Disease progression in frontotemporal dementia and Alzheimer disease: the contribution of staging scales

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Abstract

Introduction: There is a shortage of validated instruments to estimate disease progression in frontotemporal dementia (FTD). **Objectives:** To evaluate the ability of the FTD Rating Scale (FTD-FRS) to detect functional and behavioral changes in patients diagnosed with the behavioral variant of FTD (bvFTD), primary progressive aphasia (PPA) and Alzheimer disease (AD) after 12 months of the initial evaluation, compared to the Clinical Dementia Rating scale - frontotemporal lobar degeneration (CDR-FTLD) and the original Clinical Dementia Rating scale (CDR). **Methods:** The sample consisted of 70 individuals, aged 40+ years, with at least two years of schooling, 31 with the diagnosis of bvFTD, 12 with PPA (8 with semantic variant and 4 with non-fluent variant) and 27 with AD. The FTD-FRS, the CDR and the two additional CDR-FTLD items were completed by a clinician, based on the information provided by the caregiver with frequent contact with the patient. The Addenbrooke's Cognitive Examination-Revised (ACE-R) was completed by patients. After 12 months, the same protocol was applied. **Results:** The FTD-FRS, CDR-FTLD and CDR detected significant decline after 12 months in the three clinical groups (exception: FTD-FRS for PPA). The CDR was less sensitive to severe disease stages. **Conclusions**: The FTD-FRS and the CDR-FTLD are especially useful tools for dementia staging in AD and in the FTD spectrum.

Key-words: staging, dementia progression, frontotemporal lobar degeneration, frontotemporal dementia, behavioral variant, primary progressive aphasia.

Introduction

Staging dementia is a vital aspect for the proper clinical management of affected patients. Staging may guide personalized care, as care needs change as the disease progresses. In addition, staging scales may document the impact of drugs with the potential to change the course of the underlying disorder.

Dementia staging scales usually assess typical symptoms of Alzheimer disease (AD). For instance, the Clinical Dementia Rating scale (CDR) has been used for more than two decades to document disease progression in AD[1–3]. Although the CDR has brought significant contributions to the field, it has been found to be a limited staging tool for non-AD dementias. For example, the CDR failed to identify the severe stages of the behavioral variant of frontotemporal dementia (bvFTD), most likely because it does not include items probing the most frequent behavioral and functional symptoms within the spectrum of this disorder[4]. Other studies have shown that the CDR may not be able to identify decline in FTD [5-6].

Given the need of instruments for FTD staging, Mioshi et al.[4] developed and validated the FTD Rating Scale (FTD-FRS). The FTD-FRS was structured using items from the Disability Assessment Scale (DAD)[7] and the Cambridge Behavioral Inventory (CBI)[8, 9], resulting in a 75-item questionnaire covering symptoms of behavioral disorders and functional disability. The new instrument was applied in a sample of 77 patients with FTD (bvFTD = 29; semantic variant Primary Progressive Aphasia - svPPA = 28; agrammatic variant - aPPA = 20), matched for age and duration of symptoms. After psychometric and construct validity analyses, the scale was reduced to 30 items[1]. In a 12-month follow up, the FTD-FRS was able to detect decline in all three FTD variants, with faster decline for patients with bvFTD.

The FTD-FRS has been translated and validated in other countries [5, 6]. Schubert et al. [10] have replicated the finding that patients with bvFTD show faster decline in the FTD-FRS, compared to other clinical groups, and suggested that neuropsychological evaluation alone may not distinguish the distinct trajectories of bvFTD and AD patients.

Other scales have been used to measure disease progression in FTD dementia subtypes. O'Connor et al. [11] reported higher functional decline among patients with bvFTD when compared to svPPA using the CBI and the DAD. Compared to the baseline, patients with bvFTD had greater functional decline than patients with svPPA.

Also, in 12 months, patients with bvFTD decreased in disinhibition and stereotyped behaviors and had higher appetite changes, whereas patients with svPPA had higher stereotyped behaviors.

In 2008, the CDR was extended to include typical symptoms of FTD. The CDR-FTLD scale, as it is known, seems to be effective in staging patients in the FTD spectrum[12, 13]. No previous study has compared directly the ability of different staging scales to capture disease progression in FTD and AD[14].

