Original Article

Blood Biomarkers in Older Subjects with Mild Behavioral Impairment: A Cross-Sectional Study from the Memory Clinic, All India Institute of Medical Sciences, India

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Abstract

Background: The presence of neuropsychiatric symptoms (NPS) in older adults with no cognitive impairment confers a high risk of future cognitive decline. Mild behavioral impairment (MBI) is a syndrome characterized by the new onset of NPS after 50 years, which is sustained and impactful. We report the distribution of various domains of MBI in subjects with mild cognitive impairment (MCI) and subjective cognitive impairment (SCI) and the association between different blood markers in individuals with MBI. **Materials and Methods:** This cross-sectional study was conducted in the Memory clinic of the Department of Geriatric Medicine in a tertiary health center. The study duration was 1½ years. Subjects with MCI and SCI were screened for the presence of NPS and MBI. Patients with dementia, impaired activities of daily living, and psychiatric illnesses were excluded. The mild behavioral impairment checklist ascertained the presence of various domains. Levels of various blood markers were assessed. **Results:** In this study, 124 participants were included. The mean age of the population was 69.21 ± 6.64, 71.77% were male, and 28.23% were female. Fifty-one participants were diagnosed to have MBI. Among the MBI domains, impulse dyscontrol was most commonly involved (68.63%) followed by decreased motivation (60.78%). Low Vitamin D (85.71%; $P = 0.005$) and high serum triglyceride (50%; $P = 0.044$) were associated with MBI. **Conclusion:** NPS, especially impulse dyscontrol and decreased motivation, in participants without dementia, were common in the memory clinic setting. Vitamin D deficiency and high triglyceride levels were significantly associated with MBI.

Keywords: Biomarker, mild behavioral impairment, mild cognitive impairment, neuropsychiatric symptoms, subjective cognitive impairment

Introduction

Biomarker or "biological marker" is defined as a characteristic measured objectively and evaluated as an indicator of the normal biological or pathogenic process.[1] From the perspective of cognitive impairment, a biomarker could be used to delineate underlying pathology, predict conversion between clinical disease states, detect presymptomatic pathological changes, and monitor disease progression.[2] The early diagnosis of the prodromal phase of Alzheimer's disease (AD) is difficult if only clinical symptoms are taken into consideration.[3] At present, to establish clinical evidence regarding a neuropsychiatric test battery, neuroimaging including magnetic resonance imaging (MRI), fluorodeoxyglucose-positron emission tomography (PET), and amyloid PET and cerebrospinal fluid (CSF) biomarkers to predict the progression from mild cognitive impairment (MCI) to AD, a study by the Alzheimer Disease Neuroimaging Initiative is being performed. The biomarkers in dementia are divided into imaging, and CSF measures used in research settings. Brain imaging (computed tomography or MRI) is recommended in patients being investigated for dementia. It helps identify mass lesions, assess vascular damage, white matter signal changes, spongiform and gliotic changes, and regional brain atrophy.

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In contrast, functional imaging (PET, single-photon emission computed tomography) allows visualization and quantification of brain hypoperfusion and hypometabolism showing characteristic patterns. Blood-based biomarkers that are relatively noninvasive, cost-effective, and allow assessment at different times are currently unavailable for clinical use. The early detection of changes in the blood biomarkers' level can result in the preclinical diagnosis of dementia. These biomarkers can have a high impact role as a screening tool and help guide the therapeutic responses.

Neuropsychiatric symptoms (NPS) are heterogeneous, noncognitive, behavioral symptoms that are universally present across the spectrum of dementia. These include agitation, anxiety, irritability, delusions, disinhibition, depression, illusions, obsessive-compulsive behaviors, and sleep disorders. It is associated with increased caregiver burden and early institutionalization. Mild behavioral impairment (MBI) is a newly defined diagnostic entity, which is claimed to be a counterpart of MCI as a transitional stage in the spectrum of cognitive decline.[4] It consists of persistent, newly developed behavioral changes with no serious cognitive complaint and daily living activities. The previous study reports that among subjects with a diagnosis of MBI who progressed to develop dementia, 36% developed frontotemporal dementia, 28% had AD, 18% had Vascular dementia (VaD), and the rest had other types of dementia. This clinical entity is sub-classified into five domains: decreased motivation, emotional dysregulation, impulse dyscontrol, social inappropriateness, delusions, and hallucinations.

Identification of behavioral changes and NPS is central in the diagnosis of MBI. And the mild behavioral impairment checklist (MBI-C) can aid in the identification of domains involved. Being a predementia state, the identification of risk factors and associations is imperative. In this study, we report the association between MBI and various blood-based biomarkers.

