REVIEW ARTICLE

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Mild Behavioral Impairment: A New Prodromal Syndrome for Dementia

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SUMMARY

In this review, it is aimed to discuss neuropsychiatric symptoms as prodromal symptoms of dementia syndromes, to define the concept of 'Mild Behavioral Impairment', and to introduce the 'Mild Behavioral Impairment Checklist'.

Neuropsychiatric symptoms (NPS) represent non-cognitive symptoms and behaviors in dementia patients. The frequency of NPS accompanying dementia increases as the disease progresses. Studies reveal that NPS are seen in patients with dementia as well as in the elderly without cognitive complaints, individuals with subjective cognitive complaints, and individuals diagnosed with mild cognitive impairment. Based on these findings, identifying and detecting these symptoms were thought to be useful in predicting the development of dementia in cases where cognitive symptoms have not yet appeared. 'Mild Behavioral Impairment' was first defined by Taragano and Allegri, and it was introduced as a concept that includes neurobehavioral symptoms seen in elderly people for at least 6 months and that do not meet the diagnostic criteria of any other psychiatric syndrome. Mild Behavioral Impairment Checklist (MBI-C) has been developed recently which consists of 34 questions investigating apathy, mood, impulse dyscontrol, social inappropriateness, abnormal thinking, and perception. Studies on the neurobiological basis of these sub-domains and their relationship with biomarkers gained momentum with the introduction of the concept and the development of MBI-C. However, the concept is still very new and it is possible for people to be over-diagnosed and face the risk of stigmatization during the evaluation. Therefore, studies need to be conducted in large samples. Demonstrating the validity of this concept will also serve the purpose of identifying the subjects with a neurodegenerative disease without any cognitive complaints yet at a very early stage in clinical studies.

Keywords: Mild behavioral impairment, neuropsychiatric symptoms, prodromal dementia

INTRODUCTION

It has been known that psychiatric diseases emerging for the first time in later life could be a possible prodrome of dementia. Depression which develops for the first time in old age without any stressor could be a prodrome of vascular dementia in the presence of accompanying vascular diseases, as well as Alzheimer's type dementia (Hébert et al. 2000, Saczynski et al. 2010). It is known that late-life depression may not show cognitive symptoms such as guilt, thoughts of worthlessness, and anhedonia, which are known as the core symptoms of depression and are mainly characterized by somatic symptoms (Stewart et al. 1991). Therefore, old age depressions may not always meet the diagnostic criteria for major depression due to their different clinical presentations, which makes it difficult to recognize late-life depressions and make differential diagnosis with dementia in particular.

Similarly, neuropsychiatric symptoms (NPS) that emerge in later life often do not meet the definition of a syndrome and do not always meet the diagnostic criteria for a psychiatric disorder. Findings that these symptoms, which are seen for the first time in old age, may be the prodrome of a neurodegenerative disorder, are being increasingly reported in recent years.

Cognitive disorders, which are increasingly seen with the prolongation of life, and the resulting need for long-term care are now important public health problems. Among the dementia treatments approved so far, there are no disease-modifying treatments yet. One of the reasons for this is that clinical diagnoses of dementia syndromes are done at an advanced stage of the degeneration process in the brain, and the treatments tried at this stage are unable to reverse this process. For this reason, recently it is targeted to include people who are in the early stages of dementia, even in the pre-dementia stage,

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for studies aiming to develop disease-modifying treatments. To this end, while studies on the development of biomarkers to detect amyloid and tau accumulation in the early stages are carried out, clinical symptoms that might reflect a prodrome to dementia are sought on the other hand. These clinical symptoms include behavioral and psychological changes as well as cognitive changes.

Cognitive changes associated with age have long been a subject of research. It was first described by Karl in 1962 and named "Benign Senescent Forgetfulness". Afterward, "Age-Associated Memory Impairment" was defined by Crook in 1986 (Crook et al. 1987). The International Psychogeriatric Association has suggested the concept of "Aging Associated Cognitive Decline" by stating that there may be deterioration in other cognitive domains in addition to the memory in the elderly during normal aging process (Levy 1994).

After definitions of Karl, Crook and Levy; the concept of "Cognitive Impairment, No Dementia" was defined with the data obtained from the "Canadian Study of Health and Aging" (Tuokko and Frerichs 2000). Cognitive impairment without dementia is almost identical to the concept of "Mild Cognitive Impairment", which was first developed by Flicker et al.. Flicker suggested that this concept could be defined as a step between normal aging and dementia and it defines people who would progress to Alzheimer's dementia (AD) (Flicker et al. 1991). Mild Cognitive Impairment (Amnestic MCI) concept was defined and diagnostic criteria of MCI were suggested by Petersen in 1999 (Petersen et al.1999).

