%), and it showed a statistically significant association (p = 0.005). Fall history was more in the case group (29.9%) than in the control group (15.5%), with a significant statistical association (p = 0.024).

In both groups, living with a spouse had the most significant distribution concerning living arrangement, with 51.6% in the case group and 71.1% in the control group [Table 3]. More subjects lived alone in the control group (6.2%) than the case group (3.2%). The major difference with respect to the distribution was in the patients who lived with their children, with 45.2% in the cases and 22.7% in the controls. There was a statistically significant association between living arrangement and MCI (p = 0.004), showing that the loss of a spouse was associated with MCI.

The educational status was distinct between the two groups [Table 3]. The maximum frequency educational status in the case group was primary school (50.5%), while in the control group, most subjects had completed secondary education or high school (46.4%). Also, the number of subjects awarded a degree was much higher in the control group (30.9%) than the case group (10.8%). There was a strong statistical significance of the association between educational status and MCI (p < 0.001).

Table 2: Laboratory parameters and continuous variables

Variable (*n*=190)	Mean	*P*
MMSE value	24.41±3.49	N/A
Depression score	7.45±4.35	0.004
Number of drugs taken	5.15±3.28	0.003
Creatinine (mg/dL)	1.16±0.56	0.153
Urea (mg/dL)	27.28±16.4	0.210
Na (mEq/L)	134.95±5.72	0.291
K (mEq/L)	4.18±0.54	0.120
AST (U/L)	26.12±14.88	0.347
ALT (U/L)	21.27±13.74	0.548
ALP (U/L)	88.05±48	0.007
TSH (μU/mL)	3.78±9.7	0.136

Table 3: Secondary variables

Variable	Mild Cognitive Impairment (*n*=93)	Controls- no MCI (*n*=97)	*P*
Polypharmacy	40 (43%)	29 (29.9%)	0.06
Type 2 Diabetes Mellitus	47 (50.5%)	43 (44.3%)	0.392
Systemic Hypertension	68 (73.1%)	62 (63.9%)	0.173
Coronary Artery Disease	24 (25.8%)	28 (28.9%)	0.636
Living arrangement			0.004
Living alone	3 (3.2%)	6 (6.2%)	
With spouse	48 (51.6%)	69 (71.1%)	
With children	42 (45.2%)	22 (22.7%)	
Educational status			<0.001
Primary school	47 (50.5%)	22 (22.7%)	
Secondary education	36 (38.7%)	45 (46.4%)	
Degree	10 (10.8%)	30 (30.,9%)	
Positive smoking history	26 (28%)	37 (38.1%)	0.136
Benzodiazepine use	14 (15.1%)	4 (4.1%)	0.02
Positive fall history	27 (29%)	15 (15.5%)	0.024
Positive alcohol history	16 (17.2%)	34 (35.1%)	0.005

Discussion

This study compared the neuropathological comorbid conditions, lifestyle factors and systemic comorbidities seen in patients who had MCI as measured by the MMSE versus patients who did not have MCI by the same measure. Many studies analyze the risk factors associated with MCI, but there is scant data about the current population in question.[3]

There were more female individuals in the case group in our study, while more males in the control group, with statistical significance (p = 0.006). This suggests that the female gender is more associated with MCI than males. This is in accordance with a study by Khanna *et al*.,[17] which states that female sex is a risk factor for MCI in an urban Indian city. According to Li *et al*.,[18] the risk of progression of MCI to dementia is also greater in the female gender. The mean age was higher in the individuals with MCI, without a statistical association. In many studies, a statistical association between MCI and older age exists.[3,17,18]

In our study group, only 25 individuals had a diagnosis of any one of the neuropathological conditions studied based on investigations and the opinion of a neurologist in the group with MCI [Figure 1]. Parkinson's disease had the maximum frequency with nine cases, vascular pathology with eight and Alzheimer's disease in seven cases. There was a single case of traumatic brain injury in the control group. According to a study by Chen *et al*.,[6] Alzheimer's disease has the maximum distribution among neuropathological comorbid conditions (58.4%), which was not seen in the subset of patients who had a diagnosis in our study. However, no substantial conclusion can be made because most patients did not have a clearly defined diagnosis of a neuropathological comorbid condition at presentation. However, as there was no neuropathological diagnosis made in any control case except for a single case of traumatic injury, this can serve as a clue that patients with such diagnoses are more prone to developing MCI.[4,6]

Depression score and MCI showed a statistically significant association (p = 0.004), and the mean (7.45 ± 4.35) was quite close to the clinically significant cut-off value of 9.[15] This shows that the higher the depression score is based on the GDS, the more it is associated with MCI. This is in concordance with the study by Mohan *et al*.,[3] which show that depression is

positively associated with MCI (OR = 2.17). Steenland *et al*.[16] have found that late-life depression predicts the progression of normal subjects to MCI than past depressive episodes. A study by Panza *et al*.[19] has further found that late-life depression, MCI and dementia may represent a possible continuum in a subset of patients. Thus, the role of depression in cognitive decline is apparent.

