Mild behavioral impairment as a potential marker of predementia risk states in motor neuron diseases

Pilar M. Ferraro1,2 | Ester Gervino1 | Emiliano De Maria1 | Giuseppe Meo2 | Marta Ponzano3 | Matteo Pardini2,4 | Alessio Signori3 | Angelo Schenone2,4 | Luca Roccatagliata1,3 | Claudia Caponnetto2

1Neuroradiology Unit, IRCCS Ospedale Policlinico San Martino, Genoa, Italy
2Neurology Unit, IRCCS Ospedale Policlinico San Martino, Genoa, Italy
3Department of Health Sciences (DISSAL), University of Genoa, Genoa, Italy
4Department of Neuroscience, Rehabilitation, Ophthalmology, Genetics, Maternal and Child Health (DiNOGMI), University of Genoa, Genoa, Italy

Correspondence
Pilar M. Ferraro, IRCCS Ospedale Policlinico San Martino, Largo R. Benzi 10, Genoa 16132, Italy.
Email: pilarmaria.ferraro@ext.unige.it

Abstract

Background and purpose: Mild behavioral impairment (MBI) has been increasingly regarded as the neurobehavioral axis of predementia risk states, but a specific investigation of its detection as a potential marker of prodromal dementia in motor neuron diseases (MNDs) is still lacking. The aims of our study were therefore to explore MBI in MNDs both at onset and over the disease course, and to evaluate its relationship with baseline and longitudinal cognitive features.

Methods: Sixty MND patients with cognitive/behavioral, mood, and motor examinations were recruited and followed longitudinally for up to 15 months. Associations between baseline MBI symptoms and clinical features were tested using the Spearman correlation coefficient. Based on longitudinal data, relative deltas of variation for each cognitive measure were generated, and linear regression models were then used to evaluate the role of baseline MBI symptoms in predicting longitudinal rates of cognitive decline.

Results: At disease onset, the most impaired MBI domain was affective/emotional dysregulation, followed by impulse dyscontrol, apathy, and social inappropriateness. Greater MBI symptoms correlated with more severe baseline motor, cognitive/behavioral, and mood disturbances (p values from <0.001 to 0.05). Longitudinally, the greatest decline was observed in the affective/emotional dysregulation domain, followed by impulse dyscontrol, apathy, and social inappropriateness. Greater MBI symptoms at onset were significant predictors of more severe longitudinal cognitive decline in both amyotrophic lateral sclerosis (ALS)-specific and ALS-nonspecific functions (p values from <0.001 to 0.03).

Conclusions: MBI represents a valuable clinical marker of incident cognitive decline in MNDs, and its evaluation has good potential for detecting dementia in its preclinical/prodromal phase.

Keywords
amyotrophic lateral sclerosis, longitudinal cognitive decline, mild behavioral impairment, motor neuron diseases, prodromal dementia
INTRODUCTION

The increasing recognition of neuropsychiatric symptoms as common prodromal manifestations of dementia in neurodegenerative diseases has recently led to the definition of the ISTAART research diagnostic criteria for mild behavioral impairment (MBI) [1], a syndrome characterized by later life onset of continued psychiatric symptoms that are not described in other nosologies (e.g., major depression, generalized anxiety, delusional disorder), regarded as an at-risk state for incident cognitive decline and dementia.

Although encompassing a wide range of symptoms, MBI has been broken down into the five domains of motivation, affective regulation, impulse control, social cognition, and perception/thought content [1], and a specific instrument, the Mild Behavioral Impairment Checklist (MBI-C), has been developed to accurately evaluate this syndrome according to its defining criteria [2].

Preliminary studies exploring MBI in cognitively normal subjects, patients with mild cognitive impairment [3], and patients with Parkinson disease [4] have shown that its presence is significantly associated with faster cognitive decline and higher risk of conversion to dementia [5–7], suggesting that the early detection of this syndrome may help to identify the preclinical or prodromal phases of dementia.

Notably, clinical markers of upcoming cognitive deterioration might be particularly useful in the context of motor neuron diseases (MNDs), a heterogeneous group of neurodegenerative motor syndromes accompanied by cognitive and/or behavioral changes [8, 9], reaching overt frontotemporal dementia (FTD) in 5%–22% of cases [10]. Accordingly, although it is now widely accepted that comorbid FTD is a strong negative prognostic factor in MNDs [11–13], its prodromal behavioral manifestations are often subtle and difficult to evaluate [14], so early and specific markers of preclinical dementia are highly needed both in clinical and in research settings.

