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Clinical and MRI predictors of conversion from mild behavioural impairment to dementia

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1) We aimed to (i) identify the differences in baseline clinical and magnetic resonance imaging (MRI) features associated with conversion to a neurodegenerative disease in the following four years; (ii) validate, based on these data, some easy-to-use clinical and MRI criteria that could help to identify, at the individual level, those MBI subjects at higher risk to receive a clinical diagnosis of dementia over time.
2) We found that the presence of an executive deficit, severe theory of mind impairment and the presence of isolated frontal atrophy (i.e. with a spared volume within the remaining cortical regions) were associated with a higher risk of progression from MBI to a clinically evident neurodegenerative condition over the following 4 years.
3) Our results suggest that identifying MBI in the general population would help identify patients who would later present with bv-FTD.

Abstract

Objective: As an analogy with mild cognitive impairment (MCI), the mild behavioural impairment (MBI) construct has been proposed as a diagnostic label for those presenting late-onset behavioural symptoms. To date, however, the clinical, cognitive and structural imaging features associated with an increased risk of conversion from MBI to dementia are poorly understood.

Methods: We retrospectively analysed the cognitive performance and structural brain MRI of 113 subjects, with a clinical follow-up of at least 4 years available. Subjects were randomly assigned to a Group A (56 subjects; age: 65.4±7.9 years, 15 females, MMSE score: 28.4±2.3)) or to a Group B (57 subjects, age: 66.6±6.4, 17 females, MMSE score: 28.0±1.4). In the Group A, cognitive and structural variables were compared between converters (at 4 years) and non-converters and then verified in the Group B group.

Results: In the Group A, 14 patients converted to bv-FTD and 4 to Alzheimer's Disease (AD). Converters presented at baseline lower executive function scores and total Theory of Mind (ToM scores), as well as more severe focal frontal atrophy. In the Group B, 13 subjects converted to bv-FTD and none to AD. The combination of the variables identified in the Group A significantly ($p<0.001$) discriminated between converters and non-converters in the Group B with a sensitivity of 0.615 and a specificity of 1 (total accuracy 91.22%).

Conclusion: The combined presence of executive deficit, impaired ToM, and presence of isolated frontal atrophy was associated with risk of progression from MBI to a clinically evident neurodegenerative condition, mainly bv-FTD, over a 4-year period.

Introduction

Recent years have seen an increasing interest of the clinical community for newly developed behavioural symptoms as a possible early manifestation of neurodegenerative disease, mainly the behavioural-variant of frontotemporal dementia (bv-FTD)[1], but also Progressive Supranuclear Palsy (PSP), Alzheimer's disease (AD), and dementia with Lewy bodies (DLB)[2].

The observation of a possible role for behavioural symptoms as an early "red flag" for the development of a brain neurodegenerative disease led to the development of a new diagnostic entity, i.e. mild behavioural impairment (MBI), mirroring the successful mild cognitive impairment (MCI) construct.

Tarangano and colleagues (2003)[3] defined the MBI syndrome as consisting of persistent newly developed behavioural changes and mild neuropsychiatric symptoms, no serious cognitive complaint and normal activities of daily living (summarized in **Table 1**). The presence of MBI has been associated with an increased risk of progression to dementia[2,4–7].

Like MCI, that has an annual conversion rate to AD dementia of 31% [8], MBI is a heterogeneous condition, which includes late-onset psychiatric disorders (i.e. the development in late adulthood of primary psychiatric disorders in subjects with a negative psychiatric history) chronic cerebrovascular damage and neurodegenerative diseases. To increase the clinical relevance of MBI, it is needed to identify those features that characterize the presence of a subclinical neurodegenerative process as the underlying cause of MBI.

Here, focusing on a naturalistic cohort presenting to a behavioural neurology/adult psychiatric service for the onset of newly developed and progressive social difficulties, we aimed to 1) identify the differences in baseline clinical and magnetic resonance imaging (MRI) features associated with conversion to a neurodegenerative disease in the following four years; 2) validate, based on these data, some easy-to-use clinical and MRI criteria that could help to identify, at the individual level, those MBI subjects at higher risk to receive a clinical diagnosis of dementia over time in an independent MBI set.

