Utility of the global CDR® plus NACC FTLD rating and development of scoring rules : data from the ARTFL/LEFFTDS Consortium

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Utility of the global CDR® plus NACC FTLD rating and development of scoring rules: Data from the ARTFL/LEFFTDS Consortium

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Abstract

Introduction—We created global rating scoring rules for the CDR® plus NACC FTLD to detect and track early frontotemporal lobar degeneration (FTLD) and to conduct clinical trials in FTLD.

Methods—The CDR plus NACC FTLD rating was applied to 970 sporadic and familial participants from the baseline visit of Advancing Research and Treatment in Frontotemporal Lobar Degeneration (ARTFL)/Longitudinal Evaluation of Familial Frontotemporal Dementia Subjects (LEFFTDS). Each of the eight domains of the CDR plus NACC FTLD was equally weighed in determining the global score. An interrater reliability study was completed for 40 participants.

Results—The CDR plus NACC FTLD showed very good interrater reliability. It was especially useful in detecting clinical features of mild non-fluent/agrammatic variant primary progressive aphasia participants.

Discussion—The global CDR plus NACC FTLD score could be an attractive outcome measure for clinical trials in symptomatic FTLD, and may be useful in natural history studies and clinical trials in FTLD spectrum disorders.

Keywords

behavior; comportment; personality; CDR*Q*R; CDR plus NACC FTLD; frontotemporal lobar degeneration; global rating; language

1 INTRODUCTION

Frontotemporal dementia (FTD) is one of the most common causes of early onset dementia and an umbrella term for three clinical syndromes which present with behavioral/social disturbance and/or language impairment: behavioral variant FTD (bvFTD), semantic variant primary progressive aphasia (svPPA), and non-fluent/agrammatic variant PPA (nfvPPA). The term frontotemporal lobar degeneration (FTLD) is usually used to represent neuropathological diagnoses associated with neurodegeneration of the frontal and temporal lobes caused typically by aberrant accumulation of tau or TAR DNA binding protein (TDP-43). FTLD spectrum disorders include three subtypes of FTDs (bvFTD/svPPA/nfvPPA), progressive supranuclear palsy/Richardson's syndrome (PSP-RS), corticobasal syndrome (CBS), and FTD with amyotrophic lateral sclerosis (FTD-ALS). Some clinical phenotypes

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of FTLD spectrum disorders are associated with specific proteins; nfvPPA is most often associated with FTLD-tau and svPPA with FTLD-TDP. Each FTD subtype and other FTLD spectrum disorders present discriminative and unique clinical characteristics depending on the anatomical area affected, but these FTLD spectrum disorders share many characteristics that are different from Alzheimer's disease dementia (AD), with behavioral/social disturbance and/or language impairment being predominant and memory (MEM) and orientation (ORI) being relatively preserved in the early phase.

The CDR® Dementia Staging Instrument, which we will refer to as the CDR hereafter, is a global assessment scale originally developed in the early 1980s and designed to evaluate cognitive/functional levels and severity of AD patients.[1, 2] The CDR consists of six cognitive/functional domains: MEM, ORI, judgment and problem solving, community affairs, home and hobbies, and personal care (CARE). Based on the semi-structured interview from both a patient and a knowledgeable informant (typically a close family member of a patient), each category domain is rated on a five-point scale ranging from 0 (normal), 0.5 (questionably or minimally impaired), 1 (mildly but definitely impaired), 2 (moderately impaired), to 3 (severely impaired). The CARE domain does not have a rating of 0.5, and so, is rated on a four-point scale. The sum total of the ratings of the six domains is calculated to create the CDR sum of boxes (CDR-SB). The global CDR score is derived from the six domains under the published scoring rules, and rated on a five-point scale (0/0.5/1/2/3).[2] In calculating the global CDR score by these scoring rules, MEM is considered the primary domain and the five other domains as secondary so that global CDR score > 0 requires a score of 0.5 at minimum for the MEM domain. In other words, it is possible to have the global CDR score of 0 despite mild impairment in one or more non-MEM domains, which is common in mild FTLD spectrum disease patients. The CDR has served as one of the most widely used global clinical rating scales in clinical research and clinical trials for AD. On the other hand, because the CDR was originally created for evaluating AD patients, it weighs MEM impairment the highest and lacks specific domains assessing language or behavioral disturbance.