Therefore, in the present study we aimed to investigate rates of disease progression in FTD and AD using three staging tools: the FTD-FRS, CDR-FTLD sum of boxes (CDR-FTLD- SOB) and the CDR sum of boxes (CDR- SOB), over a 12-month follow-up study. We hypothesized that the FTD-FRS and the CDR-FTLD would detect significant changes in the follow-up assessment of FTD patients that would not be detected by the CDR, as the two former scales include questions regarding specific FTD symptoms. As an additional aim, we tested whether global cognitive scales could also detect change over the 12-month follow-up.

Methods

Participants

Databases from specialized university-based Neurology outpatient services were queried, and patients and their family caregivers were invited to take part in the study. Three specialist centres in Brazil were involved: Cognitive and Behavioral Neurology Group (GNCC-SP), of the University of São Paulo; Cognitive and Behavioral Neurology Group (GNCC-MG) of the Federal University of Minas Gerais and the outpatient services of the Department of Neurology of the State University of Campinas (UNICAMP).

A total of 70 individuals, comprising 31 diagnosed with bvFTD, 12 with PPA (8 semantic variant and 4 non-fluent variant), and 27 with AD were included in the study. Formal and informal caregivers who had frequent contact with the patient were interviewed in regard to the patient´s symptoms (see Supplementary Table 1 for the sociodemographic characteristics of the caregivers).

The FTD-FRS, the CDR and the CDR-FTLD items were filled out by the clinician based on the information provided by the caregivers for each item during a

clinical interview. The diagnosis of dementia was given by neurologists, based on clinical and cognitive assessments, laboratory and neuroimaging exams. Dementia was diagnosed based on the criteria from the Diagnostic and Statistical Manual 5th Edition (DSM-V)[15]. International diagnostic criteria were employed for diagnosing probable bvFTD[16]. The National Institute on Aging- Alzheimer's Association- NIA/AA criteria were used for AD diagnosis[17, 18]. The most recent PPA criteria were used for diagnosing the semantic and non-fluent variants of FTD[19].

Inclusion criteria for patients were age >40 years, education >2 years, CDR=0.5, 1 or 2, and presence of a caregiver who was involved in the daily routine of the patient; spending more than 8 hours/day with the patient. Individuals presenting with visual, auditory or motor deficits preventing them from understanding instructions or performing cognitive tasks; individuals with other uncontrolled clinical diseases (such as hypertension and diabetes); serious and debilitating psychiatric disorders such as major depression, schizophrenia, bipolar disorder; patients using unstable psychotropic drugs, clinical evidence or neuroimaging exam findings suggestive of vascular problems; dementias or etiologies other than FTD or AD, were excluded from the sample.

Instruments

Demographic Information

Sociodemographic and clinical data, including age, income, years of education, marital status, general health status, comorbidities and use of medications was collected via questionnaires completed by caregivers.

Cognitive assessment

The Mini Mental State Exam (MMSE)[20] was administered at baseline and follow up [21]. MMSE maximum score is 30. The Addenbrooke´s Cognitive Examination-Revised (ACE-R)[22, 23, 24] was also administered at baseline and follow-up. The ACE-R maximum score is 100 points and the cognitive domains evaluated include: attention and orientation (18/100), memory (26/100), verbal fluency (14/100), language (26/100) and visuospatial ability (16/100)[23].

Dementia staging scales

The CDR[9, 25] assesses the domains of memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care. The CDR-FTLD is an expanded version for the CDR scale and it assesses two additional domains: language and behavior[12], which are tailored for FTD symptoms. During data collection, the clinician makes an evaluation of each domain with scores ranging from 0, 0.5, 1, 2 and 3, and a general evaluation of the dementia stage is made using this same gradation. In the present study, the CDR and the CDR-FTLD scores refer to the sum of the scores of each domain, sum of boxes, that ranges from 0 to 18 for the CDR and from 0 to 24 for the CDR-FTLD. The CDR and CDR-FTLD scores will refer to the sum of boxes of each scale in the remaining parts of this study, unless stated otherwise. We chose to analyze the sum of boxes, instead of the global categorical score, because the sum of boxes might better reflect minor changes between the two assessment points.

The FTD-FRS detects dementia severity through a combination of decline in functional abilities (e.g. ability to use a telephone, ability to manage medications, eating behaviors), as well as neuropsychiatric symptomatology (e.g. loss of affection, impulsivity) [1, 6]. The answer options for each question are: always = 0, sometimes = 0 and never = 1. The score for each item is added and divided by the number of questions (ranging from 0 to 30) answered by the interviewee, thus generating a percentage that is subsequently converted to a logarithmic score ranging from 5.39 (normal) to - 6.66 severe/advanced, available in a table provided by the authors who validated the scale[1, 6].