Materials and Methods

Patients

Using a retrospective approach, we identified all subjects who came to the attention of our behavioural neurology/adult psychiatric services between 2007 and 2014 for the onset of informant-confirmed, newly-developed and progressive behavioural symptoms who fulfilled the following criteria: (i) age between 60 and 75 years, (ii) at least 8 years of formal education, (iii) development of new behavioural deficits fulfilling current MBI criteria[1,9] (such as reduction of empathy, emotional callousness, social inappropriate conduct), that were persistent for at least six months, evaluated during two clinical assessments separated by at least three months, not attributed by the examining neurologist or psychiatrist to a mood disorder, and confirmed by the clinical history reported by the informant, (iv) no complaint of cognitive difficulties by the patient or the caregiver, (v) no highly stressful event in the previous six months as defined by the score on the Perceived Stress Scale (PSS[10]), (vi) lack of a positive history for major depressive disorder, bipolar disorder, abuse of psychoactive drugs or any psychotic disorder, recent bereavement, dementing illnesses, or for a major medical condition, (vii) no diagnosis of a neurodegenerative condition at the end of the

baseline evaluation, (viii) availability on file of a baseline clinical MRI brain scan and brief cognitive assessment (see below for minimum requirements), and (ix) at least 4 years of clinical follow-up after the first evaluation. The focus on subjects older than 60 years is based on the work on MBI of Tarangano[9], with the aim reduce the proportion of subjects presenting with a primary late-onset psychiatric condition[11,12] , while the exclusion of subjects more than 75 years of age, was based on the need to increase consistency with published theory of mind normative data[13]. We also decided to include an education exclusion criteria, given the dependence of some of the included tests –such as the Reading the Mind in the Eyes test (see below) –to vocabulary abilities and general education[14].

Based on these criteria, we retrospectively selected 113 subjects and extracted their baseline clinical, cognitive and MRI data, focusing on the variables described below and reviewed the available follow-up data collected in the 4 years following the baseline evaluation to assess if any of the subjects converted to a neurodegenerative condition according to currently available diagnostic criteria. Due to differences in intermediate follow-up intervals, we decided to focus on the baseline clinical and MRI data evaluation and only on the clinical outcome 4 years later (i.e. not on the intermediate time-points).

The patients were then randomly divided into two sets: Group A (56 subjects, age: 65.4±7.9, 15 females, MMSE score: 28.4±2.3) and Group B (57 subjects, age: 66.6±6.4, 17 females, MMSE score: 28.0±1.4).

Cognitive and Behavioral assessment

The cognitive evaluation was based on a brief neuropsychological battery that included tests for the assessment of global cognition (MMSE[15]), Theory of Mind (ToM) abilities (‘‘Reading the Mind in the Eyes Test’’- RMET[13,16]), executive functioning (TMT A and B[17], letter fluency test[18]), verbal (Rey-Auditory Verbal Learning Test[19]) and non-verbal (Rey figure recall[20]) memory, behavioral and psychological symptoms (Neuropsychiatric Inventory - NPI[21]). Test scores for the executive functions and memory test were converted to z-scores (modified accordingly to represent a worse performance with lower z scores) according to normative data and then averaged to provide a composite “executive functions” and a composite “memory functions” *z* score.

MRI Acquisition

MRI scans were acquired according to good clinical practice at 1.5 T. given the retrospective, clinical, nature of the study, images were acquired on different scanners, however only subjects presenting with a volumetric T1 sequence with an isotropic voxel in the 1-1.5 mm range and with T2 whole brain images were considered eligible for the study.