The number of drugs taken by each patient, with a mean of 5.15 ± 3.28 between both groups, showed that polypharmacy was a common occurrence. The frequency was more in the MCI group, and there was a statistical association between the number of drugs taken and MCI. A study by Cheng *et al*.[7] demonstrates the same association and concludes that polypharmacy is associated with higher risks of MCI, especially for patients without diabetes, hypertension, or cerebrovascular diseases. Benzodiazepine use and MCI showed a significant association. Many studies show a stronger association obtained with long-term use of long-acting benzodiazepines.[8] A study by Nafti *et al*.[20] concluded that benzodiazepine use is related to cognitive decline later on but is not implicated in the pathogenesis of dementia and Alzheimer's disease.

It is not surprising that common systemic comorbidities such as diabetes mellitus, systemic hypertension and coronary artery disease did not carry a significant statistical association. The distribution in both the cases and the controls was almost identical. This is in agreement with many studies which have conducted a risk factor analysis of MCI.[6] However, the significance of these conditions becomes more relevant in the progression of MCI to dementia, which shows a positive association in many cases.[13,18]

The statistical association of alkaline phosphatase with MCI was also significant. Studies in the literature report that alkaline phosphatase is elevated in patients with Alzheimer's disease, and the level is inversely related to cognitive function.[21] This can be explained by the fact that ALP is present on neuronal membranes and increases with brain injury and cerebrovascular disease- suggesting that the increase in ALP is related to neuronal loss.

Alcohol history was more in the control group than in the case group. There was a statistical association suggesting that a history of alcohol intake has a protective role in patients without MCI compared to the cases in our study. Many studies disagree with this finding due to the neurotoxic effects of alcohol.[3,22] However, a study by Solfrizzi *et al*.[23] states that light-drinkers with MCI who consumed less than 1 drink/day (15 g of alcohol) have a lower rate of progression to dementia than abstainers. Another study by Koch *et al*.[24] further extrapolates this finding, stating that complete abstinence was associated with lower MMSE scores in patients without MCI and binge-drinking was associated with lower scores in patients with MCI.

Mild cognitive impairment is a risk factor for falls from many studies.[25] In our study, fall history was statistically associated with mild cognitive impairment. However, whether fall history can be deemed a risk factor for mild cognitive impairment remains to be seen. Depression is also a significant risk factor for falls in patients with MCI, as shown by previous studies.[26]

In both groups, most of the individuals lived with their spouse. However, more patients lived with their children in the MCI group than the control group, and there was a statistically significant association. Thus, our study showed that the loss of a spouse is a potential risk factor for mild cognitive impairment. A study by Biddle *et al*.[27] states that in older adults with normal cognition, being widowed was associated with accelerated beta-amyloid-related cognitive decline, making them susceptible to Alzheimer disease progression. A study by Smith *et al*.[28] shows that loneliness is associated with MCI in low and middle-income countries.

Educational status was statistically significant as well, with primary school education being the most common level of education in the MCI subjects. However, the strength of this association is weak, primarily because MMSE is dependent on the educational status of the subject, and it was the screening tool used to classify cases and controls.[29]

`From these findings, it is clear that there are many risk factors and associations that need to be highlighted while screening for MCI in elderly individuals by primary care physicians. Parkinson's disease is a neuropathological diagnosis that should prompt physicians to screen for MCI. Female gender and a long list of number of medications taken by the patient are other factors which should prompt a screening with MMSE. Higher levels of depression scores and loss of a spouse also show strong associations. Age did not show a strong association, so it can be inferred that elderly patients should be screened with MMSE for MCI regardless of their age, as early as possible.

Novel findings in our study include the findings of a negative alcohol association and the association of higher alkaline phosphatase levels with mild cognitive impairment, which have not been found in many studies. In our population in particular, there were no associations of MCI with common comorbidities such as hypertension, diabetes mellitus and coronary artery disease, probably because of their similar prevalence in both the case and control groups. Though such comorbidities have often been implicated as risk factors for MCI, they are of lesser importance and primary care physicians should look at more striking risk factors while considering MMSE screening of patients.

Limitations

The current study is limited because it is a retrospective study in a single institution and may not represent the population at large. Also, most patients were not specifically investigated for neuropathological comorbid conditions by a neurologist if their symptoms were not severe enough. MMSE is not the most

accurate tool for assessing MCI, mainly because it depends on the patient's educational status.

Conclusion

In conclusion, it is seen from our study that mild cognitive impairment is positively associated with the female gender, higher depression scores, a greater number of medications taken, benzodiazepine use, higher alkaline phosphatase levels, positive fall history, loss of a spouse and lower levels of education. MCI is negatively associated with positive alcohol history. The most commonly seen proven neuropathological diagnosis was Parkinson's disease. There were no significant associations between MCI and common systemic comorbidities such as type 2 diabetes mellitus, systemic hypertension or coronary artery disease. Prospective studies looking into mild cognitive impairment with better screening tools and proper assessment of neuropathological comorbid conditions can further elucidate the findings related to this study.

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Conflicts of interest

There are no conflicts of interest.

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