Ethics

An informed consent form was filled out by caregivers. This study was approved by the Ethics Committee from the University of São Paulo School of Medicine (protocol number 311.601). The study was conducted in compliance with international ethical standards expressed in the Declaration of Helsinki.

Data Analysis

The Kolmogorov-Smirnov tests indicated that the MMSE, ACE-R, FTD-FRS, CDR-FTLD and CDR did not follow a normal distribution. In the cross-sectional

analysis at baseline, the Chi-square test was used to compare the categorical variables and the Kruskall-Wallis test was used to compare the continuous variables among the three diagnostic groups. Multiple comparisons were conducted when the Kruskall-Wallis test was significant.

In the longitudinal analyses, we used the Wilcoxon signed-rank test (Z statistic) to compare the means of the ACE-R, MMSE, CDR-FTLD and CDR, and the FTD-FRS logarithmic scores. This statistical test evaluates if the means of the studied sample differ between baseline and follow-up, and the higher the Z value, the greater the difference between the mean scores in the two assessments.

The data were entered in the Epidata Program version 3.1. to create the database mask. For statistical analyses, SPSS v.17.0 and Statistica v. 7.0 were used. The significance level adopted for the statistical tests was 5%, with p-value <0.05.

Results

Table 1 shows the sociodemographic characteristics of the sample at baseline. Participants with AD were significantly older than those with bvFTD and PPA, and AD patients had fewer years of formal education than those with PPA. The clinical groups were statistically equivalent as to the categorical classification of the CDR.

Insert Table 1

Table 2 shows results for the cognitive scales (ACE-R and MMSE) and for the three staging scales (FTD-FRS, CDR-FTLD, CDR) at baseline and follow-up. Cognitive and staging scales documented significant decline after 12 months. One AD patient was lost to follow-up. The FTD-FRS did not detect significant decline in the PPA group (Table 2 and Figure 1). Effect size analyses suggested higher decline among bvFTD and PPA patients than AD (with the exception of the CDR-FTLD score).

Insert Table 2
Insert Figure 1

For illustrative purposes, Figure 2 shows the percentage of patients in each severity level of the staging tools at baseline and 12-month follow up for each diagnostic group. Figure 2 indicates that a large percentage of participants are classified as severe or very severe by the FTD-FRS and the CDR-FTLD. In contrast, when the original CDR score is assigned a severity label, a smaller percentage of patients fall into these categories (i.e., a larger percentage are categorized as moderate or mild). Supplementary Tables 2 to 5 report the corresponding CDR-FTLD scores at each FTD-FRS severity level, for baseline and follow-up, for the total sample and for each diagnostic group.

Insert Figure 2

Discussion

The present study aimed to directly compare three staging scales in their ability to detect disease progression in bvFTD, PPA and AD. We observed that all three scales, as well as the MMSE and the ACE-R, documented disease progression in the 12-month follow up. The CDR seemed less sensitive to the severe stages of the diseases (Figure 2). The study presents new and relevant information as direct comparisons of staging scales in longitudinal studies are rare.

Staging scales for dementia, such as the CDR, are considered robust assessments to characterize and track the course of AD symptoms compared to measures of functional or cognitive performance[25]. However, there are concerns whether the CDR may be used to stage FTD[1]. In the present study, the FTD-FRS and the CDR-FTLD seemed to detect the more severe stages of bvFTD, as a relevant proportion of patients that were classified as very mild and mild by the CDR were classified as being in the moderate or severe stages, according to the FTD-specific scales (FTD-FRS, CDR-FTLD).

These findings are in line with Mioshi et al.[4] and Turró-Garriga et al. [5] who also identified a larger number of patients in more severe dementia stages using the FTD-FRS, compared to the CDR. Lima-Silva et al. [6], in a cross-sectional study, observed that a sample of 12 patients with bvFTD, classified by the CDR as mild, were classified by the FTD-FRS as moderate or severe.

Although clinical groups in the present study did not differ according to CDR scores at baseline, FTD-FRS scores suggested patients with bvFTD were in more severe

disease stages compared to the other diagnostic groups. These findings are in agreement with previous studies, which used the DAD and FTD-FRS, respectively[7, 8]. Deutsch et al. [27], in a cross-sectional study with 20 patients with bvFTD and 20 with AD, observed that the bvFTD group had greater functional and cognitive impairment, greater presence of neuropsychiatric symptoms, and a higher level of disease severity assessed by the CDR-FLTD. These findings suggest that scales including FTD specific symptoms may better characterize disease stage in dementias of the FTD spectrum.

