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Utility of the CDR® plus NACC FTLD in Mild FTLD: Data from the ARTFL/LEFFTDS Consortium

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Abstract

Introduction: Behavior/Comportment/Personality (BEHAV) and Language (LANG) domains were added to the Clinical Dementia Rating (CDR®) for improving evaluation of frontotemporal lobar degeneration (FTLD) patients (CDR® plus NACC FTLD).

Methods: We analyzed the CDR® plus NACC FTLD among participants from the baseline visit of the ARTFL/LEFFTDS Consortium.

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Results: The CDR® plus NACC FTLD was able to detect early symptoms in the mildly impaired participants who were rated as CDR®-sum of boxes (CDR®-SB) =0. The CDR®-SB was not sensitive particularly in the mild non-fluent/agrammatic primary progressive aphasia participants. Familial and sporadic behavioral variant FTD participants exhibited similar CDR® plus NACC FTLD profiles except that, language impairment was more frequent in the mild sporadic participants. Adding the BEHAV and/or LANG domains to the CDR®-SB significantly enhanced discriminatory power in differentiating among the FTLD spectrum disorders.

Discussion: The BEHAV and LANG domains enable the CDR® plus NACC FTLD to capture early symptomatology of FTLD.

Keywords

CDR®; Frontotemporal lobar degeneration; Frontotemporal dementia; Primary progressive aphasia; Language; Behavior, comportment and personality; NACC FTLD Module

1. Introduction

Frontotemporal dementia (FTD) is a spectrum of heterogeneous clinical conditions resulting from neurodegeneration of the frontal and temporal lobes, neuropathologically termed as frontotemporal lobar degeneration (FTLD). Depending on the principal anatomic area of the brain affected and the associated symptomatology, the classic FTD syndromes are clinically subtyped as behavioral variant FTD (bvFTD), semantic variant primary progressive aphasia (svPPA), and non-fluent/agrammatic variant primary progressive aphasia (nfvPPA). In addition, progressive supranuclear palsy/Richardson's syndrome (PSP-RS), corticobasal syndrome (CBS), and FTD with Amyotrophic Lateral Sclerosis (FTD-ALS) are grouped into FTLD spectrum diseases. Each FTD subtype and the other FTLD spectrum disorders show distinct clinical characteristics different from Alzheimer's disease dementia (AD), with behavioral disturbance, language impairment and/or executive dysfunction being predominant, while memory and orientation are relatively preserved in the early course of the disease.

The CDR® Dementia Staging Instrument, which we will refer to as the CDR® hereafter, is a semi-structured global assessment measure developed to characterize six domains of cognitive and functional levels and to stage the severity of dementia in patients in the AD spectrum [1, 2]. It has a unique intuitive appeal to clinicians, and its ratings have obvious face validity. Five domains of Memory (MEM), Orientation (ORI), Judgement and Problem Solving (JUDG), Community Affairs (COMM), and Home and Hobbies (HOME) are each rated on a 5 point scale ranging from 0 (normal), 0.5 (questionably or minimally impaired), 1 (mildly impaired), 2 (moderately impaired) to 3 (most severely impaired); a sixth domain, Personal Care (CARE), is rated on a 4 points scale from 0 to 3 without a rating of 0.5. The ratings of the six individual domains are totaled to calculate the CDR® sum of boxes (CDR®-SB). The global CDR® score is calculated from the six domains, with the Memory domain considered to be the primary domain in calculating the global rating [2]. The global CDR® and the CDR®-SB score have been widely used at the bedside and in many clinical research projects and therapeutic clinical trials. Since the CDR® primarily focuses on AD, it

gives more weight to memory and orientation impairment, and less on behavioral and language issues.

To broaden the utility of the CDR® into FTLD spectrum disorders, Behavior/Comportment/Personality (BEHAV) and Language (LANG) domains were added to the CDR® to form the 8-domain "FTLD-CDR" [3]. The terminology "FTLD-CDR" represented the exact same group of measures now used by the updated name of "CDR® Dementia Staging Instrument PLUS NACC FTLD Behavior & Language Domains (CDR® plus NACC FTLD). Since the CDR® is now trademarked, this updated abbreviation for the 8-domain ratings was proposed by the developers of CDR® and the NACC FTLD Module, and all references to this combination of measures will be abbreviated "CDR® plus NACC FTLD" henceforth in this manuscript.

The BEHAV and LANG domains are similar to most CDR® domains, with each rated on a 5 point scale from 0 to 3. CDR® plus NACC FTLD-SB is defined as the sum of the CDR®-SB, the BEHAV domain rating, and the LANG domain rating. The CDR® plus NACC FTLD was adopted into the 2nd version of the Uniform Data Set (UDS) of the National Alzheimer's Coordinating Center (NACC) dataset as part of the National Institute on Aging (NIA)-funded Alzheimer's Disease Centers program to provide enhanced information and utility in evaluating bvFTD and PPA patients [4, 5]. Previous research examining the utility of the CDR® plus NACC FTLD include the findings that the CDR® plus NACC FTLD-SB exhibits good correlation with frontotemporal cerebral blood hypoperfusion in FTLD patients [6, 7], and that the BEHAV and LANG domains in the Spanish version of the CDR® plus NACC FTLD are useful in the characterization of the non-amnestic symptoms among relatively small number of AD, bvFTD and PPA patients[8]. There have been few studies on the detailed clinical characterization of the eight CDR® plus NACC FTLD domains in FTLD patients, and also on whether CDR® plus NACC FTLD is useful in discriminating among FTLD spectrum diseases.

We sought to characterize the relationship between CDR® plus NACC FTLD ratings, and clinical phenotypes and neuropsychological and neurological tests among participants in the Advancing Research and Treatment in FTLD (ARTFL)/Longitudinal Evaluation of Familial Frontotemporal Dementia Subjects (LEFFTDS) Consortium, using cross-sectional data collected at the initial baseline visit. The study group included participants with FTLD spectrum diagnoses, including mild cognitive impairment (MCI-cog), mild behavioral changes (MCI-beh), and clinically normal (CN) participants (see definitions below), who are in kindreds with known FTLD-related gene mutations as well as sporadic FTLD participants. Evaluating the CDR® plus NACC FTLD in detail among a large number of participants in the ARTFL/LEFFTDS Consortium will be of great utility in that we expect to gain cross-sectional and longitudinal CDR® plus NACC FTLD data for the very early phase of FTLD participants including early FTLD, MCI-cog/-beh, and the presymptomatic phase which are believed to be the optimal phases for future disease modifying therapies for FTLD. Furthermore, we sought to look into whether CDR® plus NACC FTLD is useful in differentiating not only FTLD and AD, but also among FTLD spectrum disorders.