Materials and Methods

This study is aimed to assess the proportion of MBI in subjects with MCI and subjective cognitive impairment (SCI) and to study the association between MBI and blood-based biomarkers. The participants were recruited from the memory clinic of the Geriatric medicine department, which is held once a week in a tertiary health center. It caters to a large population and provides a detailed cognitive and neuropsychological evaluation and management of the patients. The multidisciplinary team addresses caregiver stress assessment and management. Due to the absence of previous studies showing a prevalence of MBI in a clinical setting when starting the study, a convenience sample was taken. The study was conducted from January 2017 to October 2018 after receiving clearance from the institutional ethics committee. A total of 124 out of 366 subjects were included. Written informed consent was taken from all the participants. The cognitive status of the participants was assessed using the clinical dementia rating (CDR) scale. MCI was diagnosed in participants with a CDR score of 0.5. SCI, which is the earliest identifiable state of cognitive impairment, was diagnosed in participants with memory impairment complaints and a CDR score of 0. Participants with a CDR score of 1 and above and impaired activities of daily living were excluded.

A psychologist assessed all the subjects for NPS using the MBI-C. The diagnosis of MBI was made with the International Society of Advance Alzheimer's Research and Treatment-Alzheimer's Association. For the diagnosis of MBI, the participant should have one or more NPS as detected by neuropsychiatric inventory–questionnaire for at least 6 months. These symptoms were severe enough to produce impairment in interpersonal relationships, other aspects of social functioning or ability to perform in the workplace; and psychiatric disorders such as generalized anxiety disorder, major depression, manic or psychotic conditions were ruled out.

For testing of biomarkers, 5 mL of blood was drawn from subjects who gave consent. The blood was immediately sent to the laboratory for processing. The markers evaluated were active Vitamin B_{12}, serum folate, thyroid-stimulating hormone, Vitamin $D_{3,}$ and fasting lipid profile.

Statistical analysis

STATA 13 (StataCorp. 2013. Stata Statistical Software: Release 13. College Station, TX: StataCorp LP). was used to analyze the data. The categorical variables were described as frequency and percentage, whereas the noncategorical variables were expressed as mean, median, standard deviation, and range. The blood markers have been described as categorical variables (i.e., as usual or low). Association between categorical variables was assessed using the Chi-square test, and quantitative variables between the MBI and non-MBI group were compared using unpaired *t*-test or Wilcoxon ranksum test.

Results

Table 1 describes the sample characteristics (n = 124). Fifty-one (41.12%) of the participants had MBI, whereas 55.65% of individuals had NPS. The two groups differed significantly in marital status and cognitive status. There was no statistically significant difference in gender, age, socioeconomic status, and years of education.

The frequency of various domains of MBI is shown in Table 2. Impulse dyscontrol was present in 70.5% of participants with MBI, which was followed by decreased motivation. Among the serum hormones and lipid profile [Table 3] low, Vitamin D and high serum triglyceride levels were significantly associated with MBI.

Discussion

This study observed a high prevalence of NPS in subjects with MCI and SCI. NPS were present in 55.64% of the participants without dementia. Moreover, among these three-fourth (72.46%) were diagnosed to have MBI. Among the MCI

Table 1: Sample characteristics of the study population

Variables	Frequency, *n* (%)		*P*
	MBI (*n*=51)	Non-MBI (*n*=73)	
Age, mean age±SD	68.50±6.66	69.71±6.64	0.323
Gender			
Male	35 (39.33)	54 (73.97)	0.515
Female	16 (45.71)	19 (26.02)	
BMI (kg/m^2), mean±SD	23.14±4.32	23.94±3.66	0.271
Socioeconomic status			
Upper	1 (1.96)	0 (0.00)	0.238
Upper middle	17 (33.33)	32 (43.83)	
Lower middle	17 (33.33)	27 (36.98)	
Upper lower	16 (31.37)	14 (19.17)	
Years of education, median (range)	10 (0-20)	10 (0-18)	0.533
Marital status			
Married	47 (92.15)	56 (76.71)	0.024*
Widow/widower	4 (7.85)	17 (23.28)	
Working status			
Retired	23 (45.09)	35 (47.94)	0.870
Still working	14 (27.45)	21 (28.76)	
Homemaker	14 (27.45)	17 (23.28)	
Smoking			
Current	7 (13.72)	7 (9.58)	0.562
Ex-smoker	13 (25.49)	15 (20.54)	
Never	31 (60.78)	51 (69.86)	
Alcohol			
Yes	9 (17.64)	11 (15.06)	0.393
No	42 (82.35)	62 (84.93)	
Chief complains			
Memory impairment	49 (96.07)	70 (95.89)	0.958
Behavioral changes	33 (64.70)	11 (15.06)	0.000*
Neuropsychiatric symptoms			
Present	50 (98.04)	19 (26.03)	0.000*
MBI checklist, median (range)	7 (1-26)	0 (0-15)	0.000*

*Significant. BMI: Body mass index, MBI: Mild behavioral impairment, SD: Standard deviation

Table 2: Domains of mild behavioral impairment

MBI domains	SCI (*n*=11), *n* (%)	MCI (*n*=40), *n* (%)
Decreased motivation	7 (63.6)	25 (62.5)
Emotional dysregulation	6 (54.54)	23 (57.5)
Impulse dyscontrol	7 (63.6)	29 (72.5)
Social inappropriateness	0 (0)	12 (30.0)
Abnormal perception	0 (0)	2 (5.0)

MBI: Mild behavioral impairment, SCI: Subjective cognitive impairment, MCI: Mild cognitive impairment

and SCI participants, we found that impulse dyscontrol was the most commonly involved domain (72.5% and 63.6% respectively). This was followed decreased motivation (62.5% and 63.6%) and emotional dysregulation (57.5% and 54.54%). Similar findings have not been reported from a memory clinic setting. This study was the first to report the blood biomarkers, from memory clinic setting, in individuals with MBI. We observed statistically significant differences, between MBI and non-MBI groups, in Vitamin D_3 and serum triglyceride levels.