Another concept for pre-dementia period is "Subjective Cognitive Impairment" (SCI). It has been associated with an increased amyloid burden (Snitz et al. 2015), cognitive decline, and dementia risk (Mitchell et al. 2014). Reisberg et al. reported that subjective cognitive impairment in some subjects who has cognitive complaints but no objective cognitive impairment could start approximately 20 years before MCI symptoms (Reisberg 2008). This stage is also thought of as the prodrome of MCI and Alzheimer's disease (AD) (Reisberg 2008, Prichep et al. 2006).

MCI, now a well-defined clinical picture, is a condition known to have a high risk of developing dementia and is often considered a prodrome to dementia. Although cognitive symptoms and mild impairments in cognitive test performances are the main features of MCI, recently there has been increased interest in the behavioral component of the disease. In addition to cognitive symptoms, the emergence of the neuropsychiatric symptoms for the first time in later life which do not meet the diagnostic criteria of a psychiatric syndrome has been found to increase the risk of progression to dementia. Therefore these NPSs in elderly have been studied with increasing interest in recent years (Reisberg 2008), and as a result, the concept of "Mild Behavioral Impairment (MBI)" has been developed.

In this review article, MEDLINE was searched to identify research articles and reviews published in English between 2010-2021 using the search terms "mild behavioral impairment", and "mild behavioral disorder". Prominent articles in the related literature and the relevant articles referenced in these studies were included in this review.

Neuropsychiatric Symptoms Accompanying Neurocognitive Disorders

Neuropsychiatric symptoms, or "Behavioral and Psychological Symptoms of Dementia" as the International Psychogeriatric Association called, represent non-cognitive symptoms and behaviors in people with dementia. Common NPSs are agitation, anxiety, irritability, illusion, delusion, apathy, depression, disinhibition, prominent motor and obsessive-compulsive behaviors, and sleep disorders. These symptoms can be seen at any stage of the disease, regardless of the subtype of dementia, or in cognitive disorders other than dementia (Finkel et al. 1996). It has been known that these symptoms can accompany dementia since the first case Auguste D described by Alois Alzheimer in 1907. Auguste D's complaints initially had started with mood changes and delusions of infidelity, and cognitive problems consisting of progressive memory loss and language problems were added to the clinical picture later (Alzheimer 1995).

Various neuropsychiatric symptoms may accompany cognitive impairment in all stages of neurocognitive disorders. In a large study with 5-year follow-up, 97% of dementia patients had at least one psychiatric symptom, and the most common NPSs were apathy (36%), depression (32%), and agitation/aggression (30%) (Lyketsos et al. 2002). In 2011, National Institute on Aging-Alzheimers Association (NIA-AA) recommended that criteria for dementia diagnosis should involve changes in personality, behavior, and adjustment areas which include mood fluctuations, agitation, impaired motivation, apathy, impaired impulse control, social withdrawal, decreased interest in daily activities, obsessive or compulsive behaviors, and socially inappropriate behaviors (McKhann et al. 2011). Although NPSs are seen in almost all patients with dementia, they are not included in the defining criteria for dementia in DSM IV-TR and ICD 10. In DSM 5, under the heading of "Major Neurocognitive Disorder", behavioral symptoms were added as a specifier; ''without behavioral disturbance", and ''with behavioral disturbance: if the cognitive impairment is accompanied by a clinically significant behavioral disturbance (e.g., psychotic symptoms, mood disturbance, agitation, apathy, or other behavioral symptoms)", but not included in the diagnostic criteria. In addition, there is still no consensus on how to identify

and classify the behavioral and psychological symptoms of dementia (Sachdev et al. 2014).

These symptoms are frequent not only in dementia but also in the elderly with mild cognitive impairment or no cognitive complaints. The prevalence of NPS in mild cognitive impairment (50-59%) is higher than it is in the general population but lower than it is in dementia (Lyketsos et al. 2002, Di Iulio et al. 2010, Geda et al. 2008). The most frequently reported NPS in MCI are depression (27%), apathy (18.5%), and irritability (19%) (Geda et al. 2008). Neuropsychiatric symptoms are not included in the MCI diagnostic criteria, and there are not enough studies yet on the rates of their accompaniment and prediction of MCI. It has been found that the MCI accompanied by neuropsychiatric symptoms is associated with an increase in cognitive impairment, more deterioration in functional adaptation, and an increased risk of progression to dementia (Feldman et al. 2004). While the rate of progression to dementia in people with MCI is 12% per year (Petersen et al. 2001), this rate rises to 25% in the presence of one or more NPS (especially apathy and depression) (Rosenberg et al. 2013). According to another study, the risk of progression to dementia in MCI accompanied by NPS is three times higher than in MCI without NPS (Mortby et al. 2017).