To apply the CDR to assess FTLD spectrum disorders and to be used in FTLD natural history studies and clinical trials, two additional domains, behavior/comportment/personality (BEHAV) and language (LANG), were added to the CDR to create the eight-domain FTLD-modified CDR ("FTLD-CDR") published in 2008 by Knopman et al.[3, 4] The terminology "FTLD-CDR" represented the exact same clinical measure now used by the updated name of "CDR Dementia Staging Instrument PLUS National Alzheimer's Coordinating Center (NACC) Behavior and Language Domains (CDR plus NACC FTLD)." Because the CDR has recently been trademarked, this updated change of the name of eight-domain ratings was proposed by the developers of the CDR and the NACC FTLD Module, and all references to this combination of measures will be abbreviated "CDR plus NACC FTLD" in this study report.

Similar to the ratings for each domain in the CDR, the BEHAV and LANG domains in the CDR plus NACC FTLD are rated on a five-point scale structure from 0 to 3 (0/0.5/1/2/3). The semi-structured interview from patients and their reliable informants originally created for a modified Alzheimer's Disease Cooperative Study-Clinical Global Impression of

Change (ADCS-CGIC), which provides a greater degree of cognitive/behavioral/language queries than the semi-structured interview form for the CDR, is the primary method used to rate the individual domains of CDR plus NACC FTLD.[3, 5, 6] Importantly, neuropsychological data are not considered when completing the ADCS-CGIC and CDR plus NACC FTLD. The total sum of the ratings of the eight domains is calculated for the CDR plus NACC FTLD sum of boxes (CDR plus NACC FTLD-SB). The CDR plus NACC FTLD and its sum of boxes have been adopted as part of NACC Uniform Data Set starting with version 2 in 2008 (and maintained in the current version 3), and this measure has been widely used across the National Institutes of Health (NIA)-funded Alzheimer's Disease Center (ADC) program. All FTLD spectrum patients as well as non-FTLD patients enrolled in any of the 30 ADC sites have had this completed for more than 10 years. Unlike the CDR, there had been no global CDR plus NACC FTLD rating system defined prior to the launch of the Advancing Research and Treatment in Frontotemporal Lobar Degeneration (ARTFL) and Longitudinal Evaluation of Familial Frontotemporal Dementia Subjects (LEFFTDS) protocols.

We have recently reported that BEHAV and LANG domains enabled the CDR plus NACC FTLD to capture early symptomatology of FTLD from ARTFL/LEFFTDS participants.[7] In addition, we presented that adding the BEHAV and/or LANG domains to the CDR-SB significantly enhanced discriminatory power in differentiating not only between FTLD and AD, but also among the FTLD spectrum disorders including between svPPA and nfvPPA.[7]

Although the BEHAV and/or LANG domains and the CDR plus NACC FTLD-SB were shown to be highly sensitive in detecting and tracking early clinical features of FTLD spectrum disorders, having a global rating system for the CDR plus NACC FTLD consistent with what the global scores of the CDR reflect would make it much easier for clinicians and researchers to grasp the overall severity of the FTLD spectrum patients. The ARTFL/LEFFTDS Consortium believed it was desirable to create a global rating system not only for our ongoing clinical research but also to be used for future clinical trials on FTLD.

In this report, we describe the logic for creating the global CDR plus NACC FTLD score/scoring rules, and evaluate it along with the individual eight domains of the CDR plus NACC FTLD and CDR plus NACC FTLD-SB among participants in the ARTFL/LEFFTDS Consortium, using cross-sectional data at the initial baseline visit. We also present data from a reliability exercise between two ARTFL/LEFFTDS participating centers evaluating interrater reliability of global CDR plus NACC FTLD scores and CDR plus NACC FTLD-SB.