2. Methods

2.1. Participants

In this study, we performed cross-sectional analysis from the baseline visit of ARTFL/LEFFTDS Consortium. The LEFFTDS Consortium includes 8 institutions in North America evaluating individuals in kindreds with mutations in the microtubule associated protein tau (*MAPT*), progranulin (*GRN*), or chromosome 9 open reading frame 72 (*C9orf72*) genes using standardized battery of measures. The ARTFL Consortium consists of 18 institutions in North America (8 of which are also LEFFTDS sites) with similar familial FTLD participants, study targets, and methods to LEFFTDS, but also including sporadic FTLD participants. Study participants in ARTFL also included persons with strong familial history of FTLD but no known familial mutation. A few of these participants in ARTFL were found to have a mutation in the genes encoding valosin-containing protein (*VCP)* (N=4), TAR-DNA binding protein *(TARDBP)* (N=4), or Presenilin 1 *(PSEN1)* (N=2). Study participants were clinically categorized into 12 diagnostic groups; 9 neurodegenerative disorders (bvFTD, FTD-ALS, ALS, nfvPPA, svPPA, logopenic variant PPA (lpvPPA), PSP-RS, CBS, AD), 2 mildly impaired but functionally independent conditions (MCI-cog/MCI-beh), and those who were clinically normal (CN).

The diagnostic groups of bvFTD [9], nfvPPA/svPPA/lpvPPA [10], PSP-RS [11], CBS [12], and AD [13] were classified based on the widely-accepted published criteria for each disorder. The diagnosis of FTD-ALS required meeting diagnostic criteria for bvFTD or PPA plus evidence of ALS on physical examination as described in the El Escorial diagnostic criteria for ALS (although not necessarily meeting probable ALS criteria or requiring an EMG study) [14]. The study group included asymptomatic or mildly symptomatic participants who were in kindreds with known FTLD-related gene mutations. These fell into three groups. “CN” represents clinically normal and was applied when participants did not meet any of the diagnostic criteria for neurodegenerative disorders nor had any detectable cognitive impairment, behavioral changes or motor impairment. “MCI-cog” was applied to participants who had experienced a cognitive change compared to their previous level of functioning, had mild impairment in one or more domains of cognition on neuropsychological assessment, but were still independent in functional abilities and did not meet the criteria for dementia [15, 16]. Single domain amnestic MCI, multiple domain amnestic MCI, single domain non-amnestic MCI, and multiple domains non-amnestic MCI were all classified as “MCI-cog” in this study. “MCI-beh” was applied to participants who exhibited changes in behavior/comportment/personality but did not have dementia nor meet criteria for probable bvFTD. The MCI-beh designation was applied particularly to those with behavioral changes plus a known family history of FTLD and were suspected to be evolving toward bvFTD. A typical application of the MCI-beh diagnosis was in the context of any patient who exhibited features and findings consistent with clinically possible bvFTD using the Consensus criteria (see below) who had relatively preserved activities of daily living [9]. In other words, the presence of one or more of the following, in the absence of an overt dementia syndrome, were viewed consistent with the MCI-beh diagnosis:

- Disinhibition: Socially inappropriate behavior; loss of manners or decorum; impulsive, rash, or careless actions

- Apathy or inertia: Loss of interest, drive, and motivation; decreased initiation of behavior
- Loss of sympathy/empathy: Diminished response to other people's needs or feelings; diminished social interest, interrelatedness, or personal warmth
- Ritualistic/compulsive behavior: Simple repetitive movements or complex compulsive or ritualistic behaviors
- Hyperorality and appetite changes: Altered food preferences, binge eating, increased consumption of alcohol or cigarettes, oral exploration or consumption of inedible objects

Importantly, particularly in familial FTD, there are circumstances in which delusions, hallucinations, and other forms of odd behavior may be part of the evolving behavioral phenotype. Therefore, the diagnosis of MCI-beh is a loosely-defined clinical diagnosis that will be operationalized with more rigor in the future after more data is gathered and analyzed.

“Familial bvFTD” was defined when any bvFTD participant had at least one other member in their kindred with a known mutation in the FTLD-related genes; otherwise, the bvFTD participants were defined as “sporadic bvFTD”.

The ARTFL/LEFFTDS Consortium study did not specifically include recruitment of participants with AD. Those classified as AD (N=13) were initially recruited as having FTLD-like “frontal” clinical features, then labeled as “AD” when they did not completely meet the criteria of FTLD spectrum disorders but did meet AD criteria. Due to the small number and the frontal presentations, we excluded these participants for analyses, beyond the demographic characterization. Data from probable AD dementia patients from the NACC database used in the previously referenced analysis [5] was added to the comparison group to represent AD dementia (“NACC-AD”).

2.2. CDR® and CDR® plus NACC FTLD evaluation

The CDR® and CDR® plus NACC FTLD were completed by clinicians who have broad experience in using the measures. CDR®-SB and each rating for the standard six domains and the global CDR® rating were performed according to the widely used CDR® scoring rules [2]. The added BEHAV and LANG domains for CDR® plus NACC FTLD were rated according to published procedures [3, 5]. CDR® plus NACC FTLD-SB has a high inter-rater reliability (intraclass correlation = 0.95) and is comparable to CDR®-SB (intraclass correlation = 0.95) (ARTFL/LEFFTDS Consortium, unpublished data).

2.3. Other covariates

Each study participant underwent neurological and neuropsychological assessment according to the ARTFL/LEFFTDS Consortium study protocol. Participants were evaluated using the Montreal Cognitive Assessment [17] (MoCA; lower score signifies more impairment.), the Unified Parkinson’s Disease Rating Scale [18] (UPDRS; higher score signifies more motor impairment), and the Progressive Supranuclear Palsy Rating Scale [19] (PSPRS; higher score signifies more motor impairment). The Functional Activities

Questionnaire [20] (FAQ; higher score signifies more functional impairment) and the Neuropsychiatric Inventory Questionnaire [21] (NPI-Q; higher score signifies more neuropsychiatric morbidity) were completed by interview with participants' informants.