There is no significant deterioration in cognitive functions in all prodromal dementia periods. Some people to be diagnosed with neurodegenerative diseases in the future may present neuropsychiatric symptoms during very early stages when cognitive symptoms have not appeared yet. Woolley et al. found that 28% of people with neurodegenerative disease had a previous psychiatric diagnosis, and the most common diagnosis was depression (Woolley et al. 2011). Although psychiatric diagnosis in the prodromal period is more common in frontotemporal dementia (FTD), it is also common in Alzheimer's dementia (AD). Neuropsychiatric symptoms may be the first manifestation in behavioral variant FTD (Lindau et al. 2000); but AD (Ismail Z et al. 2016), vascular dementia (Ismail Z et al. 2016), some subcortical neurodegenerative diseases, dementia with Lewy bodies (LBD) (Auning et al. 2011) and Huntington's disease (Jauhar and Ritchie 2010) may also begin with behavioral and psychiatric symptoms. The neurodegenerative diseases that were diagnosed as a psychiatric syndrome the most before the diagnosis of dementia were behavioral variant FTD (50.7%), semantic dementia (24.3%), AD (23.1%), progressive nonfluent aphasia, corticobasal degeneration, and amyotrophic lateral sclerosis (12%) respectively (Woolley et al. 2011).

Neuropsychiatric symptoms are also commonly seen in Parkinson's disease and affect the majority of patients during the course of the disease. The most common and prominent neuropsychiatric symptoms seen in Parkinson's disease (PD) are depression, anxiety, apathy, and psychosis (Aarsland et al. 1999). The presence of NPS may predict cognitive decline in this patient group and may be the early signs of dementia (Pirogovsky-Turk et al. 2017).

Neuropsychiatric Symptoms in the Elderly Without Cognitive Impairment

Recent studies support that NPS, which are seen for the first time in elderly individuals without cognitive impairment, may be an early indication of cognitive dysfunction and the onset of a neurodegenerative process (Creese et al. 2019, Masters et al. 2015). Many studies have shown that the presence of NPS in cognitively healthy adults is associated with an increased risk of progression to MCI and dementia. The Alzheimer's Disease Cooperative Study has aimed to define markers sensitive to early detection that can be used in the disease prevention studies, for this purpose, behavioral changes such as anxiety, apathy, irritability, and depression have been included in these markers. The participants' self-reported behavioral complaints at the beginning have been found to predict progression to MCI and dementia in the 4-year follow-up (predicted progression 7.25% and 1.48% p=0.018, respectively), on the other hand, behavioral symptoms reported by the relatives of the patients were not found to predict progression to dementia (Banks et al. 2014).

A study conducted with the data obtained from Danish health records (Danish Psychiatric and Somatic Health Register) showed that late-onset acute and transient psychosis increased the rate of progression to dementia eight times compared to the general population (rate ratio (RR) 8.12, 95%. CI 6.77-9.74) (Kørner et al. 2009). In a cohort of 12,452 cognitively healthy participants using the Neuropsychiatric Inventory (NPI), affective symptoms (hazard ratio, HR 1.5, 95% CI 1.2-1.8), agitation (HR 1.6, 95% CI 1.3-2.1) and psychotic symptoms (HR 3.6, 95% CI 2.0–6.4) can be used to predict dementia, although psychotic symptoms are less common, they predict a higher risk of progression to dementia syndromes other than Alzheimer's (Liew TM 2020).

In a prospective study by Geda et al. using the Neuropsychiatric Inventory, attention was drawn to NPS in cognitively healthy elderly individuals and that non-psychotic NPS could predict the risk of developing MCI in these individuals, and also the presence of NPS was a stronger predictor for MCI than hippocampal atrophy (Geda et al. 2014). In another population-based study, individuals aged 70-90 who were not diagnosed with dementia, but with and without cognitive impairment were followed up for 2 years, and a significant correlation was found between some NPSs (especially anxiety and agitation) and decreased cognitive functions (Brodaty et al. 2012).

An online study using the Mild Behavioral Impairment Checklist (MBI-C) showed that MBI diagnosis was associated

with progressive deterioration in neuropsychological performance in individuals without significant cognitive impairment, and late onset mild neuropsychiatric symptoms can predict the development of MCI (Creese et al. 2019).