2 METHODS

2.1 The development of global CDR plus NACC FTLD score and scoring rules

The global CDR plus NACC FTLD score and its scoring rules were created and refined among a group of FTLD experts in the ARTFL/LEFFTDS Consortium who have had years of experience in evaluating CDR plus NACC FTLD. The global CDR plus NACC FTLD score is calculated based on individual ratings of the eight domains, and the scoring system was developed to be consistent with the widely used global CDR score, ranging from 0

(normal), 0.5 (questionably or minimally impaired), 1 (mildly but definitely impaired), 2 (moderately impaired), to 3 (severely impaired), so that it would be feasible for clinicians and researchers to grasp the disease severity. We also intended to make the scoring rules simple and clear so that raters were capable of calculating the global score without difficulty. The scoring rules for the global CDR plus NACC FTLD score were established through an iterative process whereby the weights of each domain and their contributions to the global score were scrutinized and adjusted to ultimately ensure the global score for each case satisfied face value criteria. The investigators in the ARTFL/LEFFTDS Consortium have also held periodic conference calls to discuss challenging cases to ensure consistency for completing the measure. Through the iterative process of refining the scoring rules for the global CDR plus NACC FTLD rating, the scoring rules were eventually developed to satisfy all the criteria below:

1. Mild impairment in any of the eight domains will result in a global score > 0.
2. Those who appear clinically to reflect mild cognitive impairment (MCI; including mild language impairment) and/or mild behavioral impairment, including having relatively preserved functional independence, will have a global score of 0.5.
3. Those who appear clinically to have a mild dementia syndrome regardless of the particular FTLD phenotype will have a global score of 1.
4. Those who appear clinically to have a moderate or severe dementia syndrome regardless of the particular FTLD phenotype will have a global score of 2 or 3, respectively.

The developed scoring rules for the global CDR plus NACC FTLD score calculated from each rating of the eight domains of CDR plus NACC FTLD are shown in Figure 1. Ratings of the individual eight domains were determined based on the information from ADCS-CGIC semi-structured interviews with participants and their informants as was used for the original FTLD-CDR study.[3, 5] Unlike the global CDR score for which the MEM domain is regarded as the primary domain and the others secondary, all eight domains of the CDR plus NACC FTLD are equally weighted in calculating the global CDR plus NACC FTLD score, and if any domain has rating of > 0, the global CDR plus NACC FTLD score is at least 0.5.

2.2 Participants

We performed a cross-sectional analysis of 970 participants from the baseline visit of the ARTFL/LEFFTDS Consortium between February 2015 and November 2018. The LEFFTDS Consortium includes eight institutions in North America evaluating members of familial FTLD families with three major FTLD-related mutations in the microtubule-associated protein tau (*MAPT*), progranulin (*GRN*), or chromosome 9 open reading frame 72 (*C9orf72*) genes using a standardized battery of measures. The participants are either mutation carriers with mild dementia due to FTLD spectrum diseases, mutation carriers minimally symptomatic yet non-demented (mild cognitive impairment [MCI-cog] or mild behavioral change [MCI-beh]), asymptomatic mutation carriers, or clinically normal (CN) members without the mutations themselves. The predominant phenotype in the family must be behavioral and/or cognitive and not motor (eg, motor neuron disease, parkinsonism), but

participants do not need to know their own genetic status. The ARTFL Consortium is composed of 18 institutions in North America (eight of which are also LEFFTDS sites) with similar study targets and methods to LEFFTDS, but also includes sporadic FTLD participants and participants with a strong familial history of FTLD but without a known family mutation.

The participants with dementia/motor neuron disease/movement disorder due to bvFTD, svPPA, nfvPPA, logopenic variant primary progressive aphasia (lpvPPA), FTD-ALS, ALS, CBS, PSP-RS, and AD were diagnosed and classified based on the widely accepted published criteria for each disease.[8–13] Asymptomatic or mildly symptomatic participants who were in kindreds with known FTLD-related gene mutations fell into three groups. Participants who did not have any detectable cognitive impairment, behavioral disturbances, or motor impairment were categorized as "CN." "MCI-cog" included all types of MCI (single domain amnestic MCI, multiple domain amnestic MCI, single domain non-amnestic MCI, and multiple domain non-amnestic MCI), and was applied to participants who showed objective cognitive decline not normal for age but not demented and were capable of essentially normal functioning in activities.[14–16] "MCI-beh" was applied to participants who exhibited early mild changes in BEHAV (including: 1, behavioral disinhibition; 2, apathy/inertia; 3, loss of sympathy/empathy; 4, perseverative/stereotyped/compulsive/ritualistic behavior; and 5, hyperorality/dietary changes), but were not demented nor met criteria for probable bvFTD.[8] 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-behavior is a loosely defined clinical diagnosis which will be operationalized with more rigor in the future after more data are gathered and analyzed.