2.4. Analyses

We analyzed the entire cohort regardless of level of impairment. Participants whose CDR®-SB were <4 were selected to represent the cohort of MCI and mild stage of dementia for selected analyses focused on this sub-group. Selecting CDR-SB® < 4 for this purpose is adopted from the previous report on the NACC dataset analyses [5] to enable us to compare the cohorts.

Demographic, clinical and genetic characteristics of the study participants were compared across the clinical diagnostic groups, and were analyzed by Kruskal-Wallis tests and Chi-Square tests (sex) to detect differences among the groups. Further analysis by pair-wise Wilcoxon or Chi-Square (sex) tests was performed for each feature in order to evaluate the differences between the groups described here: bvFTD vs. PPA, PPA vs. NACC-AD, bvFTD vs. NACC-AD, and NACC-AD vs. AD. The frequency of each domain of the CDR® plus NACC FTLD with abnormal ratings (≥0.5 or ≥1) was calculated to clarify which cognitive domain or function was likely to be impaired for each clinical diagnosis. Differences between familial and sporadic bvFTD were analyzed by Fisher's exact test. Logistic regression analyses were conducted to evaluate how the CDR®-SB, the LANG domain, and the BEHAV domain were able to discriminate between each pair of clinical phenotypes, and to examine whether adding LANG or BEHAV domains to CDR®-SB improved the power to differentiate compared to CDR®-SB alone. All logistic regression analyses included sex and education as covariates. Odds ratios, 95% confidence intervals (CI), and concordance statistics (c-statistic) were calculated to evaluate discriminatory power for these variables. The c-statistic is equal to the area under the ROC curve (AUC) and ranges from 0.5 to 1. In general, values over 0.7 indicate a good model and values over 0.8 indicate a strong model. A jackknife resampling method was applied to compute p-values for comparing c-statistics from the models. The Osius-Rojek Test was performed to evaluate goodness of fit. The null hypothesis is that the model fits well, and so, a significant p-value in the Osius-Rojek Test means that we can reject the null hypothesis and say that there is evidence that the model doesn't fit well, and a non-significant p-value means that there is no evidence to suggest that the model doesn't fit well. Statistical analyses were performed using SAS (version 9.4; SAS Institute, Inc., Cary, North Carolina).

3. Results

3.1. Diagnostic categorization and baseline assessments

The demographic, clinical and genetic features for the baseline visit of the entire ARTFL/LEFFTDS cohort and the probable AD patients from the NACC dataset adopted from the previous report [5] are given in Table 1. While the CDR®-SB and global CDR® scores were quite similar between bvFTD and NACC-AD, the CDR® plus NACC FTLD-SB, BEHAV and LANG domains ratings were higher for bvFTD. The combined PPA (nfvPPA + svPPA + lpvPPA) participants had higher scores on the BEHAV and LANG domains than NACC-AD

participants although their CDR®-SB, global CDR®, and CDR® plus NACC FTLD-SB scores were lower. Among PPA participants, svPPA participants had higher NPI-Q scores and BEHAV domain ratings than other PPA variants. The nfvPPA participants scored higher on UPDRS and PSPRS than the other PPA variants. The AD participants in our study, compared to NACC-AD participants, were younger, included more males, had more FTLD related genetic backgrounds, had higher scores on the NPI-Q, and had higher BEHAV domain ratings on the CDR® plus NACC FTLD. The majority of CN, MCI-cog, and MCI-beh participants were in kindreds with a known mutation.

3.2. Mildly impaired (CDR®-SB<4) participants

Among the MCI-beh and FTD (bvFTD, nfvPPA, and svPPA) participants, there were 11 participants - including 8 FTD participants - who were rated CDR®-SB =0 despite their clinical diagnoses (Table 2). Among these FTD participants, the nfvPPA participants were most likely to be rated CDR®-SB=0. All of these CDR®-SB=0 cases had abnormal ratings (≥0.5) on either the BEHAV or LANG domain, and thus had non-zero CDR® plus NACC FTLD-SB scores; 8/11 (72.7%) of the CDR®-SB=0 cases had BEHAV or LANG domain ratings of ≥1.

The frequency of participants with abnormal ratings for each of the eight domains of the CDR® plus NACC FTLD are shown in Table 3 for the mildly impaired participants in each diagnostic group; that is, for participants with CDR®-SB <4. Because cognitive and behavioral functions tend to become impaired in the later stage of a dementing illness regardless of initial presentation, evaluating these data points in the milder and earlier stages of FTLD may be more informative. Amongst these groups, bvFTD had higher frequency of ≥1 ratings in JUDG as well as BEHAV compared to mild NACC-AD participants; this pattern held in the COMM, HOME, and CARE domains. While more than half of the CDR®-SB <4 mild bvFTD participants had ≥1 ratings on the JUDG domain, there were no ≥1 rating cases in the MCI-beh participants, which might be the important clinical distinction between MCI-beh and mild bvFTD. The frequency of JUDG domain ratings being ≥1 in svPPA participants was similar to the frequency in mild bvFTD participants. Among PPA participants, svPPA participants had a higher frequency of ratings ≥1 for the BEHAV, JUDG, and MEM domains than the nfvPPA participants. CBS and PSP-RS participants showed moderately higher frequency of ≥1 ratings than NACC-AD on all domains except MEM and ORI. CBS and PSP-RS participants had higher frequencies of having ≥1 ratings on the LANG domain than on the BEHAV domain.

3.3. Familial and sporadic bvFTD

The frequency of the familial and sporadic bvFTD participants with abnormal ratings for each of the eight domains of the CDR® plus NACC FTLD are shown separately in Table 4. Whether in the whole cohort or earlier stage, familial and sporadic bvFTD participants shared similar CDR® plus NACC FTLD profiles except that sporadic bvFTD participants had more frequent ≥0.5 ratings on the LANG domain in the CDR®-SB <4 groups.