Mild Behavioral Impairment

Until recently, patients with late-onset NPS with no additional significant cognitive impairment and who did not meet diagnostic criteria of a particular psychiatric syndrome were nevertheless diagnosed with a psychiatric syndrome, and this picture wasn't considered to be a prodromal stage of a neurodegenerative disorder.

However, the concept of neuropsychiatric symptoms that emerge for the first time in old age which may reflect the early signs of neurocognitive disorders and a new-onset cognitive impairment, (Geda et al. 2014) has drawn more attention in recent years (Creese et al. 2019). Mild behavioral impairment is a new concept that aims to predict progression to dementia even before the onset of cognitive symptoms. The results of the studies to determine the prevalence of MBI vary according to the scales used and the samples studied. In a systematic review and meta-analysis, the MBI prevalence was found to be 45.5% in individuals diagnosed with MCI, 35.8% in individuals with subjective cognitive impairment (SCI) and normal cognition but also under risk, and 17.0% in cognitively normal individuals (Pan et al. 2021). The comorbidity of MBI with SCI (Ismail et al. 2021) and MCI (Taragano et al. 2018) increases the risk of progression to dementia compared to those diagnosed with only SCI and only MCI.

The concept of mild behavioral impairment was initially developed to describe the behavioral symptoms of FTD that may precede cognitive symptoms. Taragano et al. followed patients with NPS not diagnosed with dementia and thought to be at risk for frontotemporal lobar degeneration for 3 years; at the end of the follow-up, 44.93% of the patients were found to have FTD, 24.64% had AD, 7.25% had LCD, and 23.19% did not progress to dementia (Taragano and Allegri 2003). Defining MBI as a syndrome, they suggested that it can be used as a prodromal period similar to mild cognitive impairment, between normal cognition in old age and dementia. They stated that this concept includes late-onset, prominent psychiatric and related behavioral symptoms which occur in the absence of significant cognitive symptoms and that it may be a prodrome of dementia, and they defined the diagnostic criteria (Schölzel-Dorenbos CJ 2006, Taragano and Allegri 2003) (Table 1).

De Mendonça et al. (2004), on the other hand, expanded Taragano's criteria by bringing together the cognitive symptoms, behavioral symptoms, and imaging parameters that could indicate FTD and proposed the concept of "Frontotemporal Mild Cognitive Impairment" (Table 2). By observing that the criteria of Taragano, Allegri, and de Mendonça are useful for the early diagnosis of behavioral variant FTD and, by the findings that show the dementias other than FTD can also start with neuropsychiatric symptoms; the necessity of making changes on the criteria of MBI and showing its correlation to MBI has emerged.

Table 1. Mild Behavioral Impairment Diagnostic Criteria of Taragano and Allegri (Taragano and Allegri 2003)

a.	There must be a marked change in the patient's behavior
b.	This change must occur at a late age (>60) and persist for more than 6 months
c.	Complaints suggesting cognitive impairment should not be reported by the patient or their informant.
d.	Normal occupational and social functioning
e.	Normal participation in activities of daily living
f.	No dementia diagnosis

*Table is taken from "Taragano et al. 2009".

In 2016, İsmail et al. introduced and proposed diagnostic criteria for "Mild Behavioral Impairment" as it is used today (Ismail et al. 2016). MBI has been defined by these authors as a neurobehavioral syndrome that includes NPSs such as decreased motivation and interest (apathy), affective dysregulation, mood and anxiety symptoms, impulse dyscontrol, agitation, abnormal reward response, impaired social cognition (inappropriate behaviors), and abnormal perception or thought content (psychotic symptoms) that occur for the first time in later life and last for at least six months.

International Society to Advance Alzheimer's Research and Treatment (ISTAART) NPS Working Group headed by Zahinoor Ismail developed the investigational diagnostic criteria for MBI in 2016 in order to define the clinical sample to include in dementia studies, based on the criteria of Taragano, Allegri and de Mendonça, (Ismail et al. 2016) (Table 3). The rationale for developing these diagnostic criteria was described as to define late-onset psychiatric symptoms which may reflect a prodromal and preclinical stage of neurodegenerative diseases, to develop a tool which would be valid in clinical practice in terms of nosological, epidemiological, neurobiological, and treatment response, and to investigate the correlation between MBI and MCI more clearly.

As a result of the development of the mild behavioral impairment concept, psychiatric syndromes or chronic psychiatric symptomatology were separated from late onset psychiatric symptoms. These late-onset psychiatric symptoms that do not meet the diagnostic criteria of a psychiatric syndrome and thought to be the leading symptoms implying cognitive impairment formed the basis of the MBI concept (Cieslak et al. et al. 2018).