2.3 CDR plus NACC FTLD and CDR evaluation

CDR plus NACC FTLD and CDR were completed by clinicians who have years of experience using these measures as part of NACC Uniform Data Set at NIA-funded ADC programs. CDR-SB and each rating for the six domains and the global CDR rating were decided according to the widely used CDR scoring rules.[2] The added BEHAV and LANG domains for CDR plus NACC FTLD and the CDR plus NACC FTLD sum of boxes (FTLD-CDR-SB) were rated according to published procedures[3, 4]. Additional information available for the raters included medical history and neurological examination of the participants. The global CDR plus NACC FTLD score was calculated according to the scoring rules created by a group of FTLD experts in the ARTFL/LEFFTDS Consortium (Figure 1). Ratings for individual domains were determined independently of the neuropsychological data.

An interrater reliability study was performed between two institutions, University of California San Francisco and Mayo Clinic Rochester, on 40 participants at the baseline visit of the ARTFL/LEFFTDS Consortium. Each site evaluated 20 participants in person and rated the other 20 participants according to the detailed written descriptions created by the other site that performed the in-person evaluation. These written descriptions included free descriptions of clinical information such as chief complaint, history of present illness, social history, past medical history, current medications, physical examination, neurological

examinations, and any other information from participants and informants useful in rating the individual domains of the CDR plus NACC FTLD and the CDR. They were created from information obtained by interview of participants and their reliable informants, and the objective neurological and physical examinations performed by neurologists. Each site was blinded to the other site's ratings and clinical diagnoses. All of the protected health information was removed. The 40 cases were selected to include not only neurodegenerative disorders but also MCI-cog, MCI-beh, and CN participants to confirm that the scale is sensitive in the preclinical phase of FTLD.

2.4 Other clinical rating scales and neuropsychological tests

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] (lower score signifies more impairment), Unified Parkinson's Disease Rating Scale[18] (higher score signifies more motor impairment), and Progressive Supranuclear Palsy Rating Scale[19] (higher score signifies more motor impairment). The Functional Activities Questionnaire[20] (FAQ; higher score signifies more functional impairment) and Neuropsychiatric Inventory Questionnaire[21] (higher score signifies more neuropsychiatric morbidity) were completed by interview with participants' informants.

2.5 Analyses

Cross-sectional analyses were performed on the baseline visit of the ARTFL/LEFFTDS Consortium study. Demographic, clinical, and genetic characteristics of the study participants were compared among each clinical diagnostic group, and were analyzed by the Kruskal-Wallis test to assess differences. The frequency of global CDR plus NACC FTLD or global CDR scores for MCI-beh, MCI-cog, and three subtypes of FTDs (bvFTD, svPPA, and nfvPPA) were calculated to evaluate how well the CDR plus NACC FTLD and CDR detected the early clinical changes of the diagnoses. Weighted kappa statistics measured interrater reliability of the two sites on the global CDR plus NACC FTLD score and the global CDR score, and the intraclass correlation (ICC) measured interrater reliability on the CDR plus NACC FTLD-SB and CDR-SB. Weighted Kappa statistics or ICC values of > 0.8 are considered having a very good strength of agreement. Statistical analyses were performed using SAS (version 9.4; SAS Institute, Inc., Cary, North Carolina).

3 RESULTS

The CDR plus NACC FTLD and CDR assessment by diagnostic groups, along with the demographic, clinical, and genetic data for the baseline visit of the 970 ARTFL/LEFFTDS Consortium study participants, are shown in Table 1. Most participants with the diagnoses of CN and MCI-beh were in kindreds of familial FTD with known FTLD related genetic mutations. The MCI-beh participants were younger than the MCI-cog participants. Although the CDR-SB was smaller in the MCI-beh participants than in the MCI-cog participants, the CDR plus NACC FTLD was larger in the MCI-beh participants. Among three subtypes of FTDs, the bvFTD participants were the youngest and scored the highest on the global CDR, CDR-SB, global CDR plus NACC FTLD, and CDR plus NACC FTLD-SB. The bvFTD

participants also were more likely to have known FTLD-related genetic mutations. The nfvPPA participants were the oldest and scored the lowest on these four global and sum of boxes scores. The nfvPPA participants also scored the lowest on the BEHAV domain.