3.4. Logistic regression analyses

Logistic regression analyses were performed to evaluate how well the CDR®-SB, BEHAV, LANG, and CDR®-SB combined with the BEHAV and/or LANG domains were able to discriminate among the whole cohort of bvFTD, nfvPPA, svPPA, and NACC-AD (Table 5). We applied a jackknife resampling method to compute p-values for comparing c-statistics, and performed the Osius-Rojek Test for assessing goodness of fit.

The CDR®-SB alone was not useful in discriminating bvFTD from NACC-AD with a c-statistic of 0.597, and adding the BEHAV domain with or without the LANG domain to the CDR®-SB significantly improved the c-statistic to 0.930 (CDR®-SB + BEHAV) and 0.931 (CDR®-SB + BEHAV + LANG). In differentiating svPPA or nfvPPA from NACC-AD, higher CDR®-SB made svPPA or nfvPPA less likely with a moderate c-statistics of 0.731 and 0.772, respectively, and the LANG domain with the CDR®-SB significantly raised the c-statistics to 0.934 and 0.957, respectively. For svPPA and NACC-AD, the BEHAV domain with the CDR®-SB also significantly raised the c-statistic to 0.898. Adding both the LANG domain and the BEHAV domains to the CDR®-SB significantly enhanced the c-statistic from 0.731 to 0.961 for svPPA and NACC-AD, and from 0.772 to 0.961 for nfvPPA and NACC-AD.

Among three subtypes of FTD (bvFTD, svPPA, and nfvPPA), higher CDR®-SB made bvFTD more likely with a c-statistic of 0.738 for bvFTD and svPPA, and 0.802 for bvFTD and nfvPPA. Adding the LANG domain and/or the BEHAV domain to the CDR®-SB significantly raised the c-statistics for discriminating bvFTD and svPPA or nfvPPA with adding the BEHAV domain to the CDR®-SB in discriminating bvFTD and svPPA being the one exception. For svPPA and nfvPPA, the CDR®-SB was not helpful in discriminating them with a c-statistic of 0.667. Adding only the LANG domain or the BEHAV domain to the CDR®-SB did not enhance the c-statistic for discriminating between svPPA and nfvPPA, but adding both the LANG domain and the BEHAV domains to the CDR®-SB significantly improved the c-statistic from 0.667 to 0.822.

We performed the Osius-Rojek Test to evaluate goodness of fit for the models. For the four comparisons (bvFTD vs NACC-AD, nfvPPA vs NACC-AD, bvFTD vs nfvPPA, and svPPA vs nfvPPA), the models with just CDR®-SB had significant goodness of fit tests, indicating that we can reject the null hypothesis that the model fits well. By adding the LANG and/or the BEHAV domains to the CDR®-SB in these four comparisons, the p-values for the Osius-Rojek Test became not significant, implying that the models with these additional domains added to the CDR®-SB fit better than the models with the CDR®-SB alone. The two exceptions to this were adding only the LANG domain for discriminating bvFTD vs. nfvPPA and svPPA vs. nfvpPA.

4. Discussion

Designing clinical trials with disease modifying therapies in FTLD spectrum disorders is challenging. First, pathological and genetic heterogeneity of FTLD and lack of established biomarkers make it more difficult to target specific pathological proteins. Second, there are few neuropsychological and global scales specific for FTLD to evaluate participants' clinical

features and changes in these features. The main goals for the ARTFL/LEFFTDS Consortium study are to discover new biomarkers for disease activity, support the development of new therapies and diagnostic instruments, and identify potential participants for clinical trials of new targeted therapeutic agents. The CDR® plus NACC FTLD was developed to enhance the utility of the CDR® in FTLD spectrum disorders, and to be used for future clinical trials in FTLD.

Although the CDR® and CDR® plus NACC FTLD were not created for differentiating the dementia syndromes, our findings indicate that adding the BEHAV/LANG domains to the CDR®-SB enhances discriminatory power not only between FTLD and AD, but also among the FTLD spectrum disorders. Our logistic regression analyses show that adding the BEHAV or LANG domain to the CDR®-SB results in enhanced c-statistics when comparing to the models with CDR®-SB without these additional domains. This was true for discriminating between all pairs of diagnoses with a few exceptions: adding the BEHAV domain for bvFTD and svPPA, and adding the BEHAV or LANG domain for svPPA and nfvPPA. The absence of discrimination between these pairs seems reasonable based on their overlapping features. Also, as shown with the Osius-Rojek test, we demonstrated that for most of the cases, the models with just CDR®-SB had significant goodness of fit tests and the models that added the BEHAV and/or LANG domains to the CDR®-SB tended to be non-significant, indicating that CDR®-SB alone was not sufficient for distinguishing these diagnoses, and the BEHAV and LANG domains added important information. As our findings demonstrate, the CDR® plus NACC FTLD indeed has added value in capturing early symptomatology of FTLD, where the CDR® is not sensitive in detecting. In particular, the mild nfvPPA was the most difficult diagnostic group to detect clinical disturbances by the CDR®.

Clinical manifestations assessed by the eight domains of CDR® plus NACC FTLD were similar between familial and sporadic bvFTD, but language impairment was more frequent in the sporadic bvFTD participants in the familial bvFTD cohort. This difference in language impairment was not seen in the whole bvFTD cohort. Since it is sometimes difficult to differentiate bvFTD and svPPA in their early phase, it is possible that early svPPA, mostly observed as sporadic, was initially diagnosed as sporadic bvFTD. Ongoing longitudinal analyses will reveal their final diagnoses, and whether sporadic bvFTD shows more language impairment than familial bvFTD in the mild stage.

In svPPA patients, and particularly the right temporal-dominant form of svPPA, behavioral disturbances such as mental rigidity and loss of empathy may be prominent initial features - even before language impairment [3, 5, 22, 23]. Among PPA participants in our study, svPPA participants had higher scores on the NPI-Q and a higher frequency of ratings ≥1 for the BEHAV, JUDG, and MEM domains than the nfvPPA participants. Of note, the frequency of JUDG domain ratings being ≥1 in mild svPPA participants was similar to the frequency in mild bvFTD participants.