Despite these considerations, no study to date has explored the construct of MBI as operationalized by the ISTAART criteria in MNDs and, more importantly, no longitudinal studies have been carried out to test its potential as a clinical marker of predementia risk states in these heterogeneous diseases.

The aims of the present study were therefore to (i) explore MBI and its domains in MNDs both at onset and over disease course; (ii) investigate possible associations between MBI symptoms and motor, cognitive, and mood disturbances at onset; and (iii) evaluate the relationship between onset MBI features and longitudinal trajectories of cognitive decline.

METHODS

Participants

In the period between October 2019 and July 2021, 60 MND patients (28 patients with classic amyotrophic lateral sclerosis [ALS], 14 patients with a clinical pure/predominant upper motor neuron [pUMN] phenotype, and 18 patients with a clinical pure/predominant lower motor neuron [pLMN] phenotype) were consecutively recruited at our referral MND clinic.

Inclusion criteria were (i) absence of overt FTD according to current diagnostic criteria [15, 16] and (ii) absence of severe depressive and/or anxiety symptoms (score < 11) on the Hospital Anxiety and Depression Scale (HADS) [17].

Diagnosis of classic ALS was made according to the revised Escorial criteria [18]. pUMN (including primary lateral sclerosis and pyramidal phenotypes) and pLMN (including pure LMN, and flail arm and flail leg phenotypes) cases were defined according to current classifications [19].

At study entry, all patients underwent a comprehensive evaluation, including neurological history, neurophysiological assessment, and clinical, cognitive/behavioral, and mood examinations.

Fifty-five percent of patients (n = 33) also underwent a detailed genetic screening, including both C9orf72 GGGGCC repeat length analysis and next generation sequencing analysis with two multiple gene panels including respectively 23 and 27 genes known to be associated or possibly associated with ALS. The genes included in the panels are given in Table S1.

Experienced neuropsychologists performed all the clinical examinations. Site of disease onset and disease duration were recorded. Disease severity was assessed using the Amyotrophic Lateral Sclerosis Functional Rating Scale–Revised (ALSFRS-r), and the rate of baseline disease progression was calculated as follows: (48 – ALSFRS-r score at the time of examination)/months from symptom onset to examination.

Experienced neuropsychologists performed all the cognitive/behavioral and mood examinations. Cognitive and behavioral symptoms were evaluated using the Italian version of the Edinburgh Cognitive and Behavioural ALS Screen (ECAS) [20, 21].

The presence of MBI was evaluated using the Italian version of the MBI-C [2, 22]. The MBI-C is a 34-item questionnaire administered to patients’ caregivers and organized according to the five MBI domains: (i) apathy: Six questions including assessments of cognitive, behavioral, and emotional apathy; (ii) affective/emotional dysregulation—six items including low mood, anhedonia, hopelessness, guilt, worry, and panic; (iii) impulse dyscontrol—12 questions assessing agitation, aggression, impulsivity, recklessness, and abnormal reward and reinforcement; (iv) social inappropriateness—five questions describing sensitivity, empathy, and tact; and (v) abnormal thoughts/perception—five questions assessing suspiciousness, grandiosity, and auditory and visual hallucinations. For each item, a “yes” or “no” question is followed by a severity rating scale of 1 (mild), 2 (moderate), or 3 (severe).

Both the behavioral ECAS screen and the MBI-C were completed by the same carer for all the included patients.

Anxiety and depression were evaluated using the HADS [23].

Scores on the ECAS were age-, sex-, and education-corrected using corresponding normative values [24] and, according to current criteria for cognitive/behavioral impairment in ALS [15], patients were subsequently classified as MND with normal cognition.
LONGITUDINAL STUDY OF MBI IN MNDS

(MND-motor) and MND with either cognitive or behavioral impairment or a combination of both (MND-CBI).

Patients were then followed longitudinally with clinical, behavioral, and mood examinations approximately every 3 months, and with cognitive evaluations approximately every 6 months, for up to 15 months.

For all the included patients, the carer who provided the baseline behavioral ECAS screen and MBI-C scores was the same one rating the symptoms on both scales over the follow-up examinations.

Approval of the institutional review board (Comitato Etico Regionale della Liguria) and written informed consent from all participants were obtained. The study was conducted in agreement with the Declaration of Helsinki.