In our study, among the participants with MBI, 85% had Vitamin D deficiency compared to one-half of the participants without MBI. Vitamin D deficiency was prevalent in older adults[5] and was associated with substantial cognitive decline.[6,7] There are biologically plausible links between cognitive function and Vitamin D. Their receptors are present in various cells, including glial cells and neurons. And also, genes encoding the enzymes involved in Vitamin D's metabolism are expressed in the brain.[8] It also emphasized that Vitamin D may be neuroprotective through immunomodulation, anti-oxidative mechanisms, detoxification mechanisms, neuronal calcium regulation, and enhanced nerve conduction.[9] Its role in brain detoxification is explained by mechanisms that include reducing cellular calcium level, increasing glutathione levels (an antioxidant) and inhibiting the synthesis of inducible nitric oxide synthase.[10] A meta-analysis showed that there was a nonlinear relationship between serum Vitamin D levels and cognitive function.[11] Although no previous studies have reported an association between Vitamin D and MBI, a significant association between low Vitamin D levels and depressive symptoms has been reported.[12,13] The possible role of Vitamin D in NPS is suggested by the expression of Vitamin D receptors in the thalamus, cingulate cortex, substantia nigra, cerebellum, hippocampus, and amygdala.[14]

Conflicting data show that dyslipidemia, a modifiable risk factor, is associated with a higher risk of dementia. Reduced high-density lipoprotein (HDL)[15] and apolipoprotein A-I levels,[16] as well as increased levels of lipoprotein (a), have been observed in VaD in some but not all studies.[17,18] In our study, half of the participants with MBI had an elevated serum triglyceride compared to only one-fourth of the participants without MBI (P = 0.044). A study in diabetes mellitus reported that hypertriglyceridemia is correlated with decreased digit span test and digit substitution test and slowed reaction time.[19] Numerous studies have shown an association of high triglycerides with poor immediate, recent and delayed recall,[20] verbal test.[21] Animal studies suggest that high triglyceride induced leptin resistance results in cognitive impairment through its effects on the hippocampus.[22] Other proposed mechanisms include increased transport of ghrelin and insulin,[23,24] and altered expression of orexigenic hypothalamic peptides,[25] affecting cognition. Several hypotheses explain the connection between lipids and neuropsychiatric disorders[26] such as the insufficiency of docosahexaenoic acid, protein kinase C, and phosphatidylinositol changes in signal transduction which leads to alteration in brain functioning and therefore might cause neuropsychiatric disorders. However, no previous studies have documented the association between MBI and serum triglyceride levels.

There was no significant difference in Vitamin B12, serum folate, thyroid-stimulating hormone, total cholesterol, HDL, and low-density lipoprotein levels in our study. Our research is the first one to report an association between these markers and MBI.

Table 3: Blood biomarkers between the groups

Serum level	MBI (%)	Non-MBI (%)	*P*
Vitamin B12 (91)	4 (10.81)	6 (11.11)	0.964
Folate (92)	7 (18.42)	9 (16.67)	0.827
TSH (100)	3 (7.50)	4 (6.67)	0.873
Vitamin D (64)	24 (85.71)	19 (52.78)	0.005*
Total cholesterol (68)	5 (20.83)	11 (25.00)	0.699
Serum Triglyceride (67)	12 (50.00)	11 (25.58)	0.044*
HDL (67)	12 (50.00)	19 (44.19)	0.647
LDL (67)	5 (20.83)	12 (27.91)	0.523

*Significant. MBI: Mild behavioral impairment, HDL: High-density lipoprotein, LDL: Low-density lipoprotein, TSH: Thyroid-stimulating hormone

This study has numerous strengths and limitations. The participants were included from a tertiary center clinic that catered to individuals referred for concern regarding cognition. Thus, our research reports on a representative sample of patients. CDR, a validated rating tool, which identifies mild and significant cognitive impairment, was used to assess cognition. Ours is the first study on MBI from India to report on blood-based biomarkers.

All the participants included in the study (n = 124) did not consent for drawing blood, reducing the sample size by a small number. The study could not assess the causality between biomarkers and MBI due to its cross-sectional design.

Conclusion

NPS are relatively common among individuals with MCI and SCI. Impulse dyscontrol and decreased motivation were prevalent in both groups. Low Vitamin D_3 and high serum triglycerides were significantly associated with MBI. Further, longitudinal studies with a larger sample size are needed to study the progression of the individual domain and the causal role of these biomarkers.

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Conflicts of interest

There are no conflicts of interest.

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