It should be noted that the neuropsychiatric symptoms in MBI diagnostic criteria cannot be attributed to a psychiatric disorder, and these mild psychiatric symptoms should be separated from psychiatric diseases considering the risk of

Table 2. FrontoTemporal- Mild Cognitive Impairment Diagnostic Criteria (de Mendonça et al., 2004)

1. **Impairment in frontotemporal functions**
   a. Behavioral symptoms
   Changes in self-awareness, neglect of hygiene and care, changes in social awareness and lack of tact, criminal behavior; early signs of disinhibition, changes in sexual behavior, violence, sarcasm, restless pacing, mental rigidity and loss of flexibility, hyperorality, stereotypical and repetitive movements, utilization behavior, distractibility, impulsivity, impersistence, loss of insight.
   b. Affective symptoms
   Depression, anxiety, hypersensitivity, suicidal ideation and fixed-mindedness, delusion; hypochondriasis, somatic preoccupations, emotional indifference and remoteness, apathy, lack of empathy and sympathy, loss of facial expressions, inertia, loss of spontaneity
   c. Speech impairment
   Decreased speech or stereotypical speech
   These symptoms should be confirmed by the informant.
   The patient may also have memory complaints.

2. **Impairment in at least one test of frontal lobe-related executive functions**
   Attention (cancellation task), verbal initiative, motor initiative, grapho-motor initiative and conceptual thinking (verbal, interpretation of proverbs, or nonverbal, progressive matrices test)
   (DSM IV, American Psychiatric Association (1994); a score of 1 standard deviation below the mean for age and education is considered impaired; memory tests may also be impaired)

3. **Maintained activities of daily living**
   The patient should be able to maintain both professional, social and family activities by clinical evaluation. The patient should have a score of < 3 on daily activities and change in habits part on the Blessed Dementia Rating Scale.
4. **Normal CT/MR imaging or frontotemporal atrophy**

*Table has been created from "de Mendonca et al. 2004".

Table 3. ISTAART Mild Behavioral Impairment Research Diagnostic Criteria (Ismail et al., 2016)

1. **Late onset (≥50 years), changes in behavior and personality (observed by patient, informant, or clinician), must persist for at least 6 months (at least intermittently)**
   The person should have at least one of the following reflecting a change from their usual behavior and personality traits,
   a. Decreased motivation (e.g., apathy, loss of spontaneity, indifference)
   b. Affect dsyregulation (e.g., anxiety, dysphoria, changeability, euphoria, irritability)
   c. Impulse control disorder (e.g., agitation, disinhibition, gambling, behavioral repetitions, obsessiveness)
   d. Social inappropriateness (e.g., lack of empathy, lack of insight, loss of socially appropriate behaviors and attitudes, inflexibility, exaggeration of previous personality traits)
   e. Abnormal perception and thought content (e.g., delusions, hallucinations)

2. **Behaviors must be severe enough to cause at least minimal impairment in at least one of the following:**
   a. Interpersonal relations
   b. Other aspects of social functioning
   c. Workplace performance
   In general, the patient should be able to maintain independence in activities of daily living with minimal assistance.

3. **Changes in behavior and personality should not be attributable to another psychiatric disorder, traumatic or general medical condition, or to the effect of a substance or medication, although there may be co-occurring conditions.**

4. **The patient should not meet the criteria for a dementia syndrome (AD, FTD, LCD, etc.).**
   Mild cognitive impairment can be diagnosed concurrently with MBI.

*Table is taken from "Zahinoor et al. 2016" .

progression to dementia. Because the concept has not yet become widespread, psychiatrists may also be inclined to attribute these mild symptoms in later life to a psychiatric diagnosis. In a retrospective study of the psychiatric patients over the age of 50, it was stated that this lack of acknowledgment could be the reason for the low rate of diagnosis of MBI (3.5%) (Matsuoka et al. 2019).

In another study, individuals aged 60 and over without a diagnosis of dementia were grouped into MBI, MCI, and general psychiatric disorders (diagnoses of major depression, generalized anxiety disorder, schizoaffective disorder, personality disorder, post-traumatic stress disorder, bipolar disorder type 1 and 2) according to DSM IV diagnostic criteria and the risk of progression to dementia was compared between the groups. The risk was highest in the MBI group (71.5%), 59.6% in people with MBI and MCI, and 13.9% in the psychiatric disease group. The same study had shown that the MCI group progressed to Alzhiemer's dementia at a higher rate, while the participants in the MBI and psychiatric disease groups tended to progress to LBD and FTD (Taragano et al. 2018).