Compared to svPPA, social comportment and personality are usually preserved early in the course of nfvPPA. The nfvPPA had higher scores on the UPDRS and PSPRS than the other PPAs. This finding is consistent with the fact that tau pathology tends to be the underlying proteinopathy for nfvPPA, and most nfvPPA patients are known to later develop PSP-RS or

CBS [24]. Our study includes only six lpvPPA participants, and while the underlying histology is usually typical of Alzheimer's disease, it remains to be seen if that is the case in lpvPPA in our cohort. [25, 26].

PSP-RS and CBS have been reported to present frontal behavioral disturbances during the course of the disease, or mimic bvFTD in the early stage preceding motor symptoms [27, 28]. Histologically-confirmed corticobasal degeneration (CBD) sometimes manifests as bvFTD or nfvPPA as the initial clinical phenotype [29, 30]. PSP-RS and CBS participants in our study presented with a moderately high frequency of ≥1 ratings on the LANG, BEHAV, and JUDG domains. The LANG domain had a higher frequency of ≥1 ratings than the BEHAV domain in both CBS and PSP-RS, although this was more apparent in CBS participants. The high UPDRS and PSPRS scores in nfvPPA participants, and high frequency of language impairment in CBS and PSP-RS, supports the overlap between nfvPPA and CBS/PSP-RS. There have been no prior reports on the characteristics and utility of the CDR® plus NACC FTLD in CBS and PSP-RS, and these findings are encouraging in this regard.

The most important strength of our study was the large number of participants with no or minimal impairment in cognition, behavior, and language who were members of kindreds with familial FTLD. In our ongoing longitudinal study, we expect to see changes in clinical features and a variety of biomarkers and neuroimaging data at the time of phenoconversion from CN to MCI, or from MCI to diagnosis of an FTLD spectrum disorder. Longitudinal data of preclinical and MCI participants as well as dementia participants may further support the CDR® plus NACC FTLD as an instrument for detecting the early clinical changes in the FTLD spectrum diseases. Since some FTLD syndromes are closely associated with the specific proteinopathies (e.g., the svPPA and FTD-ALS with TDP-43 pathology, the nfvPPA and PSP-RS with tau pathology, and lpvPPA associated with AD pathology), it will be very important to detect clinical features and changes to discriminate among them in their early stage which is believed to be the optimal period for commencing disease modifying therapies targeting the pathological proteins. Our findings suggested CDR® plus NACC FTLD has the substantial potential to assume that role in upcoming clinical trials in FTLD.

Due to the nature of the ARTFL/LEFFTDS Consortium study target, one of the limitations of this study was that our cohort did not include AD dementia participants, aside from a few cases initially recruited as FTLD and then labeled as AD. We therefore included the NACC dataset on AD dementia as a point of comparison. Although the ARTFL/LEFFTDS Consortium dataset and the NACC dataset had different inclusion criteria, and methods of recruitment, bvFTD and PPA participants in both studies appeared to have comparable demographic features. Another limitation was that the analyses were conducted cross-sectionally across the baseline visit of the ARTFL/LEFFTDS study. Further analyses with longitudinal data from the ARTFL/LEFFTDS will be essential, and are expected to better clarify the utility of the CDR® plus NACC FTLD in predicting the phenotype that will occur upon phenoconversion in familial FTLD. Lastly, our diagnostic classification of the study participants was based on clinical features, and was made by clinicians with expertise in FTLD diagnoses. Neuropathological confirmation will be necessary to determine the

accuracy of these clinical diagnoses, with tau- or TDP-43-predominant pathology expected in the vast majority of participants.

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Abbreviations

AD
Alzheimer's disease dementia

ALS
amyotrophic lateral sclerosis

ARTFL
Advancing Research and Treatment for Frontotemporal Lobar Degeneration

BEHAV
Behavior/Comportment/Personality

bvFTD
behavioral variant frontotemporal dementia

C9orf72
gene encoding chromosome 9 open reading frame 72

CARE
Personal Care

CBS
corticobasal syndrome

CDR®-SB
CDR® sum of boxes

CDR® plus NACC FTLD
CDR® Dementia Staging Instrument plus NACC FTLD Behavior and Language Domains

CDR® plus NACC FTLD-SB
CDR® Dementia Staging Instrument plus NACC FTLD Behavior and Language Domains sum of boxes

COMM
Community Affairs

FTD
frontotemporal dementia

FTLD
frontotemporal lobar degeneration

GRN
gene encoding progranulin

HOME
Home and Hobbies

JUDG
Judgment and Problem Solving

LANG
Language

LEFFTDS
Longitudinal Evaluation of Familial Frontotemporal Dementia Subjects

lpvPPA
logopenic variant primary progressive aphasia

MAPT
gene encoding microtubule associated protein tau

MEM
Memory

MRI
magnetic resonance imaging

NACC
National Alzheimer's Coordinating Center

nfvPPA
non-fluent/agrammatic variant primary progressive aphasia

ORI
Orientation

PPA
primary progressive aphasia

PSP-RS
progressive supranuclear palsy - Richardson's syndrome

svPPA

semantic variant primary progressive aphasia

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Research in Context

Systematic review: The authors reviewed the literature using traditional (e.g., PubMed) sources and meeting abstracts and presentations. The CDR® plus NACC FTLD was developed in 2008 to improve characterization of cognitive and global function in FTLD. A few studies have shown the utility of CDR® plus NACC FTLD in FTLD participants. These relevant citations are appropriately cited.

Interpretation: The additional two domains of the CDR® plus NACC FTLD are essential for use in persons with FTLD syndromes.

Future directions: The manuscript proposes a framework for detecting early clinical changes of the FTLD spectrum diseases. Further studies to address the utility of the CDR® plus NACC FTLD should include: (a) longitudinal data showing detection capability of clinical decline or improvement; (b) optimizing the combination of neuropsychological batteries with the CDR® plus NACC FTLD; and (c) correlation with biofluid and/or neuroimaging biomarkers.

Highlights

- The CDR® plus NACC FTLD was completed at the baseline visit in participants of the ARTFL/LEFFTDS Consortium
- The CDR® plus NACC FTLD and particularly the BEHAV and LANG domains captured early features of FTLD
- In the early stage, language impairment was more frequent in sporadic than in familial bvFTD participants.
- Behavioral disturbance was often present in semantic variant PPA participants
- Adding the BEHAV or LANG domain to the CDR® enhanced discriminatory power.