**Statistical analyses**

All data were analyzed using CRAN R version 3.4.1. Associations between baseline total MBI-C and MBI-C domain scores and baseline motor, cognitive/behavioral, and mood symptoms were tested using the Spearman correlation coefficient. To avoid increasing the risk of type I error due to the numerous correlations, we further evaluated, in additional analyses, which exact p values remained significant after Bonferroni adjustment for multiple comparisons (specifically, the Bonferroni method was used to calculate the significance level taking into account the k = 70 correlations evaluated, so it was set to α/k = 0.05/70 = 0.0007).

In exploratory analyses, using the previously reported MBI-C cut point of 7.5 [4], MND patients were further classified as MND with high MBI-C scores, referred to as “MND-MBI,” and MND with low MBI-C scores, referred to as “MND-noMBI,” and differences in demographic and clinical features between the two groups were analyzed using the Mann–Whitney U-test and chi-squared test, as appropriate.

Based on longitudinal data, relative deltas of variations were generated for total MBI-C and MBI-C domain scores as well as for each ECAS-derived cognitive measure.

Linear regression models were then used to evaluate the role of baseline MBI features in predicting longitudinal rates of cognitive decline.

**RESULTS**

**Cross-sectional findings**

**MBI features**

Demographic, genetic, and clinical features of the whole MND sample are reported in Table 1. Fifty-one cases (85.00%) showed at least one MBI symptom; the most impaired MBI domain was affective/emotional dysregulation (mean score = 3.38, SD = 3.48), followed by impulse dyscontrol (mean score = 1.70, SD = 2.45), apathy (mean score = 1.38, SD = 3.12), and social inappropriateness (mean score = 0.20, SD = 0.83; Figure 1). None of the patients scored >0 on the abnormal thoughts/perception MBI domain.

**Associations between MBI features and motor, cognitive/behavioral, and mood symptoms**

At onset, significant correlations were observed between higher total MBI-C and affective/emotional dysregulation domain scores and lower ALSFRS-r scores (r = −0.27, p = 0.03 and r = −0.31, p = 0.01, respectively) and higher rates of baseline disease progression (r = 0.28, p = 0.03 and r = 0.35 p = 0.006, respectively; Table 2).

Concerning the relationship with cognitive features, greater apathy was significantly associated with lower ECAS ALS nonspecific function scores (r = −0.26, p = 0.05); greater impulse dyscontrol was significantly associated with lower ECAS total scores (r = −0.25, p = 0.05), ECAS ALS specific functions scores (r = −0.25, p = 0.05), and ECAS language scores (r = −0.27, p = 0.04; Table 2).

As expected, total MBI-C scores and scores on all its domains significantly correlated with higher ECAS carer behavior screen scores (r ranging from 0.42 to 0.80, p < 0.001; Table 2).

Significant correlations were also observed between higher total MBI-C scores and greater HADS total scores (r = 0.28, p = 0.04) as well as between higher total MBI-C and affective/emotional dysregulation domain scores and greater HADS depression scores (r = 0.38, p = 0.007 and r = 0.32, p = 0.02, respectively; Table 2).

In the additional analyses using the Bonferroni adjustment, exact p values remained significant for the association between total MBI-C scores and scores on all its domains and the ECAS carer behavior screen.

**Comparison between MND-MBI and MND-noMBI**

Demographic, genetic, and clinical features of the whole MND sample stratified by MBI status are reported in Table 1. Nineteen patients (31.66%) were categorized as having MND-MBI (Table 1). Notably, among them, five cases (26.31%) were classified as MND-motor according to current criteria for cognitive/behavioral impairment in ALS. The remaining 41 cases (68.34%) were categorized as MND-noMBI.

In exploratory analyses comparing the two groups, we found that MND-MBI cases showed significantly more severe functional impairment (lower ALSFRS-r scores, p = 0.02), greater frequency of MND-CBI diagnosis (p < 0.001), and higher total HADS (p = 0.04) and HADS depression scores (p = 0.01), and as expected given their defining criteria, also higher ECAS carer behavior screen scores (p < 0.001; Table 1).

**Longitudinal findings**

Of the whole sample, five cases (8.33%) deceased before the first longitudinal examination, two cases (3.33%) dropped out from the study, and six cases (10%) were not yet in the 3-month time window to execute the first longitudinal examination by the time of study closure.
The remaining 47 cases (78.33%) underwent at least one longitudinal examination and therefore constituted the final longitudinal sample.

**Longitudinal trajectories of MBI**

Individual slopes of decline for the total MBI-C and its domains scores are shown in Figure 2. A significant worsening of MBI symptoms was already evident by the time of the first longitudinal assessment at 3 months.