MBI was also evaluated in Parkinson's disease, and the frequency of MBI was 84.1% in a sample of Parkinson's patients, and the frequency increased with the progression of the disease (Baschi et al. 2019). MBI was also found to

be associated with attention, executive functions, language, memory, visuospatial functions, and medial temporal cortex atrophy in patients with Parkinson's disease without dementia (Yoon et al, 2019).

The Neurobiology of Mild Behavioral Impairment

With the definition of the mild behavioral impairment concept and the development of the research criteria, the neurobiology of MBI and its relation with other biomarkers have begun to be studied. In a study which included subjects with subjective cognitive complaints and mild cognitive impairment, MBI presence was found to be associated with atrophy of the entorhinal cortex and hippocampus. The authors emphasized that temporal rather than frontal regions played a role in the development of NPS (Matuskova et al. 2021).

MBI total score was found to be correlated with impaired affective dysregulation and decreased functional connectivity between the left posterior parietal cortex and right middle frontal gyrus. In addition, decreased functional connectivity has been shown in the left frontal pole and superior frontal gyrus in MBI implying that the dysfunction in the frontoparietal control network may be associated with MBI. However, in this study, neural connections of MBI sub-domains such as decreased motivation, social inappropriateness, and abnormal perception and thought content could not be detected in the participants because these symptoms were relatively less common and mild in this sample (Matsuoka et al. 2021).

In another study, cognitively healthy individuals and patients diagnosed with MCI or Alzheimer's disease were evaluated with NPI, and in those with impaired impulse control (presence of at least one criterion in the impulse dyscontrol domain), lower white matter density was shown in tracts including cingulum, fornix, superior fronto-occipital fasciculus, and uncinate fasciculus. Impulse dyscontrol was found to be correlated to the decreased fractional anisotropy, and greater mean, axial, and radial diffusivity in the fornix; decreased fractional anisotropy, and greater radial diffusivity in the superior fronto-occipital fasciculus; and greater axial diffusivity in the cingulum, greater axial and radial diffusivity in the uncinate fasciculus, gray matter atrophy, particularly decreased cortical thickness in the parahippocampal gyrus. These results point to the role of fronto-striatal networks in the regulation of these behaviors (Gill et al. 2021).

Detection of easily applicable biomarkers such as plasma markers and imaging methods and evaluating their correlations with MBI will increase the predictive power in dementia research. Among those patients with MBI with normal cognition or mild cognitive impairment, plasma Aβ42/Aβ40 levels were found to be low, indicating that diagnosing MBI may be effective in detecting prodromal Alzheimer's disease (Miao et al. 2021). In another study, which included cognitively unimpaired Aβ-positive subjects which can be defined as preclinical Alzheimer's pathological change or preclinical AD according to the NIA-AA research framework, emotion disturbance and impulse dsycontrol were found to be associated with tau-PET standardized uptake value ratios in BRAAK I-II regions (entorhinal cortex and hippocampus) and CSF p-Tau181 levels (Johansson et al. 2021). In cognitively normal individuals, the presence of MBI was found to be associated with global and striatal amyloid PET signals, but no significant correlation was found with tau-PET (Lussier et al. 2020).

Although studies on the genetics of MBI are still very few, a study found a correlation between 5 late-onset Alzheimer's disease genetic risk factors (APOE, MS4A, BIN1, EPHA1, NME8, and ZCWPW1) and MBI subdomains (Andrews et al. 2018). In another study evaluating people over 50 years of age without dementia, it was found that polygenic risk scores of Alzheimer's disease were associated with cognitive impairment in the MBI group, but no such relationship was found in those without MBI (Creese et al. 2021).

Scales Used in the Evaluation of Neuropsychiatric Symptoms and Mild Behavioral Impairment - Checklist

Neuropsychiatric symptoms have long been described in dementia, but the rating scales for NPS in neurodegenerative diseases target the patients diagnosed with dementia who have more severe symptoms than MBI (Cieslak et al. 2018). Existing scales used to assess NPS in dementia patients so far can be grouped as general scales and symptom-specific scales. General scales such as Behavioral Pathology in Alzheimer's Disease Rating Scale (BEHAVE-AD) (Reisberg et al. 1987) and Neuropsychiatric Inventory (NPI) (Cummings et al. 1994) allow a more comprehensive assessment, while focused scales such as Cornell Scale for Depression in Dementia (Alexopoulos et al. 1988), Geriatric Depression Scale (Burke et al. 1991) and Cohen-Mansfield Agitation Inventory (Cohen-Mansfield J 1986) are used to assess one or more behavioral symptoms. The Neuropsychiatric Inventory is the most commonly used tool to evaluate neuropsychiatric symptoms in dementia studies. It usually includes information from the caregiver. The clinician version has also been developed recently (de Medeiros et al. 2010).