The frequency and distribution of global CDR plus NACC FTLD and CDR scores of the diagnostic groups of MCI-beh, MCI-cog, and FTDs (bvFTD, svPPA, and nfvPPA) are shown in Figure 2. All 970 participants were rated with both the CDR plus NACC FTLD and CDR. Among the FTDs, the bvFTD participants had the highest frequency of the maximum global rating (global score of 3 = floor effects), 10% by CDR plus NACC FTLD and 5% by CDR. All bvFTD participants who were rated with a global CDR plus NACC FTLD score of 3 and were rated on the FAQ had FAQ scores of 25 or more (max functional impairment: 30) and half of the participants were rated as 30. The maximum global rating in the svPPA participants was seen in 1% by the CDR plus NACC FTLD and 0% by the CDR and maximum global rating in the nfvPPA participants was seen in 3% by both the CDR plus NACC FTLD and CDR. No MCI-beh or MCI-cog participant was rated as global score of 2 or 3 by CDR or CDR plus NACC FTLD. Despite their diagnoses of dementia or mild cognitive/behavioral impairment, 29% of the MCI-beh, 23% of the MCI-cog, and 21% of the nfvPPA participants were rated normal (global score of 0) by CDR.

The detailed profile of CDR plus NACC FTLD and CDR in these global CDR scores of 0 cases are listed in Table 2. Eighty-one percent of the FTD cases with the global CDR score of 0 were the nfvPPA participants. The CDR plus NACC FTLD was able to detect their impairment (global score of > 0) in all of the global CDR score of 0 cases. Most of these cases had abnormal BEHAV and/or LANG ratings, resulting in global CDR plus NACC FTLD score > 0. Three MCI-cog cases had ratings of 0 for BEHAV and LANG, but had an abnormal rating within the six domains of the CDR (cases 6,10,11). In these cases, MEM domain was rated as 0; thus, the global CDR score was rated as 0 and the global CDR plus NACC FTLD score was rated as > 0.

Table 3 demonstrates the interrater reliability study regarding two sites and 40 study participants, and the ratings for each case for each of the sites are shown in the supporting information. Most participants were middle aged, and all were white with nearly equal sex ratio and at least 12 years of education. All participants with the diagnoses of CN, MCI-beh, and MCI-cog were members of familial FTD with either *MAPT*, *c9orf72*, or *GRN* mutations. Twenty participants (50%) were CN; nine participants (22.5%) were either MCI-beh or MCI-cog; eleven participants (27.5%) were diagnosed as FTD, ALS, or AD. Interrater reliability of global CDR plus NACC FTLD scores assessed by weighted kappa statistic was very good (weighted $\kappa = 0.84$ [95% confidence interval (CI) 0.72–0.96]) and comparable to the global CDR scores (weighted $\kappa = 0.84$ [95% CI 0.72–0.97]). Interrater reliability of the CDR plus NACC FTLD-SB assessed by ICC was also very good (ICC = 0.95 [95% CI 0.87–0.98]) and comparable to the CDR-SB (ICC = 0.95 [95% CI 0.86–0.98]).

DISCUSSION

FTLD is a spectrum of neuropathologically and clinically heterogeneous disorders, making it difficult to use a single outcome measure to conduct clinical trials with disease-modifying therapies. The CDR plus NACC FTLD, which includes the two additional BEHAV and LANG domains, was developed to enhance the utility of the CDR in FTLD spectrum disorders, and to be used for future clinical trials in FTLD.3 Though the CDR plus NACC FTLD had shown its utility in evaluating unique clinical features of FTLD, there had been no global rating for the CDR plus NACC FTLD.[3, 4, 22–24] One of the primary goals for the ARTFL/LEFFTDS Consortium study is to support the development of new diagnostic instruments and identify potential participants for clinical trials. From this objective, we developed global score and scoring rules for CDR plus NACC FTLD, which was shown to have very good interrater reliability comparable to global CDR scores, to enhance the utility of CDR plus NACC FTLD in clinical trials and clinical research.