Overall, the greatest decline (highest relative delta of variation) was observed in the affective/emotional dysregulation domain (mean delta = 113.33, SD = 190.74), followed by the impulse dyscontrol (mean delta = 66.60, SD = 139.00), apathy (mean delta = 54.78, SD = 86.52), and social inappropriateness domains (mean delta = 12.50, SD = 25.00; Figure 3).

In five patients, all belonging to the MND-MBI group, the progressive worsening of behavioral and cognitive symptoms over the follow-up period met criteria for an ALS-FTD diagnosis.

**Relationship between MBI features at onset and longitudinal cognitive decline**

Higher total MBI-C scores at onset were significant predictors of greater decline in visuospatial functions ($\beta = -0.65, p = 0.001$; Table 3).

Higher scores on the impulse dyscontrol domain were significant predictors of greater decline in the ECAS total score ($\beta = -0.41, p = 0.01$), executive functions ($\beta = -2.47, p = 0.001$), and verbal fluency ($\beta = -1.01, p = 0.01$; Table 3).

Higher scores on both apathy and affective/emotional dysregulation domains were associated with greater decline in visuospatial functions ($\beta = -2.27, p < 0.001$ and $\beta = -0.91, p = 0.03$, respectively; Table 3).

**DISCUSSION**

To our knowledge, this is the first study to explore MBI in patients with MND both at onset and over the disease course and, more importantly, the first one to evaluate its potential as a clinical marker of upcoming cognitive decline in this neurodegenerative condition. A
LONGITUDINAL STUDY OF MBI IN MNDS

A detailed discussion of the obtained cross-sectional and longitudinal findings is provided below.

**Cross-sectional findings**

**MBI features**

At disease onset, 85.00% of MND patients showed at least one MBI symptom, while using the previously reported cutoff of 7.5 [4], overt MBI was observed in 31.66% of cases.

**TABLE 2** Results of the correlation analyses between baseline MBI-C scores and baseline motor, cognitive/behavioral, and mood features

| Feature                        | MBI-C total score | MBI-C apathy   | MBI-C affective/ emotional dysregulation | MBI-C impulse dyscontrol | MBI-C social inappropriateness |
|-------------------------------|-------------------|----------------|------------------------------------------|--------------------------|---------------------------------|
| Motor measures                |                   |                |                                          |                          |                                 |
| ALSFRS-r score                | -0.27 (0.03)      | -0.22 (0.08)   | -0.31 (0.01)                             | -0.11 (0.39)             | -0.05 (0.68)                    |
| ALSFRS-r rate of progression  | 0.28 (0.03)       | 0.18 (0.15)    | 0.35 (0.006)                             | 0.11 (0.38)              | 0.02 (0.83)                     |
| Cognitive measures            |                   |                |                                          |                          |                                 |
| Total ECAS score              | -0.15 (0.27)      | -0.24 (0.07)   | -0.04 (0.76)                             | -0.25 (0.05)             | -0.08 (0.55)                    |
| Language functions            | -0.20 (0.13)      | -0.18 (0.16)   | -0.01 (0.89)                             | -0.27 (0.04)             | -0.09 (0.50)                    |
| Verbal fluency                | -0.006 (0.96)     | -0.23 (0.08)   | -0.04 (0.76)                             | -0.02 (0.83)             | -0.15 (0.25)                    |
| Executive functions           | -0.11 (0.38)      | -0.08 (0.55)   | -0.04 (0.72)                             | -0.19 (0.14)             | -0.06 (0.61)                    |
| ALS-specific functions        | -0.13 (0.32)      | -0.21 (0.12)   | -0.06 (0.64)                             | -0.25 (0.05)             | -0.10 (0.45)                    |
| Memory functions              | -0.12 (0.36)      | -0.24 (0.07)   | -0.01 (0.90)                             | -0.08 (0.54)             | -0.02 (0.87)                    |
| Visuospatial functions        | -0.15 (0.27)      | -0.22 (0.09)   | -0.003 (0.97)                            | -0.18 (0.17)             | -0.02 (0.86)                    |
| ALS-nonspecific functions     | -0.14 (0.28)      | -0.26 (0.05)   | -0.03 (0.79)                             | -0.09 (0.47)             | -0.03 (0.79)                    |
| Behavioral symptoms           |                   |                |                                          |                          |                                 |
| ECAS carer behavior screen    | 0.76 (<0.001)     | 0.80 (<0.001)  | 0.50 (<0.001)                            | 0.70 (<0.001)            | 0.42 (<0.001)                   |
| Mood symptoms                 |                   |                |                                          |                          |                                 |
| Total HADS score              | 0.28 (0.04)       | 0.19 (0.19)    | 0.26 (0.06)                              | 0.15 (0.27)              | 0.08 (0.55)                     |
| HADS depression score         | 0.38 (0.007)      | 0.24 (0.09)    | 0.32 (0.02)                              | 0.22 (0.12)              | 0.08 (0.55)                     |
| HADS anxiety score            | 0.19 (0.19)       | 0.09 (0.51)    | 0.23 (0.11)                              | 0.05 (0.73)              | 0.06 (0.64)                     |

Note: Values are given as Spearman correlation coefficient (p value).