Although the concept of mild behavioral impairment references a time range of 6 months, these scales generally evaluate a shorter time frame like 2-4 weeks. Using these scales for the evaluation of MBI might cause false-positive results and an over-diagnosis due to the reactive and transient statuses observed within a short time frame being defined as NPS (Cieslak et al. 2018). In a population-based study using NPI, the prevalence of MBI was found to be 34.1%, 48.9% amongst those with MCI, and 27.6% amongst those with normal

cognition (Mortby et al. 2018). On the other hand, in a study conducted using the Mild Behavioral Impairment Checklist (MBI-C) which was developed to evaluate MBI specifically, the prevalence of MBI in the patients in primary care settings with MCI was found to be 14.2% (Mallo et al. 2018), and in a similar study, 5.8% in those with SCD (Mallo et al. 2019). This significant difference may be a result of using NPI which evaluates a short period of time (1 month) to diagnose MBI as well the presence of false positives in the sample.

Therefore, with the development of the MBI concept and the definition of the diagnostic criteria, a need arose to assess it with a valid and reliable tool to consider MBI as a dementia prodrome in the preclinical population. For this purpose, an international working group of 18 experts (psychiatrists, neuropsychiatrists, neurologists, neuroscientists, epidemiologists) has developed the Mild Behavioral Impairment Checklist (MBI-C) (http://www.mbitest.org/) to assess and capture MBI symptoms in the preclinical population (Ismail et al. 2017).

According to MBI-C, the behavior in the question must have been going on for at least 6 months and must be different from the person's long-standing behavior pattern to be considered positive. If so, the severity of the behavior should be rated as mild (1 point), moderate (2 points), or severe (3 points) by marking "yes". The checklist consists of 34 questions in 5 domains. The apathy domain consists of 6 questions regarding cognitive, behavioral, and emotional apathy. The affect domain consists of 4 questions for depressed mood, anhedonia, hopelessness and guilt, and 1 question each for worry and panic. The impulse dyscontrol domain constitutes the largest part; includes 12 questions related to agitation, aggression, impulsivity, recklessness, abnormal reward, and reinforcement. The social inappropriateness domain consists of 5 questions assessing sensitivity, empathy, and tact. The abnormal thought and perception domain evaluates suspiciousness, grandiosity, and auditory and visual hallucinations with 5 questions (Ismail et al. 2017).

This checklist can be rated by a clinician, informant, or the patient himself. In a recent study, two forms of MBI-C (self-reported and informant reported) were administered in a large sample to evaluate the MBI profile and factor structure. In this study including 5,742 subjects over the age of 50 without dementia, the most frequently reported item by both the participants and the caregivers was affective dysregulation followed by impulse dyscontrol, decreased interest/motivation, social inappropriateness, and abnormal thought and perception. However, it has been concluded that self-report and informant report of the MBI-C work differently and do not give consistent results in all domains and that it would not be appropriate to use these two forms interchangeably (Creese et al. 2020).

The authors emphasize the importance of conducting comparative studies of this new screening tool with standardized clinical interviews. They also agreed that studies are needed to evaluate the effects of different time ranges (1-6 months) on NPS prevalence, the reliability of MBI-C in different samples, the validity of the scoring and the cut-off scores, the effect of different domains in predicting prognosis and dementia subtypes, and the clinical validity of the clinician rated or self-reported MBI-C forms (Ismail et al. 2017).

DISCUSSION

Studies aiming to identify people who will develop dementia syndrome before the symptoms occur and to evaluate the effectiveness of preventive approaches and early intervention methods in the samples recruiting these relevant candidates constitute a significant portion of dementia research in recent years. As mentioned before, earlier studies have shown that the presence of NPSs and MBI increases the risk of cognitive decline and progression to dementia in various samples including cognitively healthy individuals or subjects with MCI diagnosis. Therefore, the growing interest in NPSs and the concept of "Mild Behavioral Impairment" indicating pre-dementia stages is noteworthy, on the other hand, the necessity of a new pre-dementia category to draw attention to NPSs and their devastating effects is debated (Canevelli et al. 2016).