As demonstrated with our analysis, the CDR was not sensitive in detecting early symptomatology of FTLD. The CDR was originally developed for assessing global functions and cognition on AD dementia patients. While there were domains for MEM impairment and disorientation typically seen in AD patients, there were no domains on behavioral disturbances or language impairment. Furthermore, the six domains of the CDR were not weighed equally in determining the global CDR score; the MEM domain was designated as the primary domain and the other five domains as secondary. If only one domain, other than the MEM domain, is rated > 0, global CDR is calculated to be 0. In developing the scoring rules for the global CDR plus NACC FTLD rating, eight domains, including the BEHAV and LANG domains, were weighted equally to determine the global score, and the global CDR plus NACC FTLD score will become > 0 if any of the eight domains were rated as > 0.

The CDR global rating of 0 = normal cognition/function was seen in > 25% of the MCI-beh, MCI-cog, and nfvPPA participants despite their diagnoses. We previously reported that the mild nfvPPA participants in the ARTFL/LEFFTDS Consortium study tended to have less frequent impairment on the six domains of the CDR, resulting in difficulty in detecting clinical features by the CDR.7 With the CDR plus NACC FTLD and the global scoring rules we developed, we were able to detect clinical impairment in all of the MCI-beh, MCI-cog, and FTD cases who had a global CDR score of 0. There was a higher frequency of a global rating of 3 = severe impairment seen in the bvFTD participants than in the svPPA and the nfvPPA participants. One of the reasons for this result might be that, although the ARTFL/LEFFTDS Consortium study targeted the mild phase of FTLD, severely impaired FTD participants were sometimes registered in the study to co-register other preclinical members of kindreds of the familial FTD. For this purpose, the bvFTD participants were more likely to have known FTLD-related gene mutations and to be enrolled in the study even if they were severely impaired and untestable. Indeed, all of the bvFTD participants with the global CDR plus NACC FTLD score of 3 and who were rated on the FAQ had FAQ scores of 25 or more, which indicated severe functional impairment.

Our study has several limitations. First, it was only conducted cross-sectionally, and future longitudinal data analyses to assess the usefulness of the CDR plus NACC FTLD in detecting the chronological clinical changes are needed. In addition to longitudinal data analyses, it is desirable to determine what will be the optimal combination of neuropsychological assessments to complement CDR plus NACC FTLD. Understanding associations with biofluid and/or neuroimaging biomarkers will also be important. Although our diagnostic classification of the study participants was based on widely used published clinical criteria, we did not have neuropathological confirmation. Our study participants were largely highly educated, white, and lacked diversity. Future research on more diverse populations is required for application of our findings to FTLD spectrum disorders universally. Our entire study cohort at baseline was heavily weighted toward CN and bvFTD, while individuals with MCI-beh and MCI-cog were fewer. Although the duration of the MCI in FTLD is relatively short in general and it was difficult to recruit participants in this phase, we expect to be able to evaluate this important MCI period through our longitudinal study of FTLD mutation carriers. From this purpose, we believe having a large number of preclinical FTLD participants who are likely to develop into MCI is very important. Finally, we had a relatively small number of participants and uneven group size for interrater reliability study. We intended to include earlier phases of FTLD to match to our hypothesis that CDR plus NACC FTLD was especially useful in detecting early clinical changes of FTLD, and succeeded to have a moderate number of MCI cases. On the other hand, half of our cohort was CN, and only one case of PPA was included. In addition, due to the restriction of ARTFL/LEFFTDS Consortium, we were able to review only written (but not audio or video) descriptions of cases from participating investigators. We are currently planning to have video recordings for interrater reliability analyses in the ARTFL LEFFTDS Longitudinal Frontotemporal Lobar Degeneration (ALLFTD) study, which is the next phase of our multicenter FTLD program, which begins in early 2020.

The unique strength of our study was the large number of CN and preclinical participants who were members of kindreds with familial FTLD. The global CDR plus NACC FTLD score and scoring rules presented here had very good interrater reliability. The CDR plus NACC FTLD and the two additional BEHAV and LANG domains were uniquely informative, especially in the early/mild phase of FTLD, which is an optimal time window for testing disease-modifying therapies targeting the pathologic FTLD related proteins or genes. The CDR plus NACC FTLD and its global score will also be useful in natural history studies and potentially in clinical trials in FTLD spectrum disorders.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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David Knopman—serves on the Data and Safety Monitoring Board of the Dominantly Inherited Alzheimer Network Trials Unit (DIAN-TU) study; is a site PI for clinical trials sponsored by Biogen, Lilly, and the University of Southern California; and is funded by NIH.