T1-weighted Images were all resliced to an isotropic voxel size of 1.5 mm and then visually evaluated using standardized scales for the presence of global cortical atrophy[22], medial temporal lobe (MTL) atrophy[23] and frontal lobe atrophy based on the composite assessment of orbito-frontal, anterior cingulate and frontal-insular regions as previously described[24]. Two separated raters evaluated the scans and then a consensus evaluation was reached. The scores were then simplified into no relevant atrophy (scores 0-1) or relevant atrophy (scores of 2 or more)[24] except for the Scheltens scale that was simplified as no relevant atrophy (scores 0-2) or relevant atrophy (scores of 3 or more) as in previous studies[25]. Lastly, the Fazekas scale[26] was used to evaluate the global burden of chronic white matter vascular disease in T2-weighted images.

Statistical analysis

In the Group A we compared the baseline clinical and MRI features (the cognitive and behavioural assessment, the presence of global, medial-temporal and frontal atrophy) between converters to dementia and non-converters, using t-tests (for continuous variables) or chi-square statistics (for binary variables). All significant results were then confirmed correcting for age, sex, education, MMSE and NPI respectively using an ANCOVA and logistic regression.

We then used the results to suggest imaging and clinical indices that could help identifying those MBI subjects more at risk to develop a clinical diagnosis of dementia over time, and then used these criteria to predict which patients in the Group B group would develop dementia.

Based on the results obtained in the Group A we defined the following two indices to be used in the Group B (summarized in **Table 2**):

- Cognitive and behavioural (Cog-Behav) index, the presence of all of the following: a composite executive function z score lower than -1, a RMET score lower than 21 (i.e. the accepted cut off for a pathological RMET score[27]) and a composite memory function z score higher than -1.
- MRI index: presence of isolated frontal atrophy (i.e. relevant frontal atrophy with preserved volume within the remaining cortical areas).

We have not included the NPI in these two dimensions as this scale overlaps with the diagnostic criteria of MBI and FTD, it does not present with a clear cut-off, and was used as correction variable in the statistical analysis.

These two indices of conversion risk, derived from the Group A, represent easy-to-recognize features that could be used by clinicians to identify which MBI patients at baseline are at higher risk to conversion to dementia. We used to indices to categorize patients in the Group B.

Data are reported as mean ± standard deviation. P values are reported as uncorrected, as well as corrected for multiple comparisons using a false discovery rate approach; lastly we also reported if they survived the Bonferroni's correction.

Data reported in the study were acquired during clinical practice in line with the principles of the Helsinki declaration. Retrospective analysis of anonymized data was approved by the local ethics committee.

Results

Group A: Baseline demographics, clinical, MRI characteristics and conversion rate

Demographic and clinical data for the Group A are reported in **Table 3**. There was no difference in age, sex distribution, education and MMSE score between converters and non-converters.

At 4 years, we observed that 18 patients converted to dementia during the follow-up (14 to bv-FTD[28] and 4 to AD[29] and; the cumulative 4-year conversion rate was thus 18/56 (32,14%).

As compared to non-converters, converters showed at baseline a lower executive function composite and total RMET scores and a higher NPI score. The correlations between the cognitive and behavioural metrics are reported in **Supplementary Table 1.**

Moreover, compared to non-converters, converters showed a more marked frontal atrophy while there was no difference between the two groups in white matter vascular load, MTL atrophy, and whole brain atrophy. All these significant statistical findings survived Bonferroni's correction for multiple comparisons.

See **Table 3** for p-values, t-values and degrees of freedom.

Group B: Baseline demographics, clinical, MRI characteristics and conversion rate

Demographic and clinical data for the Group B are reported in **Table 4**.

Thirteen patients converted to dementia in the course of follow-up (all to bv-FTD); the cumulative 4-year conversion rate was thus 13/57 (22,8%).

We explored at the single-subject level, the presence and frequency of the Cog-Behav index and MRI conversion risk indices obtained in the Group A.

There was a significant difference between converters (10 out of 13) vs non-converters (3 out of 44) in the presence of isolated frontal atrophy. There was also a significant difference between converters (9 out of 13) and non-converters (2 out of 44) in the executive function and RMET scores.

Lastly, there was a significant difference between converters (8 out of 13) vs non-converters (0 out of 44) for both the MRI and Cog-Behav indices.

All these significant statistical findings survived Bonferroni's correction for multiple comparisons.

See **Table 4** for p-values, t-values and degrees of freedom.