Table 1.

Demographic, clinical and genetic features of participants, by diagnostic group

Feature	CN	MCI-cog	MCI-beh	bvFTD	FTD-ALS	ALS	nfvPPA	svPPA	lpvPPA	CBS	PSP-RS	AD	NACC-AD	P-value
N	255	24	13	236	19	9	56	67	6	68	95	13	2550	
Age at visit	44.7 (14.3)	62.7 (8.5)	56.9 (11.1)	62.0 (9.3)	62.8 (8.7)	61.7 (6.5)	69.5 (8.1)	66.2 (7.4)	67.8 (3.7)	67.3 (9.1)	69.4 (6.6)	66.8 (6.9)	77.2(9.5)	<0.0001#♭♮§
Age at onset	NA	57.2 (9.8)	53.9 (10.2)	55.7 (9.7)	59.6 (8.0)	57.9 (9.2)	65.0 (7.8)	59.8 (7.6)	65.2 (3.9)	62.3 (9.4)	63.8 (7.0)	62.3 (5.7)	NA	<0.0001#
Sex (% female)	60.4	37.5	46.2	39.4	42.1	33.3	60.7	50.7	66.7	48.5	45.3	30.8	52.3	
Race (%white)	96.9	100.0	100.0	94.9	100.0	100.0	94.6	98.5	100.0	97.1	88.4	84.6	84.0	
Education (years)	15.6 (2.5)	15.1 (2.7)	14.6 (2.4)	15.6 (2.6)	15.3 (2.5)	15.3 (2.6)	16.0 (3.0)	16.7 (2.7)	17.0 (2.8)	16.1 (2.9)	16.1 (2.6)	15.4 (2.9)	14.7 (3.2)	<0.0001#♭♮
MAPT (%)	83 (32.5)	0 (0)	3 (23.1)	23 (9.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (7.7)	NA	
C9orf72 (%)	82 (32.2)	12 (50.0)	4 (30.8)	30 (12.7)	4 (21.1)	4 (44.4)	0 (0.0)	2 (3.0)	0 (0.0)	1 (1.5)	0 (0.0)	1 (7.7)	NA	
GRN(%)	58 (22.7)	4 (16.7)	3 (23.1)	5 (2.1)	0 (0.0)	0 (0.0)	2 (3.6)	0 (0.0)	1 (16.7)	3 (4.4)	0 (0.0)	2 (15.4)	NA	
Any known mutations	227 (89.0)	16 (66.7)	10 (76.9)	61 (25.8)	4 (21.1)	4 (44.4)	3 (5.4)	3 (4.5)	1 (16.7)	4 (5.9)	0 (0.0)	4 (30.8)	NA	
MoCA total score	27.3 (2.2)	23.6 (5.1)	24.5 (3.7)	18.1 (7.1)	17.2 (6.4)	21.6 (6.9)	19.5 (7.2)	15.9 (6.6)	12.6 (6.8)	21.8 (4.7)	20.8 (5.1)	14.0 (10.0)	NA	<0.0001
FAQ total score	0.1 (0.3)	3.5 (5.9)	2.5 (5.3)	19.0 (8.5)	20.7 (8.6)	7.1 (8.5)	9.9 (10.6)	13.6 (7.6)	10.7 (11.1)	13.1 (9.0)	16.4 (7.6)	16.6 (8.8)	18.9 (9.6)	<0.0001##
NPI-Q total score	1.0 (2.1)	4.8 (3.9)	8.2 (6.0)	11.3 (7.0)	10.4 (5.8)	4.0 (5.0)	4.3 (4.3)	9.9 (6.2)	1.6 (0.9)	4.9 (3.9)	5.9 (4.9)	12.0 (6.3)	4.6 (4.6)	<0.0001#♭♮§
UPDRS total score	0.0 (0.0)	1.9 (3.3)	0.2 (0.8)	4.8 (9.6)	6.9 (9.0)	2.8 (3.1)	8.6 (10.9)	1.5 (3.2)	1.0 (2.2)	24.6 (14.7)	29.9 (14.0)	6.3 (6.1)	NA	<0.0001
PSPRS total score	0.0 (0.0)	1.6 (1.6)	1.5 (2.0)	6.6 (7.6)	9.1 (11.6)	9.0 (7.4)	8.5 (10.6)	2.6 (3.3)	3.0 (3.3)	23.0 (12.2)	35.9 (13.8)	10.3 (6.1)	NA	<0.0001#
CDR® global	0.0 (0.0)	0.4 (0.2)	0.3 (0.2)	1.1 (0.7)	1.3 (0.8)	0.6 (0.6)	0.7 (0.7)	0.9 (0.5)	0.8 (0.7)	0.8 (0.6)	0.9 (0.7)	1.0 (0.6)	1.2 (0.8)	<0.0001##
CDR®-SB	0.0 (0.0)	1.4 (1.2)	1.2 (0.9)	6.8 (3.9)	7.4 (4.4)	3.0 (3.4)	3.4 (3.9)	4.6 (2.9)	3.8 (3.9)	4.1 (3.3)	5.6 (3.6)	6.6 (3.7)	6.9 (4.7)	<0.0001##

Feature	CN	MCI-cog	MCI-beh	bvFTD	FTD-ALS	ALS	nfvPPA	svPPA	lpvPPA	CBS	PSP-RS	AD	NACC-AD	P-value
CDR® plus NACC FTLD-SB	0.0 (0.0)	1.9 (1.7)	2.2 (1.2)	9.2 (4.9)	9.9 (5.3)	3.9 (4.2)	5.4 (4.8)	7.0 (3.8)	5.3 (4.8)	5.2 (3.9)	7.2 (4.3)	8.3 (4.9)	7.9 (5.6)	<0.0001 #♭♮
BEHAV + LANG	0.0 (0.0)	0.5 (0.6)	1.0 (0.5)	2.4 (1.2)	2.5 (1.2)	0.9 (1.1)	2.0 (1.1)	2.4 (1.1)	1.4 (0.9)	1.1 (1.0)	1.6 (1.0)	1.7 (1.3)	1.0 (1.3)	<0.0001 ♭♮§
LANG	0.0 (0.0)	0.2 (0.3)	0.1 (0.2)	0.8 (0.8)	0.9 (0.8)	0.3 (0.4)	1.5 (0.7)	1.3 (0.6)	1.3 (0.6)	0.7 (0.7)	0.9 (0.7)	0.5 (0.6)	0.5 (0.7)	<0.0001 #♭♮
BEHAV	0.0 (0.0)	0.3 (0.5)	0.9 (0.4)	1.7 (0.7)	1.5 (0.7)	0.6 (0.8)	0.5 (0.6)	1.1 (0.8)	0.2 (0.4)	0.4 (0.5)	0.7 (0.7)	1.2 (1.0)	0.5 (0.7)	<0.0001 #♭♮§