Abbreviations: ALS, amyotrophic lateral sclerosis; ALSFRS-r, Amyotrophic Lateral Sclerosis Functional Rating Scale–Revised; ECAS, Edinburgh Cognitive and Behavioural ALS Screen; HADS, Hospital Anxiety and Depression Scale; MBI-C, Mild Behavioral Impairment Checklist.

*Significant p values after Bonferroni correction for multiple comparisons.

Significant p values are reported in bold.

In accordance with previous studies of MBI in cognitively normal adults [25], we found that the most impaired domain was affective/emotional dysregulation, followed by impulse dyscontrol, apathy, and social inappropriateness.

Whereas prior investigations in ALS have selectively evaluated overt behavioral symptoms, reporting apathy as the commonest behavioral manifestation of the disease [26, 27], our focus on mild behavioral changes has enabled us to reveal a predominance of affective/emotional dysregulation and impulse dyscontrol symptoms in our cohort.

Emotional dysregulation has been previously reported in ALS, and it has been further suggested that, although probably
underestimated, this behavioral feature may underlie the inappropriate reactions to emotional stimuli frequently described in ALS patients [28–30].

Similarly, disinhibition and impulsivity are well known behavioral manifestations of ALS [31, 32], and recent studies have further proved that these symptoms represent the strongest predictors of greater burden on patients’ caregivers [33].

Conversely, the mild nature of social inappropriateness symptoms and the absence of psychotic features observed in our cohort are in line with the notion that these domains are usually preserved until advanced disease stages in ALS [34], mainly characterizing cases with overt FTD and more specifically those carrying C9Orf72 mutations [35].

Associations between MBI features and motor, cognitive/behavioral, and mood symptoms

Intriguingly, already at disease onset, the severity of MBI symptoms was significantly associated with greater motor, mood, and cognitive disturbances.

In the whole sample, we found that higher total MBI-C scores and, in particular, higher scores in the affective/emotional dysregulation domain, correlated with more severe motor impairment and depressive symptoms. Accordingly, when we compared the MND-noMBI to the MND-MBI group, we observed that the latter had significantly lower ALSFRS-r and significantly higher HADS depression scores.
The association we found between the severity of MBI symptoms and motor functional impairment is in line with previous studies reporting worse prognosis in ALS patients with behavioral impairment [36, 37].

Additionally, in line with our hypothesis that MBI may represent a marker of upcoming cognitive decline, the relationship we observed with more severe motor impairment well fits with recent evidence showing that ALS patients developing cognitive impairment are those presenting with lower ALSFRS-r score at the time of first evaluation [38].

Concerning the correlation between MBI features and depression, this finding is in agreement with previous studies reporting more severe depressive symptoms in ALS patients with behavioral impairment [34, 39], and further confirms the well-known link between behavioral and neuropsychiatric manifestations of the disease.

Notably, as previously observed in Parkinson disease [4], the severity of MBI symptoms was also associated with greater cognitive deficits in our MND cohort.

The interplay between behavioral and cognitive symptoms in MNDs is still poorly clarified. Although it is now widely accepted that behavioral changes can occur either alone or together with cognitive impairment [15], a growing body of evidence is now suggesting a strong link between the presence of cognitive decline and the severity of frontal lobe-mediated behavioral dysfunction [27, 40].

Finally, as expected given the large overlap between the investigated behavioral domains, we observed significant correlations (further surviving the Bonferroni correction for multiple comparisons) between MBI-C and ECAS carer behavior screen scores. Although this finding highlights a significant concordance between the two behavioral scales, it is noteworthy that 26.31% of the MND-MBI cases were classified as pure motor MND according to current criteria for cognitive and behavioral impairment in ALS, suggesting that, compared to the ECAS behavior screen, MBI-C may provide a more sensitive tool for detecting upcoming cognitive/behavioral decline in its preclinical phase.

### Longitudinal findings

#### Longitudinal trajectories of MBI

Our longitudinal findings confirmed the cross-sectional observations, with the greatest deterioration observed in the affective/emotional dysregulation domain, followed by impulse dyscontrol, apathy, and social inappropriateness domains.