Sensitivity, Specificity and total Accuracy

Based on the Group B results, we evaluated the sensitivity and specificity of the MRI and the Cog-Behav conversion risk indices. The MRI index had a sensitivity of 0.769 and a specificity of 0.931 (total accuracy 89.47%); the Cog-Behav index had a sensitivity of 0.692 and a specificity of 0.954 (total accuracy 89.47%); the combined presence of the MRI and Cog-Behav criteria had a sensitivity of 0.615 and a specificity of 1 (total accuracy 91.22%). Lastly, the sensibility and specificity of the single components of the Cog-Behav index are reported in **Supplementary Table 2.**

Clinical outcomes of non-converters

In group A, among the 38 non-converters, 12 reverted from MBI to their baseline functioning, 7 were diagnosed with a late-onset primary psychiatric disorders and 19 remained stable.

In group B among the 44 non-converters, 10 reverted to their baseline functioning, 8 were diagnosed with a late-onset primary psychiatric disorder and 26 remained stable.

Discussion

In this retrospective study, we evaluated which clinical characteristics and conventional MRI features were associated with the risk of conversion from MBI to dementia over time.

Overall, we found that the presence of an executive deficit, severe theory of mind impairment and the presence of isolated frontal atrophy (i.e. with a spared volume within the remaining cortical regions) were associated with a higher risk of progression from MBI to a clinically evident neurodegenerative condition over the following 4 years.

The diagnosis of MBI, similar to the usefulness of an MCI diagnosis, represents a good initial screening in order to identify patients most at risk for converting to one of the FTD-spectrum disorders over the following four years. Indeed, the development of new behavioural symptoms is a source of concern, especially for caregivers, and thus often leads to prompt clinical evaluations in a psychiatric or neurological setting [30]. Moreover, population studies suggest that subjects with MBI are at higher risk to convert to a FTD-related disorder than those presenting with other constructs such as amnestic MCI[9]

We found a higher risk of conversion from MBI to bv-FTD than to AD. This finding is not unexpected, given the previous observations of an involvement of behavioural changes in the earliest phases of bv-FTD[27,31]. Our results suggest that identifying MBI in the general population would help identify patients who would later present with bv-FTD.

Like MCI, MBI is a relatively heterogeneous construct, and also includes subjects who will not progress to dementia. Thus, the identification of features able to dissect the MBI construct in order to distinguish who will develop dementia and what type of dementia would be useful. A first issue is represented by the concomitant presence of cognitive deficits. The presence of subjective cognitive complaints is an exclusion criteria for MBI[9], however the presence of objective cognitive deficits is not. Indeed, subjects with MBI have been shown to present with a more marked cognitive decline over time compared to those without MBI[32]. Against this background, our data suggest that isolated executive and mentalizing deficits could allow clinicians to discriminate among MBI subjects those at risk to develop an underlying neurodegenerative condition.

ToM is the ability to recognize emotions and inner states in others[16]. It is often involved in neurodegenerative conditions including the earliest phases of FTD[27]). ToM is partly independent of executive functions[33] and indeed subjects without executive function deficits can present with ToM difficulties. These observations are in line with our findings of reduced ToM abilities in MBI subjects with an underlying neurodegenerative condition. It must be noted that ToM is a heterogeneous construct only partly probed by RMET, and thus it is possible that other ToM tests could have yielded different results. The RMET, however, lacks a ceiling effect even in healthy subjects, thus making it an ideal test to be included in a first level battery.

Overall, our observation of an association between the presence of cognitive deficits and the risk of progression from MBI to dementia, is in keeping with the findings in MCI, where the involvement of multiple cognitive domains is associated with a worse prognosis[34] as well as with the observed difference in cognitive patterns between very late-onset primary psychiatric conditions and neurodegenerative dementia[35].

Furthermore, our data suggest that evidence of neurodegeneration at MRI (evaluated with simple scales) can be useful to evaluate the risk of conversion from MBI to bv-FTD, similar to what has been observed in MCI[36]. In the MBI setting, moreover, the identification of an FTD-related atrophy pattern, presents an added value, i.e. its differentiation with late-onset psychiatric conditions, as those are often associated only with specific MRI findings[37].