John Kornak—has provided expert witness testimony for Teva Pharmaceuticals in *Forest Laboratories Inc. et al. v. Teva Pharmaceuticals USA, Inc.*, Case Nos. 1:14-cv-00121 and

1:14-cv-00686 (D. Del. filed January 31, 2014 and May 30, 2014) regarding the drug Memantine; for Apotex/HEC/Ezra in *Novartis AG et al. v. Apotex Inc.*, No. 1:15-cv-975 (D. Del. filed October 26, 2015) regarding the drug Fingolimod. He has also given testimony on behalf of Puma Biotechnology in *Hsingching Hsu et al. v. Puma Biotechnology, INC.*, *et al.* 2018 regarding the drug Neratinib. He receives research support from the NIH.

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John Q. Trojanowski—may accrue revenue in the future on patents submitted by the University of Pennsylvania wherein he is coinventor and he received revenue from the sale of Avid to Eli Lily as coinventor on Aβ amyloid imaging-related patents submitted by the University of Pennsylvania. He receives research support from the NIH and several nonprofits.

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HIGHLIGHTS

- We created scoring rules for the global CDR plus NACC FTLD rating.
- The CDR plus NACC FTLD was completed at the baseline visit in 970 participants of the ARTFL/LEFFTDS Consortium.
- The CDR plus NACC FTLD showed very good interrater reliability.
- The CDR plus NACC FTLD was especially useful in the mild non-fluent/agrammatic variant PPA.

RESEARCH IN CONTEXT

1. Systematic review: The authors reviewed the literature using traditional (eg,PubMed) sources and meeting abstracts and presentations. The CDR plus NACC FTLD (previously called FTLD-CDR) was developed in 2008 to improve characterization of cognitive and global function in FTLD, although there had been no global rating scale for it. These relevant citations are appropriately cited.
2. Interpretation: The global scoring system we created for the CDR plus NACC FTLD is valuable for use in persons with FTLD syndromes.
3. 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.

1) If all domains are 0, the global CDR® plus NACC FTLD score is 0.

2) If the maximum domain score is 0.5, the global CDR® plus NACC FTLD score is 0.5.

3) If the maximum domain score is above 0.5 in any domain, then the following applies:

A) If the maximum domain score is 1 and all other domains are 0, the global CDR® plus NACC FTLD score is 0.5.

B) If the maximum domain score is 2 or 3 and all other domains are 0, the global CDR® plus NACC FTLD score is 1.

C) If the maximum domain score occurs only once, and there is another rating besides zero, the global CDR® plus NACC FTLD score is one level lower than the level corresponding to maximum impairment

D) If the maximum domain score occurs more than once, then the global CDR® plus NACC FTLD score is that maximum domain score.

Figure 1.