It is necessary to note that the assessment strategy of each instrument may have had an influence on present findings. The CDR and the CDR-FTLD offer a response anchor with five options (0, 0.5, 1, 2, 3), whereas the FTD-FRS offers only three options (always = 0, sometimes = 0 and never = 1), and the 0 score indicates that the symptom may be present with varying frequencies. Therefore, the FTD-FRS may overestimate mild symptoms and generate a higher percentage of more severe cases. These differences among assessment tools highlight the value of follow-up data, as they may elucidate how each instrument may capture change. Effect size analyses may also add relevant information, as seen in Table 2.

The follow-up analyses revealed that the three staging scales (FTD-FRS, CDR-FTLD, CDR) showed significant decline from baseline in all diagnostic groups. The FTD-FRS failed to identify significant disease progression in PPA, but the results were close to statistical significance. This may be due to the fact that the PPA sample was smaller, thus reducing statistical power. Alternatively, this finding may be related to the fact that the FTD-FRS does not include items probing specifically on language difficulties. However, the PPA group showed, from baseline to follow up, a score change in this scale that approached significance in mean and SE, respectively, -0.30 (0.89) and -1.61 (0.70), with a large effect size, indicating an important decline.

Mioshi et al. [4], using the CDR and the FTD-FRS, concluded that the FTD-FRS was more sensitive to assess the clinical changes in patients with FTD [4]. In the follow-up data of the present study, according to z-score values (Figure 1), patients with bvFTD seemed to decline more significantly, than patients with PPA and AD, in both FTD-FRS and CDR-FTLD. Our findings corroborate the findings from O'Connor et al. [8], with a four-year follow-up of a sample of patients diagnosed with FTD variants, when the bvFTD group presented the highest rate of decline in the DAD [8]. In general, longitudinal studies with patients with FTD are still scarce and have reached different conclusions as to the rate of decline [27–30].

Our study confirms that bvFTD may progress at a faster pace than other dementias, in agreement with Mioshi et al. [32] and Wicklund et al. [33]. A recent study characterized the longitudinal changes in 161 patients with bvFTD (n = 77) and the semantic (n = 45) and non-fluent (n = 39) variants of PPA. Declines in functional and neuropsychological measures, as well as frontal and temporal cortical volumes and white matter microstructure, were detected in all groups. Changes in imaging parameters were significantly correlated with change, and explained a substantial portion of variance, in most clinical measures[34]. The slower progression in semantic variant PPA, also observed in our study (tentatively due to small sample size), is in line with the prolonged survival shown in a consecutive series of 100 patients[35].

The present analyses suggest that cognitive tests can also detect disease progression. Our findings support Schubert et al. [7], who found decline in cognitive and staging scores of patients with bvFTD and AD at the three-year follow-up evaluation. Follow-up studies focusing on cognitive scores have been conducted in small samples using the MMSE [36,37] and have suggested that in one year there was significant decline in MMSE scores in patients with FTD.

Among the limitations of the study, we shall mention the small sample of patients with PPA, In addition, we highlight that the fact that the PPA variants were not separated in the analyses is an important limitation, as each variant has particular clinical, genetic markers and progression rates, according to previous literature data[19]. Therefore, future studies on clinical trajectories in PPA should include larger samples of each variant. Also, a 12-month follow up may be too short for studying dementia progression, although the investigated tools were able to detect significant change in this period.

In summing up, we conclude that the FTD-FRS, CDR-FTLD and the CDR are useful tools in dementia management. Although cognitive tests were able to capture change in 12 months, staging based on cognitive scores may be limited, as they are heavily dependent on language skills. In addition, cognitive cutoff scores may be inadequate for staging dementia in developing countries, because of the influence of education, which may vary greatly. Therefore, scales such as the FTD-FRS may provide a better understanding of progression in FTD by showing which skills are impaired at the beginning and in later stages of the disorder. This information may aid in care management and rehabilitation efforts.

Funding

This project was supported by the São Paulo Research Foundation (FAPESP) grant number: 11/04804-1, Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq), grant number: 151684/2014-6 and by Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES), grant number: 88881.131619/2016-01.