In agreement with these results, our data shows that specific and isolated frontal atrophy rather than global atrophy represents an easy-to-use marker to identify those MBI subjects more at risk to present a clinical conversion to bv-FTD. This is in keeping with the current inclusion of focal frontal atrophy in the diagnostic criteria for probable bv-FTD[28].

While the low number of incident dementia cases prompts caution in the interpretation of sensitivity, specificity and accuracy in our sample, the observed data suggests that the combination of cognitive/behavioural features and a simple assessment of brain atrophy at MRI could be useful to identify those MBI subjects more at risk to develop dementia. The increase in accuracy thanks to the combination of cognitive/behavioural data with structural MRI is in agreement with what is observed in MCI[38], including diagnostic accuracy. The improvement in specificity due to the addition of an atrophy measure to the cognitive evaluation stems from the presence of executive and mentalizing deficits in subjects with late-onset psychiatric conditions – a common differential diagnosis of MBI – that however usually do not present with a specific brain atrophy pattern [39].

While selection of the metrics included in the Cognitive-Behavioral index were based on the findings in Group A, they are in line with the known neuropsychological profile of FTD[40], with a

relative sparing of memory an involvement of social cognition and executive functions. As shown in the analysis of the sensitivity and specificity of each component of the Cognitive-Behavioral index, the focus on a "neuropsychological pattern" rather than a single test allowed to increase the specificity of the proposed approach, allowing to better differentiate FTD from - for example - late-onset mood disorders that can present with an isolated ToM deficit[41]. Moreover, the combination of multiple tests to quantify the extent of the executive deficit allowed us to take into account the heterogeneity of the early cognitive deficits in FTD (i.e. the fact that in the earliest phases of bvFTD, patients can present with a pathological performance only in a single facet of executive functioning[42]). Indeed, the fact that the components of the indices probe different constructs is also confirmed by the moderate correlations between them.

Thus, we decided to propose a set of indices (see **Table 2**) that may easily been followed to confirm the MBI conversion. Since the specificity of the cognitive and behavioural components is higher taken together rather than one by one, we decided to consider this aspect as a single index. Taking into account the single components of the Cognitive-Behavioral index, ToM task was the test presenting with the higher sensitivity. This suggest the importance of adding a formal evaluation of social cognition during neuropsychological assessment and it is in line with previous studies pointing to an early involvement of ToM in FTD[27].

Caution is needed in the clinical translation of our findings due to the retrospective nature of the study and our strict inclusion criteria. Thus, further, prospective, naturalistic studies are needed to confirm our findings. Moreover, the retrospective nature of the study did not allow us to collect data regarding caregiver burden.

Despite these limitations, our four-year follow-up, detailed cognitive and behavioural data, and systematically-assessed structural imaging scans gives us confidence in the clinical utility of our results and increases our understanding of the heterogeneity of patients fulfilling MBI diagnostic criteria.

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Table 1: *Tarangano et al. (2003) MBI criteria*

1. Persistent behavioral changes and mild psychiatric symptoms, especially disinhibition
2. No serious memory complaints
3. Normal activities of daily living
4. Absence of dementia

Table 2: *Indices of MBI conversion*

Cognitive-Behavioral
- Executive functions z score < -1
- RMET score < 21
- Memory function z score > -1
MRI
- Isolated frontal atrophy

Table 3: *Demographic and clinical results in Group A. (df=degrees of freedom; bv-FTD=Behavioural Variant-Frontotemporal Dementia; AD=Alzheimer's Disease; ToM=Theory of Mind; n.s=not ignificant))*