Notably, by applying a short time interval between follow-up examinations, we were able to reveal that these mild behavioral changes were already evident after 3 months from the first evaluation, suggesting a rapid evolution of MBI disturbances in MNDs.

Given the relative paucity of longitudinal studies in MNDs, the evolution of behavioral symptoms in these fatal neurodegenerative syndromes is still poorly understood.

Although multiple studies have reported progressive behavioral deterioration in ALS [41–43], it has also been suggested that its detection is highly dependent upon the clinical measure used to evaluate it. In particular, a recent study from Poletti and coworkers failed to identify longitudinal behavioral changes using the ECAS, but found an increase of behavioral symptoms using the Frontal Behavioral Inventory [44], confirming the urgent need for more sensitive behavioral screening tools in MNDs.

#### Relationship between MBI features at onset and longitudinal cognitive decline

In line with our initial hypothesis that MBI may represent a clinical marker of upcoming cognitive deterioration, we found that the severity of MBI symptoms at onset was a significant predictor of the longitudinal rate of cognitive decline.

To date, the few available longitudinal studies of MBI have been focused on cognitively normal subjects and patients with mild cognitive impairment, all showing that MBI is associated with greater frequency of conversion to dementia and cognitive decline [5, 6, 45].
In this study, we have provided the first evidence of the same phenomenon in MNDs, further confirming the usefulness of MBI evaluation as a tool for detecting upcoming cognitive deterioration in its preclinical phase.

Greater impulse dyscontrol at onset was a significant predictor of more severe longitudinal decline in ALS-specific functions, mainly verbal fluency and executive measures, whereas greater apathy and affective/emotional dysregulation were significant predictors of more severe decline in ALS-nonspecific measures, visuospatial functions in particular.

The relationship we observed between greater impulse dyscontrol and progressive verbal fluency decline is in accordance with recent cross-sectional studies reporting a significant link between more severe symptoms of disinhibition and greater verbal fluency impairment in ALS [34, 46].

As regards the association between greater apathy and affective/emotional dysregulation symptoms and more severe longitudinal decline in visuospatial functions, it has to be noted that, although poorly investigated, visuospatial deficits have been increasingly reported in ALS [47, 48].

Additionally, a recent study by Crockford and coworkers found a slight deterioration of nonspecific functions across advancing disease stages in ALS [34], in line with previous reports suggesting their significant impairment in patients with comorbid FTD [49].

Taken together, these observations suggest that more severe impulse dyscontrol, apathy, and emotional/dysregulation at disease onset are predictive of an accelerated path of cognitive deterioration in MNDs, in accordance with our initial hypothesis.

Limitations and conclusions

This study is not without limitations. The first shortcoming deals with the longitudinal sample size, as only 78.33% of cases were able to perform at least one follow-up examination. Second, although our longitudinal approach has enabled us to track the path and rate of progressive cognitive decline, longer follow-up times are needed to establish the exact frequency of conversion to overt FTD states in our MND sample.

Despite these shortcomings, our study provides preliminary evidence that MBI may represent an early clinical marker of incident cognitive decline in MNDs, supporting the usefulness of its evaluation to detect dementia in its preclinical phase.

AUTHOR CONTRIBUTIONS

Conception and study design: Pilar M. Ferraro, Luca Roccatagliata, Claudia Caponnetto. Data collection: Pilar M. Ferraro, Ester Gervino, Emiliano De Maria, Giuseppe Meo. Statistical analysis: Pilar M. Ferraro, Ester Gervino. Interpretation of results: Pilar M. Ferraro, Marta Ponzano, Alessio Signori, Luca Roccatagliata, Claudia Caponnetto. Drafting the manuscript or revising it critically for important intellectual content: Pilar M. Ferraro, Matteo Pardini, Angelo Schenone, Luca Roccatagliata, Claudia Caponnetto. Approval of final version to be published and agreement to be accountable for the integrity and accuracy of all aspects of the work: all authors.

ACKNOWLEDGMENTS

The authors are grateful to the patients and their families for participating in the study. Open access funding provided by BIBLIOSAN.