The concept of MBI is useful for categorizing later life-onset behavioral disorders and psychiatric symptoms that do not meet a diagnostic criteria, and it could also be helpful to diagnose dementia at a very early stage in which no cognitive symptoms have emerged yet. However, ambiguous expressions such as ''not attributable to a psychiatric disease", '' criteria unmet for a dementia syndrome", and ''causing minimal impairment" in MBI criteria could lead to the disappearance of the border between the sick and the healthy, and may cause many people to be unnecessarily treated and exposed to the side effects of over-medication. The pros and cons of this new concept on health systems and patients have not been discussed so far (Glasziou P et al. 2013).

In addition, the item that behavioral changes must be present for at least 6 months according to the specified criteria may lead to the acceptance of all the patients with prolonged sub-threshold neuropsychiatric symptoms as subjects at a pre-dementia stage. For example, subthreshold depression may cause functional impairment and could exist for a period of time that meets the criteria. In this case, a misdiagnosis of MBI may lead to the actual disease being left untreated (Grabovich et al. 2010).

The criteria did not adequately assess the reversibility of MBI. There may be prolonged psychiatric symptoms due to internal and external stressors, so the presence of these

symptoms should not be considered an inevitable progression to dementia. In addition, the presence of false positives in the samples also reduces the effect size of possible interventions. On the other hand, more precise identification of people who would progress to dementia could improve the design and interpretation of clinical trials. Aiming to detect dementia by expanding the risk zone in cases where the clinical picture has not fully settled or who are at a very early stage increases the possibility of interventions in the early stages of pathophysiological changes. However, it may also lead to increased rates of misdiagnosis, unnecessary anxiety and stress, stigma, unnecessary and excessive treatment attempts, increased unregistered drug use, and misinterpretation of the effect size of interventions in studies (Canevelli et al. 2016). On the other hand, using NPSs together with neurodegenerative biomarkers may improve the value of the MBI in predicting dementia, as in other prodromal conditions. Clarifying the neurobiology of MBI domains will guide in elucidating the pathogenesis of dementia and identifying new biomarkers. Biomarkers that indicate the neuropathological changes may help detect the underlying neurodegenerative process, and they can predict the risk of progression to dementia with a higher probability. Imaging methods, blood biomarkers, and genetic data may be used for this purpose, yet, there are few studies on their relationship with MBI and its domains. Since the routine use of biomarkers in today's clinical practice is not yet possible, it would be valuable to adapt this new concept and its clinical implications for research in the near future (Canevelli et al. 2016).

The definition of MBI diagnostic criteria and the development of MBI-C will facilitate to interpret the results of the clinical studies by enabling more homogeneous clinical samples to be recruited. However, risks such as the possibility of clinicians from different specialties (psychiatrists, neurologists, family physicians, etc.) misdiagnosing sub-threshold neuropsychiatric symptoms or attributing them to a psychiatric diagnosis should be considered. Subsequent work should focus on whether assessing MBI would provide an additional benefit in enriching the samples of clinical studies to develop modifying or preventive interventions for dementia syndromes, on the effect of the concept when used with the biomarkers in predicting the risk and on the elucidation of the neurobiological basis of MBI domains.

CONCLUSION

In clinical practice, physicians encounter many clinical pictures which do not meet the diagnostic criteria of a psychiatric syndrome in elderly patients, for this reason, the definition of the MBI concept is important to explain these clinical phenomena and to provide a different perspective for the pre-clinical phase of cognitive disorders. Overlook of the neurodegenerative process may cause a delay in the appropriate treatment and interventions, worsening the course and prognosis of neurodegenerative disease. Therefore, the patients' histories with symptoms emerging at an older age and which are not attributable to a psychiatric diagnosis (such as schizophrenia, obsessive-compulsive disorder, bipolar affective disorder) should be carefully taken keeping in mind the possibility of neurodegenerative diseases, appropriate neuropsychological evaluations should be made, risk factors should be investigated, and biomarkers should be evaluated if necessary.

There are not enough studies yet to determine the cut-off scores of MBI-C, which was developed to assess MBI in people at risk and to determine which domain is more predictive in diagnosing MBI and the neurodegenerative process. The use of MBI-C in combination with other biomarkers (CSF, blood, imaging, etc.) in clinical studies to detect neurodegenerative diseases at the pre-clinical stage will contribute to dementia studies. However, it is obvious that using the scale in this current form will lead to overdiagnosis and stigmatization. For this reason, investigation of the predictive power of MBI-C for dementia in large follow-up studies in which each domain is assessed, and clarification of the neurobiological basis of the concept and its relationship with biomarkers are necessary for the near future.

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