	Non-converters	**Converters (bv-FTD and AD)**	**Converters (bv-FTD only)**	**Converters (all) vs. non-converters uncorrected p value**	**T value (df = 54)**	**Effect size**	**Converters (all) vs. non-converters p value (FDR corrected*)**	**Converters (bv-FTD) vs. non-converters uncorrected p value**	**T value (df = 50)**	**Effect size**	**Converters (bv-FTD) vs. non-converters p value (FDR corrected*)**
N (56)	38	18	14								
Age (m±sd)	65.4±7.9	64.5±6.3	63.9±8.5	p=0.673	t= 0.423	d=0.12	p=0.76	p=0.554	t= 0.595	d=0.18	p=0.946
Sex (m/f)	22/16	11/7	8/6	p=0.9			p=0.9	p=0.9			p=0.946
T-test											
MMSE (m±sd)	28.4±2.3	28.0±3.4	28.2±2.9	p=0.606	t= 0.518	d=0.14	p=0.756	p=0.796	t= 0.259	d=0.07	p=0.946
ToM (m±sd)	0.4±1.0	-1.2±0.9	-1.2±0.6	p<0.001(p=0.008)[a]	t=5.767	d=2.49	p=0.002	p<0.001(p=0.007)[a]	t= 5.605	d=3.71	p=0.002
Executive functions score (m±sd)	0.3±0.6	-1.5±0.8	-1.9±0.4	p<0.001(p=0.008)[a]	t=9.397	d=2.54	p=0.002	p<0.001(p=0.008)[a]	t=12.67	d=4.31	p=0.002
NPI (m±sd)	5.3±2.6	8.2±2.0	9.3±2.8	p=0.001(p=0.004)[b]	t=5.175	d=1.57	p=0.002	p<0.001(p=0.003)[b]	t=4.821	d=1.48	p=0.002
Memory score (m±sd)	0.1±0.8	-0.2±1.2	-0.1±0.8	p=0.270	t= 1.110	d=0.29	p=0.510	p=0.423	t=0.799	d=0.25	p=0.930

Chi-square											
Isolated frontal atrophy (yes/no)	2/36	14/4	12/2	p<0.001(p=0.006)[c]			p=0.002	p<0.001(p=0.005)[c]			p=0.002
Isolated MTL atrophy (yes/no)	4/34	1/17	1/13	p=0.556			p= 0.756	p=0.784			p= 0.946
Global atrophy (yes/no)	3/36	2/15	1/13	p=0.623			p= 0.756	p=0.946			p= 0.946
WM load (Fazekas scale; m±sd)	1.2±0.4	1.4±0.3	1.2±0.5	p=0.065	t=1.881	d=0.56	p= 0.138	p=0.9	t=0	d=0	p= 0.946

a=ancova with MMSE, NPI age and education; b=ancova with MMSE, age and education; c=logistic regression with MMSE, NPI, age and education ***(Wald chi-square (df = 1))***

****based on all 17 tests reported in Table 3 and 4 . The same tests were used also for Bonferroni's correction for multiple comparisons.***

*T**able 4:** Demographic and clinical results in Group B (df=degrees of freedom; FTD=Frontotemporal Dementia; Cog-Behav=Cognitive-Behavioura; n.s=not significantl)*

	Non-converters	**Converters (bv-FTD only)**	**Converters vs. non-converters uncorrected p value**	**T value (df = 55)**	**Converters vs. non-converters p value (FDR corrected*)**
N (57)	44	13			
Age	66.6±6.4	65.3±6.2	p=0.519	t=0.647	p= 0.756
Sex (m/f)	23/21	7/6	p=0.9		p= 0.9
MMSE (m±sd)	28.0±1.4	27.5±3.0	p=0.400	t=0.847	p= 0.68
Chi-squared					
MRI criterion (fullfilled/not fulfilled)	3/41	10/3	p<0.001(p=0.006)[a]		p=0.002
Cog-Behav criterion (fullfilled/not fulfilled)	2/42	9/4	p<0.001(p=0.007)[a]		p=0.002
MRI+Cog-Behav criteria (fullfilled/not fulfilled)	0/44	8/5	p<0.001(p=0.006)[a]		p=0.002

*a=logistic regression with MMSE, NPI, age and education **(Wald chi-square (df = 1))***

based on all 17 tests reported in Table 3 and 4 . The same tests were used also for Bonferroni's correction for multiple comparisons.