Abbreviations: MoCA, Montreal Cognitive Assessment (higher score=less impairment); FAQ, Functional Activity Questionnaire (higher score=more impairment); NPI-Q, Neuropsychiatric Inventory-Questionnaire (higher score=more impairment); UPDRS, Unified Parkinson's Disease Rating Scale motor subtest (higher score=more impairment); PSPRS, Progressive Supranuclear Palsy Rating Scale (higher score=more impairment).

The genetic data refers to the number of participants who are members of kindreds with a known mutation in the genes encoding microtubule associated protein tau (*MAPT*), progranulin (*GRN*), chromosome 9 open reading frame 72 (*C9orf72*), or any of these three genetic groups.

CDR® global, standard 6 item CDR® global rating; CDR®-SB, sum of the boxes score of the 6 domains of the CDR®; CDR® plus NACC FTLD-SB, sum of the boxes score of the 6 domains of the CDR® plus the behavior/comportment and language domains

Values in table are mean (standard deviation) unless noted.

*Comparisons simultaneously made among all diagnostic groups using the Kruskal–Wallis test for all features but sex (chi-square test). For features with significant differences, pair-wise comparisons were made among participants with bvFTD/FTD-ALS, PPA, and NACC-AD using Wilcoxon rank sum tests for all features but sex (Chi-square tests).

#FTD +/− ALS significantly different from all PPAs.

♭bvFTD +/− ALS significantly different from NACC-AD.

♮All PPAs significantly different from NACC-AD.

§AD significantly different from NACC-AD.

Table 2.

The FTD and MCI-beh participants who were rated CDR®-SB=0.

	CDR®-SB	LANG	BEHAV	CDR® plus NACC FTLD-SB
MCI-beh	0	0	1	1
MCI-beh	0	0	0.5	0.5
MCI-beh	0	0	1	1
bvFTD	0	0	0.5	0.5
nfvPPA	0	2	0	2
nfvPPA	0	1	0	1
nfvPPA	0	1	0.5	1.5
nfvPPA	0	1	0.5	1.5
nfvPPA	0	0.5	0	0.5
nfvPPA	0	1	0	1
svPPA	0	2	0.5	2.5

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Table 3.

Frequency of abnormal ratings on the eight CDR® plus NACC FTLD domains in the mildly impaired participants of CDR®-SB <4

Among participants with CDR®-SB<4	MCI-cog N = 23	MCI-beh N = 13	bvFTD N = 54	FTD/ALS N = 5	ALS N = 6	nfvPPA N = 41	svPPA N = 31	CBS N = 37	PSP-RS N = 32	NACC-AD N = 653
% participants with ratings ≥ 0.5										
LANGUAGE	34.8	23.1	53.7	80.0	50.0	100.0	100.0	70.3	78.1	24.2
BEHAVIOR	43.5	100.0	100.0	100.0	50.0	43.9	80.6	40.5	62.5	12.7
MEMORY	65.2	38.5	70.4	100.0	50.0	39.0	87.1	43.2	62.5	96.0
ORIENTATION	13.0	23.1	31.5	60.0	16.7	12.2	12.9	10.8	31.3	59.1
JUDGMENT	56.5	53.8	96.3	100.0	50.0	56.1	83.9	56.8	84.4	67.7
COMMUNITY AFFAIRS	34.8	61.5	81.5	80.0	33.3	73.2	77.4	62.2	71.9	55.7
HOME AND HOBBIES	26.1	38.5	81.5	80.0	16.7	61.0	74.2	73.0	62.5	56.0
PERSONAL CARE	0.0	0.0	7.4	0.0	0.0	0.0	0.0	5.4	9.4	1.5
% participants with ratings ≥ 1.0										
LANGUAGE	4.3	0.0	13.0	60.0	0.0	92.7	90.3	29.7	25.0	3.7
BEHAVIOR	8.7	61.5	79.6	80.0	0.0	7.3	32.3	13.5	18.8	3.8
MEMORY	8.7	15.4	9.3	0.0	0.0	4.9	25.8	2.7	6.3	47.0
ORIENTATION	0.0	0.0	3.7	0.0	0.0	2.4	3.2	5.4	0.0	12.9
JUDGMENT	17.4	0.0	57.4	40.0	0.0	17.1	54.8	24.3	25.0	10.4
COMMUNITY AFFAIRS	8.7	0.0	29.6	40.0	0.0	19.5	29.0	18.9	21.9	4.9
HOME AND HOBBIES	4.3	0.0	18.5	0.0	0.0	9.8	12.9	16.2	21.9	6.9
PERSONAL CARE	0.0	0.0	7.4	0.0	0.0	0.0	0.0	5.4	9.4	1.5

Eight domains for the CDR® plus NACC FTLD are: LANGUAGE (LANG); BEHAVIOR, COMPORTMENT AND PERSONALITY (BEHAV); MEMORY (MEMO); ORIENTATION (ORI); JUDGMENT AND PROBLEM SOLVING (JUDG); COMMUNITY AFFAIRS (COMM); HOME AND HOBBIES (HOME); PERSONAL CARE (CARE).

Table 4.