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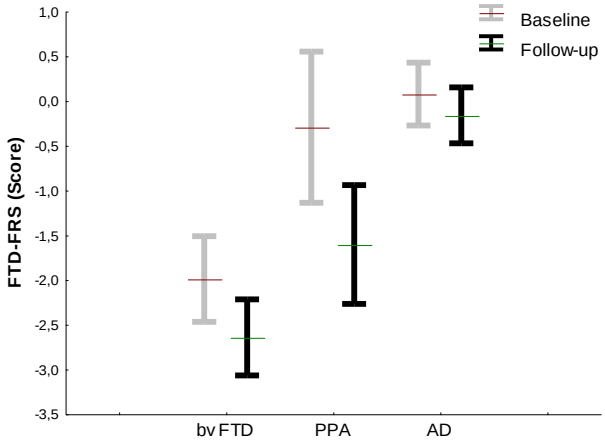
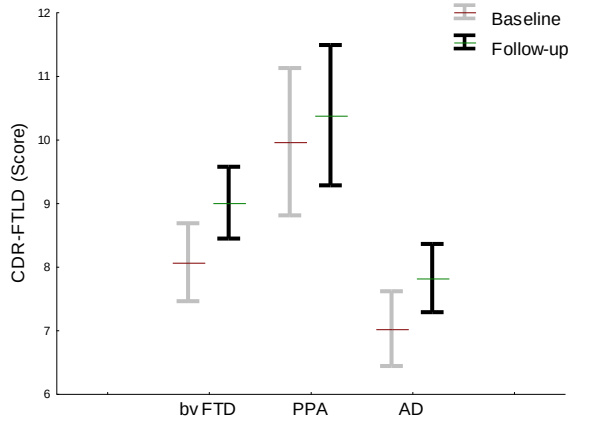
Table 1. Sociodemographic description of the sample stratified by clinical group at baseline.

Variables	bvFTD (n=31)		PPA (n=12)		AD (n=27)		p-value
	Mean	Standard Error	Mean	Standard Error	Mean	Standard Error	
Age (50-87 years)	66.94	(1.66) †	61.42	(1.69) †	74.15	(1.77) #‡	**<0,001***
Schooling (2-21 years)	11.74	(0.82)	14.33	(1.27) †	9.26	(0.86) ‡	**0.007 ***
Sex (% women)	41.94		41.67		62.96		**0.228****
Marital status (% married)	51.60‡		55.60#†		100‡		**0.012****
CDR category (%)							**0.091****
0.0	0.00		8.33		3.70		
0.5	25.81		0.00		40.74		
1.0	54.84		66.67		44.44		
2.0	19.35		25.00		11.11		
CDR – sum of boxes	5.90	(0.50)	7.04	(0.97)	5.74	0.45	**0.432***

Note: bvFTD = behavioral variant frontotemporal dementia, PPA = primary progressive aphasia, AD = Alzheimer disease, CDR = Clinical Dementia Rating scale.
*Kruskal-Wallis test: H (2, N= 70) =1,677237 p =0,432.
**Results of $\chi 2$ test.
#Differ from bvFTD.
‡Differ from PPA.
†Differ from AD.





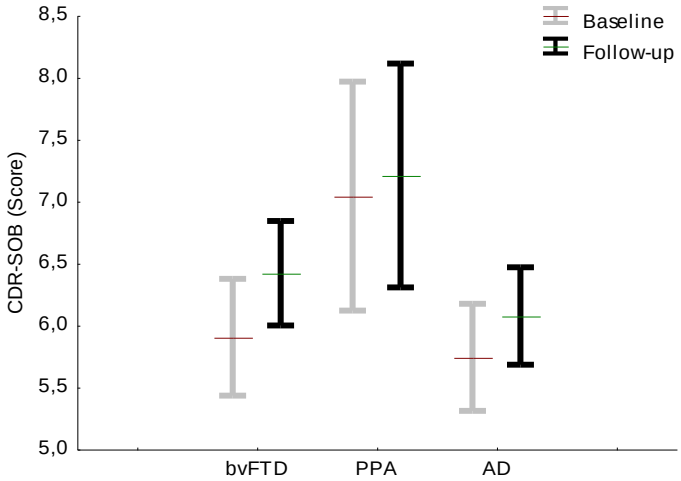


Figure 1. Changes in the FTD-FRS, CDR-FTLD sum of boxes and CDR sum of boxes for the clinical groups at baseline and 12-month follow up.

Table 2. Means and standard errors for cognitive and staging scales at baseline and 12-month follow-up.