CONFLICT OF INTEREST

All authors have no competing interests.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ORCID

Pilar M. Ferraro https://orcid.org/0000-0002-5547-3900
Marta Ponzano https://orcid.org/0000-0003-4091-4686
Matteo Pardini https://orcid.org/0000-0002-4740-1982
Alessio Signori https://orcid.org/0000-0001-6289-9144
Luca Roccatagliata https://orcid.org/0000-0001-8029-3947
Claudia Caponnetto https://orcid.org/0000-0002-5547-3900

REFERENCES

1. Ismail Z, Smith EE, Geda Y, et al. Neuropsychiatric symptoms as early manifestations of emergent dementia: provisional diagnostic criteria for mild behavioral impairment. Alzheimers Dement. 2016;12:195-202. doi:10.1016/j.jalz.2015.05.017
2. Ismail Z, Agüera-Ortiz L, Brodaty H, et al. The Mild Behavioral Impairment Checklist (MBI-C): a rating scale for neuropsychiatric symptoms in pre-dementia populations. J Alzheimers Dis. 2017;56:929-938. doi:10.3233/JAD-160979
3. Pan Y, Shea YF, Li S, et al. Prevalence of mild behavioural impairment: a systematic review and meta-analysis. Psychogeriatrics. 2021;21:100-111. doi:10.1111/psyg.12636
4. Yoon EJ, Ismail Z, Hangau A, et al. Mild behavioral impairment is linked to worse cognition and brain atrophy in Parkinson disease. Neurology. 2019;93:e766-e777. doi:10.1212/WNL.0000000000007968
5. Taragano FE, Allegrf RF, Heisecke SL, et al. Risk of conversion to dementia in a mild behavioral impairment group compared to a psychiatric group and to a mild cognitive impairment group. J Alzheimers Dis. 2018;62:227-238. doi:10.3233/JAD-170632
6. Ismail Z, McGirr A, Gill S, Hu S, Forkert ND, Smith EE. Mild behavioral impairment and subjective cognitive decline predict cognitive and functional decline. J Alzheimer Dis. 2021;80:459-469. doi:10.3233/JAD-201184
7. Orso B, Mattei C, Arnaldi D, et al. Clinical and MCI predictors of conversion from mild behavioural impairment to dementia. Am J Geriatr Psychiatry. 2020;28:755-763. doi:10.1016/j.jagp.2019.12.007
8. Montuschi A, Iazzolino B, Calvo A, et al. Cognitive correlates in amyotrophic lateral sclerosis: a population-based study in Italy. J Neurol Neurosurg Psychiatry. 2015;86:168-173. doi:10.1136/jnnp-2013-307223
9. Phukan J, Pender NP, Hardiman O. Cognitive impairment in amyotrophic lateral sclerosis. Lancet. 2007;6:994-1003. doi:10.1016/S1474-4422(07)70265-X
10. Saxon JA, Thompson JC, Jones M, et al. Examining the language and behavioural profile in FTD and ALS-FTD. J Neurol Neurosurg Psychiatry. 2017;88:675-680. doi:10.1136/jnnp-2017-315667
27. Witgert M, Salamone AR, Strutt AM, et al. Prognostic factors in ALS: a critical review. *Amyotroph Lateral Scler*. 2009;10:310-323. doi:10.3109/17482906082566824

28. Passamonti L, Fera F, Tessitore A, et al. Executive dysfunction is a negative prognostic indicator in patients with ALS without dementia. *Neurology*. 2011;76:1263-1269. doi:10.1212/01.wnl.0b013e318214359f

29. Wolf J, Safer A, Wöhrle JC, et al. Variability and prognostic relevance of different phenotypes in amyotrophic lateral sclerosis – Data from a population-based registry. *J Neurol Sci*. 2014;345:164-167. doi:10.1016/j.jns.2014.07.033

30. Consonni M, Iannaccone S, Cerami C, et al. The cognitive and behavioural profile of amyotrophic lateral sclerosis: application of the consensus criteria. *Behav Neurol*. 2013;27:143-153. doi:10.3233/BEN-2012-110202

31. Lillo P, Mioshi E, Zoiing MC, Kiernan MC, Hodges JR. How common are behavioural changes in amyotrophic lateral sclerosis? *Amyotroph Lateral Scler Frontotemporal Degener*. 2017;18:153-174. doi:10.1080/21678421.2016.1267768

32. Rascovsky K, Hodges JR, Knopman D, et al. Sensitivity of revised diagnostic criteria for the behavioural variant of frontotemporal dementia. *Brain*. 2011;134:2456-2477. doi:10.1093/brain/awr179

33. Hansson M, Chotai J, Nordström A, Bodlund O. Comparison of two self-rating scales to detect depression: HADS and PHQ-9. *Br J Gen Pract*. 2009;59:e283-e288. doi:10.3399/bjp09x045070