Frequency of abnormal ratings on the eight CDR® plus NACC FTLD domains in the familial and sporadic bvFTD

	familial bvFTD N = 61	**sporadic bvFTD N = 175**	**P-value**		**familial bvFTD CDR®-SB <4 N = 15**	**sporadic bvFTD CDR®-SB <4 N = 39**	**P-value**
% participants witd ratings ≥ 0.5							
LANGUAGE	67.2	74.3	0.32		26.7	64.1	0.017 *
BEHAVIOR	100.0	100.0			100.0	100.0	
MEMORY	83.6	89.1	0.26		66.7	71.8	0.75
ORIENTATION	68.9	67.4	0.87		26.7	33.3	0.75
JUDGMENT	98.4	99.4	0.45		93.3	97.4	0.48
COMMUNITY AFFAIRS	91.8	97.1	0.13		66.7	87.2	0.12
HOME AND HOBBIES	93.4	96.6	0.29		73.3	84.6	0.44
PERSONAL CARE	63.9	56.0	0.30		6.7	7.7	1.00
% participants with ratings ≥ 1.0							
LANGUAGE	45.9	35.4	0.17		0.0	17.9	0.17
BEHAVIOR	95.1	91.4	0.58		80.0	79.5	1.00
MEMORY	57.4	61.7	0.55		6.7	10.3	1.00
ORIENTATION	49.2	39.4	0.23		6.7	2.6	0.48
JUDGMENT	88.5	89.7	0.81		53.3	59.0	0.76
COMMUNITY AFFAIRS	77.0	81.1	0.58		20.0	33.3	0.51
HOME AND HOBBIES	73.8	78.3	0.48		6.7	23.1	0.25
PERSONAL CARE	63.9	56.0	0.30		6.7	7.7	1.00

* P<0.05 for the difference between familial and sporadic bvFTD (Fisher's exact test)

Table 5.

Logistic regression analyses with c-statistic for CDR®-SB, LANG, BEHAV, and CDR®-SB with BEHAV/LANG in discriminating among the whole cohort of bvFTD, svPPA, nfvPPA, and NACC-AD.

Table 5a. Logistic regression analyses between FTLD and NACC-AD.

	bvFTD vs NACC-AD			svPPA vs NACC-AD			nfvPPA vs NACC-AD		
	OR (95% CI)	**c-statistic**	**Osius P**	**OR (95% CI)**	**c-statistic**	**Osius P**	**OR (95% CI)**	**c-statistic**	**Osius P**
CDR®-SB	1.01 (0.98-1.03)	0.597	<0.001	0.89 (0.82-0.95)	0.731	0.577	0.76 (0.68-0.84)	0.772	0.001
CDR®-SB + LANG		0.651***	0.291		0.934****	0.850		0.957****	0.522
CDR-SB	0.92 (0.88-0.96)			0.57 (0.51-0.64)			0.48 (0.41-0.55)		
LANG	2.16 (1.72-2.71)			28.1 (16.1-51.7)			56.2 (28.8-120.6)		
CDR®-SB + BEHAV		0.930****	0.581		0.898****	0.933		0.819*	0.760
CDR®-SB	0.63 (0.59-0.67)			0.60 (0.52-0.67)			0.63 (0.55-0.72)		
BEHAV	25.7 (18.5-36.8)			15.1 (9.43-25.0)			5.03 (2.91-8.62)		
CDR®-SB + LANG + BEHAV		0.931****	0.636		0.961****	0.955		0.961****	0.844
CDR®	0.61 (0.56-0.66)			0.37 (0.31-0.45)			0.43 (0.35-0.51)		
LANG	1.25 (0.93-1.67)			28.4 (14.3-60.8)			57.1 (28.2-128.1)		
BEHAV	25.7 (18.4-36.8)			14.8 (8.03-28.6)			2.67 (1.19-6.11)		

The models predict each diagnosis relative to the other. For example, the bvFTD vs NACC-AD model discriminate bvFTD from NACC-AD. All logistic regression analyses included sex and education as covariates. bvFTD includes bvFTD and FTD-ALS.

A jackknife resampling method was applied to compute p-values for comparing the c-statistics from the models to the model with CDR®-SB alone.

* P<0.05

** P<0.01

*** P<0.001

**** P<0.0001

Osius P: p-value for Osius-Rojek Test.

Table 5b. Logistic regression analyses among key FTLD spectrum disorders.

	bvFTD vs svPPA			bvFTD vs nfvPPA			svPPA vs nfvPPA		
	OR (95% CI)	**c-statistic**	**Osius P**	**OR (95% CI)**	**c-statistic**	**Osius P**	**OR (95% CI)**	**c-statistic**	**Osius P**
CDR®-SB	1.23 (1.12-1.36)	0.738	0.126	1.40 (1.25-1.59)	0.802	<0.001	1.13 (1.01-1.28)	0.667	0.003
CDR®-SB + LANG		0.855****	0.458		0.917****	0.003		0.729	0.003
CDR®-SB	1.56 (1.37-1.80)			1.74 (1.51-2.05)			1.25 (1.09-1.44)		
LANG	0.12 (0.06-0.22)			0.07 (0.03-0.14)			0.32 (0.15-0.65)		
CDR®-SB + BEHAV		0.759	0.127		0.916***	0.191		0.774	0.675
CDR®-SB	1.10 (0.98-1.24)			0.84 (0.70-1.00)			0.80 (0.65-0.96)		
BEHAV	2.43 (1.43-4.28)			50.4 (16.4-189.2)			11.5 (4.02-41.3)		
CDR®-SB + LANG + BEHAV		0.861***	0.408		0.958****	0.706		0.822*	0.875
CDR®	1.44 (1.24-1.70)			1.00 (0.81-1.25)			0.85 (0.68-1.05)		
LANG	0.14 (0.07-0.25)			0.10 (0.04-0.22)			0.28 (0.11-0.61)		
BEHAV	1.69 (0.94-3.12)			46.3 (11.6-245.1)			15.3 (4.68-64.7)		

The models predict each diagnosis relative to the other. For example, the bvFTD vs NACC-AD model discriminate bvFTD from NACC-AD. All logistic regression analyses included sex and education as covariates. bvFTD includes bvFTD and FTD-ALS.

A jackknife resampling method was applied to compute p-values for comparing the c-statistics from the models to the model with CDR®-SB alone.

* P<0.05

** P<0.01

*** P<0.001

**** P<0.0001

Osius P: p-value for Osius-Rojek Test.