Variables	bvFTD (n=31)		PPA (n=12)		AD (n=27)	
	Baseline	**Follow-up**	**Baseline**	**Follow-up**	**Baseline**	**Follow-up**
ACE-R	71.71 (3.09)	68.70 (2.80)	65.75 (4.53)	65.50 (4.22)	67.09 (2.39)	66.64 (2.21)
	Z=3.180	p=0.001	Z=1.992	p=0.046	Z=2.023	p =0.043
	Effect size= 0.571		Effect size=0.575		Effect size=0.389	
MMSE	23.61 (0.94)	22.13 (0.89)	23.75 (1.35)	21.80 (0.95)	23.09 (0.72)	22.64 (0.75)
	Z=2.803	p=0.005	Z=2.201	p=0.028	Z=2.028	p=0.042
	Effect size=0.503		Effect size=0.635		Effect size=0.390	
FTD-FRS	-1.99 (0.50)	-2.65 (0.45)	-0.30 (0.89)	-1.61 (0.70)	0.07 (0.37)	-016 (0.33)
	Z=2.856	p=0.004	Z=1.820	p=0.069	Z=2.201	p=0.028
	Effect size=0.513		Effect size=0.525		Effect size=0.424	
CDR-FTLD	8.06 (0.65)	9.00 (0.59)	9.96 (1.22)	10.38 (1.16)	7.02 (0.62)	7.81 (0.56)
	Z=3.408	p=0.001	Z=2.023	p=0.043	Z=3.180	p=0.001
	Effect size=0.612		Effect size=0.584		Effect size=0.612	
CDR	5.90 (0.50)	6.42 (0.44)	7.04 (0.97)	7.21 (0.95)	5.74 (0.45)	6.07 (0.41)
	Z=3.059	p=0.002	Z=1.826	p=0.068	Z=2.665	p=0.007
	Effect size=0.549		Effect size=0.527		Effect size= 0.513	

Note: Z and p-level of Wilcoxon Matched Pairs Test.

Effect Size: According to Cohen's classification of effect sizes: 0.1 (small effect), 0.3 (moderate effect) and 0.5 and above (large effect).

bvFTD = behavioral variant frontotemporal dementia, PPA = primary progressive aphasia, AD = Alzheimer disease,

ACE-R/Total indicates Addenbrooke cognitive examination-revised; MMSE, mini-mental state exam; FTD-FRS, frontotemporal dementia rating scale; CDR-FTLD=clinical dementia rating scale for frontotemporal lobar degeneration; CDR = Clinical Dementia Rating scale.