34. Brooks BR, Miller RG, Swash M, Munsat TL. El Escorial revisited: revised criteria for the diagnosis of amyotrophic lateral sclerosis. *Amyotroph Lateral Scler*. 2000;1:293-299. doi:10.1080/146608200300079536

35. Chiò A, Calvo A, Moglia C, et al. Phenotypic heterogeneity of amyotrophic lateral sclerosis: a population based study. *J Neurol Neurosurg Psychiatry*. 2011;82:740-746. doi:10.1136/jnnp.2010.235952

36. Abrahams S, Newton J, Niven E, Foley J, Bak TH. Screening for cognition and behaviour changes in ALS. *Amyotroph Lateral Scler Frontotemporal Degener*. 2014;15:9-14. doi:10.3109/21678421.2013.805784

37. Poletti B, Solca F, Carelli L, et al. The validation of the Italian Edinburgh Cognitive and Behavioural ALS Screen (ECAS). *Amyotroph Lateral Scler Frontotemporal Degener*. 2016;17:489-498. doi:10.1080/21678421.2016.1183679

38. Elefante C, Lattanzi L, Ismail Z, et al. Mild behavioral impairment: presentation of the diagnostic criteria and the Italian version of the MBI-Checklist. *Riv Psichiatr*. 2019;54:59-66. doi:10.1708/3142.31246

39. Zign mund AS, Snath RP. The Hospital Anxiety and Depression Scale. *Acta Psychiatr Scand*. 1983;67:361-370. doi:10.1111/j.1600-0447.1983.tb09716.x

40. Siciliano M, Trojano L, Troisi F, et al. Edinburgh Cognitive and Behavioural ALS Screen (ECAS)-Italian version: regression based norms and equivalent scores. *Neurool Sci*. 2017;38:1059-1068. doi:10.1007/s10072-017-2919-4

41. Creese B, Griffiths H, Brooker H, et al. Profile of mild behavioral impairment and factor structure of the Mild Behavioral Impairment Checklist in cognitively normal older adults. *Int Psychogeriatr*. 2020;32:705-717. doi:10.1017/S1041610219001200

42. Lillo P, Mioshi E, Zoiing MC, Kiernan MC, Hodges JR. How common are behavioural changes in amyotrophic lateral sclerosis? *Amyotroph Lateral Scler*. 2011;12:45-51. doi:10.3109/17482968.2010.520718

43. Wittgert M, Salamone AR, Strutt AM, et al. Frontal-lobe mediated behavioral dysfunction in amyotrophic lateral sclerosis. *Eur J Neurol*. 2010;17:103-110. doi:10.1111/j.1468-1331.2009.02801.x

44. Passamonti L, Fera F, Tessitore A, et al. Dysfunctions within limbic-motor networks in amyotrophic lateral sclerosis. *Neurobiol Aging*. 2013;34:2499-2509. doi:10.1016/j.neurobiolaging.2013.05.016

45. Creese B, Brooker H, Ismail Z, et al. Mild Behavioral Impairment as a marker of cognitive decline in cognitively normal older adults. *Am J Geriatr Psychiatry*. 2019;27:823-834. doi:10.1016/j.jagp.2019.01.215
46. Grossman A, Woolley-Levine S, Bradley W, Miller R. Detecting neurobehavioral changes in amyotrophic lateral sclerosis. *Amyotroph Lateral Scler*. 2007;8:56-61. doi:10.1080/17482960601044106

47. Yoshizawa K, Yasuda N, Fukuda M, et al. Syntactic comprehension in patients with amyotrophic lateral sclerosis. *Behav Neurol*. 2014;2014:1-8. doi:10.1155/2014/230578

48. Strong MJ, Grace GM, Orange JB, Leeper HA, Menon RS, Aere C. A prospective study of cognitive impairment in ALS. *Neurology*. 1999;53:1665. doi:10.1212/wnl.53.8.1665

49. Watanabe Y, Ogino M, Ichikawa H, Hanajima R, Nakashima K. The Edinburgh Cognitive and Behavioural ALS Screen (ECAS) for Japanese ALS and FTD patients. *Amyotroph Lateral Scler Frontotemporal Degener*. 2021;22:66-72. doi:10.1080/21678421.2020.1801751

**SUPPORTING INFORMATION**

Additional supporting information can be found online in the Supporting Information section at the end of this article.

---

**How to cite this article:** Ferraro PM, Gervino E, De Maria E, et al. Mild behavioral impairment as a potential marker of predementia risk states in motor neuron diseases. *Eur J Neurol*. 2023;30:47-56. doi: 10.1111/ene.15570