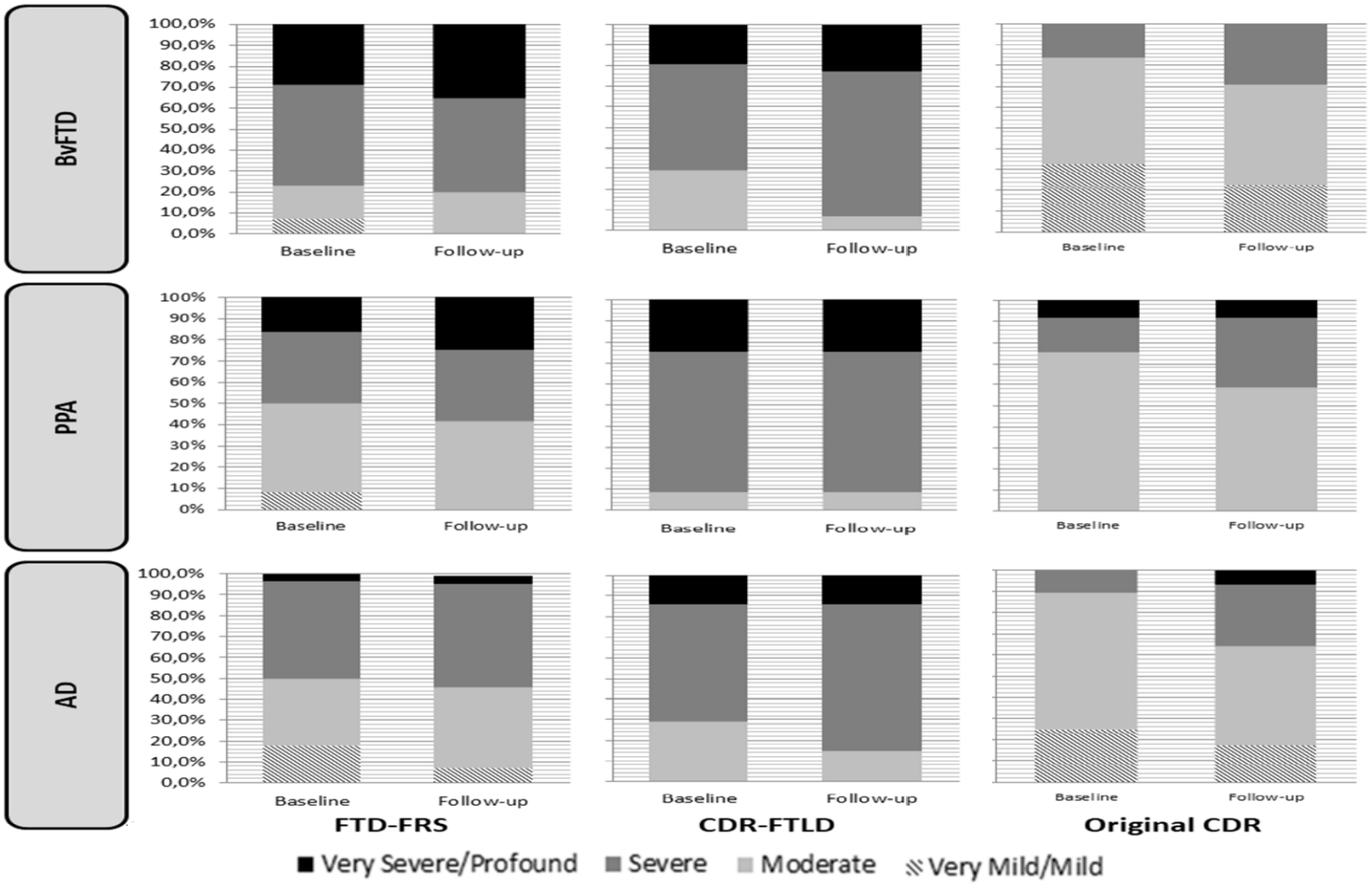


Figure 2. Proportion of patients in each severity stage for frontotemporal dementia (bvFTD), Alzheimer's disease (AD) and primary progressive aphasia (PPA) according to Frontotemporal Dementia Rating Scale (FTD-FRS) and to Clinical Dementia Rating Scale (CDR-SOB) and CDR-FTLD.

Supplementary Table 1. Sociodemographic description of the caregiver sample stratified by clinical group at baseline.

Variables	bvFTD (n=31)		PPA (n=12)		AD (n=27)		
	n/Mean	%/SD	n/Mean	%/SD	n/Mean	%/SD	*p-value*
Age	54.61	10.54	51.75	19.01	50.18	17.38	0.671*
Schooling	13.48	3.81	13.17	2.48	13.18	3.65	0.884*
Sex (n, % women)	27	87.1	9	75.0	20	71.4	0.873**
Relationship							
Spouse (n, %)	16	51.6	6	50.0	10	35.7	0.639**
Son	11	35.5	5	41.7	12	42.9	
Other	4	12.9	1	8.3	6	21.4	
Hours caring/day	14.19	8.51	15.67	6.90	13.00	7.45	0.414*

Note. bvFTD = behavioral variant frontotemporal dementia, PPA = primary progressive aphasia, AD = Alzheimer disease. *= Kruskal-Wallis test, ** = Pearson Chi-square test.

Supplementary Table 2. CDR-FTLD scores (means and standard deviations) according to FTD-FRS severity stages in the total sample (N= 70).

FTD-FRS	Time CDR-FTLD	n	Mean	Std.Dev.	Std.Error	Minimum	Median	Maximum
Very Mild	Baseline	3	5.70	2.59	1.16	3.00	5.00	9.50
	Follow-up	3	6.10	2.48	1.11	3.00	6.50	9.50
Mild	Baseline	5	8.83	4.31	2.49	5.00	8.00	13.50
	Follow-up	5	9.00	4.58	2.65	5.00	8.00	14.00
Moderate	Baseline	18	7.83	3.39	0.80	3.50	7.50	16.00
	Follow-up	18	8.39	3.11	0.73	5.00	8.00	16.00
Severe	Baseline	32	8.69	4.11	0.73	2.50	7.75	19.00
	Follow-up	32	8.77	3.62	0.64	3.50	7.75	19.00
Very Severe	Baseline	7	9.29	2.84	1.07	5.50	10.50	13.00
	Follow-up	7	10.21	2.81	1,06	6.00	10.50	14.00
Profound	Baseline	5	10.40	2.16	0.97	7.50	10.00	13.00
	Follow-up	5	10.80	2.66	1.19	7.50	10.00	14.00

Note. FTD-FRS, frontotemporal dementia rating scale; CDR-FTLD=clinical dementia rating scale for frontotemporal lobar degeneration

Supplementary Table 3. CDR-FTLD scores (means and standard deviations) according to FTD-FRS severity stages in the bvFTD group (N=31)

FTD-FRS	Time CDR-FTLD	n	Mean	Std.Dev.	Std.Error	Minimum	Median	Maximum
Very Mild	Baseline	1	8.00	-	-	8.00	8.00	8.00
	Follow-up	1	8.00	-	-	8.00	8.00	8.00
Mild	Baseline	-	-	-	-	-	-	-
	Follow-up	-	-	-	-	-	-	-
Moderate	Baseline	7	8.03	3.58	0.89	2.50	7.75	15.00
	Follow-up	7	8.19	3.26	0.82	3.50	7.75	15.00
Severe	Baseline	16	9.64	4.23	1.60	3.50	9.50	16.00
	Follow-up	16	10.21	3.86	1.46	5.50	9.50	16.00
Very Severe	Baseline	5	9.30	2.66	1.19	5.50	9.00	11.00
	Follow-up	5	9.60	3.07	1.37	6.00	10.00	14.00
Profound	Baseline	2	10.25	3.89	2.75	7.50	10.25	13.00
	Follow-up	2	10.25	3.89	2.75	7.50	10.25	13.00

Note. FTD-FRS, frontotemporal dementia rating scale; CDR-FTLD=clinical dementia rating scale for frontotemporal lobar degeneration

Supplementary Table 4. CDR-FTLD scores (means and standard deviations) according to FTD-FRS severity stages in the PPA group (N= 12).

FTD-FRS	Time CDR-FTLD	n	Mean	Std.Dev.	Std.Error	Minimum	Median	Maximum
Very Mild	Baseline	2	7.17	2.52	1.45	4.50	7.50	9.50
	Follow-up	2	7.67	2.36	1.36	5.00	8.50	9.50
Mild	Baseline	-	-	-	-	-	-	-
	Follow-up	-	-	-	-	-	-	-
Moderate	Baseline	3	9.25	6.01	4.25	5.00	9.25	13.50
	Follow-up	3	9.50	6.36	4.50	5.00	9.50	14.00
Severe	Baseline	6	11.58	4.62	1.89	6.50	10.25	19.00
	Follow-up	6	12.08	4.13	1.69	8.00	10.50	19.00
Very Severe	Baseline	-	-	-	-	-	-	-
	Follow-up	-	-	-	-	-	-	-
Profound	Baseline	1	10.00	-	-	10.00	10.00	10.00
	Follow-up	1	10.00	-	-	10.00	10.00	10.00

Note. FTD-FRS, frontotemporal dementia rating scale; CDR-FTLD=clinical dementia rating scale for frontotemporal lobar degeneration

Supplementary Table 5. CDR-FTLD scores (means and standard deviations) according to FTD-FRS severity stages in the AD group (N=27).

FTD-FRS	Time CDR-FTLD	N	Mean	Std.Dev.	Std.Error	Minimum	Median	Maximum
Very Mild	Baseline	-	-	-	-	-	-	-
	Follow-up	-	-	-	-	-	-	-
Mild	Baseline	5	5.70	2.59	1.16	3.00	5.00	9.50
	Follow-up	5	6.10	2.48	1.11	3.00	6.50	9.50
Moderate	Baseline	8	6.50	2.30	0.81	4.00	6.00	10.00
	Follow-up	8	7.06	1.90	0.67	5.00	6.50	10.00
Severe	Baseline	10	6.40	3.51	1.11	3.50	5.25	13.00
	Follow-up	10	7.70	2.97	0.94	4.00	6.75	13.00
Very Severe	Baseline	2	11.75	1.77	1.25	10.50	11.75	13.00
	Follow-up	2	11.75	1.77	1.25	10.50	11.75	13.00
Profound	Baseline	2	10.75	1.77	1.25	9.50	10.75	12.00
	Follow-up	2	11.75	3.18	2.25	9.50	11.75	14.00

Note. FTD-FRS, frontotemporal dementia rating scale; CDR-FTLD=clinical dementia rating scale for frontotemporal lobar degeneration