The scoring rules for determining the global CDR plus NACC FTLD score

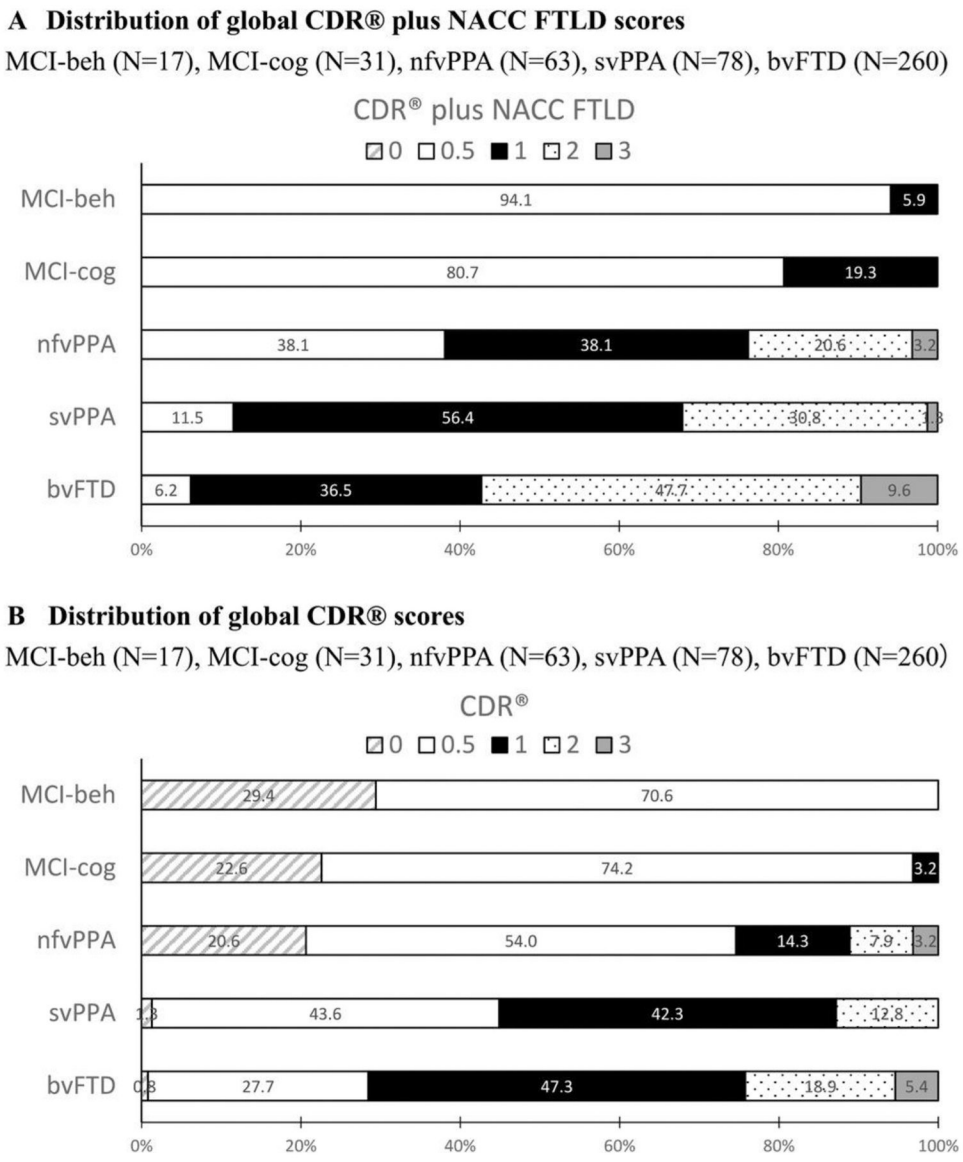

Figure 2.
Distribution of global CDR and CDR plus NACC FTLD scores by diagnostic groups

Table 1.

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

Clinical feature	Asymptomatic/ preclinical	Prodromal		Dementia/motor neuron disease/movement disorder									
Diagnostic group	**CN**	**MCI-cog**	**MCI-beh**	**bvFTD**	**FTD/ALS**	**ALS**	**nfvPPA**	**svPPA**	**lpvPPA**	**CBS**	**PSP-RS**	**AD**	***P*-value***
N	277	31	17	260	20	10	63	78	10	76	113	15	
Age at visit	44.5 (14.1)	60.0 (10.6)	55.5 (11.0)	61.8 (9.4)	62.6 (8.6)	62.3 (5.1)	69.7 (8.0)	65.8 (6.7)	68.1 (9.7)	67.0 (8.9)	69.2 (6.7)	67.3 (6.8)	<0.001
Age at onset	NA	55.9 (10.5)	51.6 (10.1)	56.4 (9.4)	59.4 (7.8)	59.5 (5.4)	65.0 (7.9)	60.1 (7.3)	64.9 (9.3)	62.7 (8.8)	63.5 (7.0)	62.7 (5.8)	<0.001
Sex (% female)	61.7	41.9	35.3	40.0	45.0	40.0	57.1	48.7	60.0	51.3	46.9	33.3	
Race (% white)	97.5	100.0	100.0	95.0	100.0	100.0	95.2	97.4	100.0	97.4	86.7	86.7	
Education (years)	15.6 (2.4)	15.3 (2.8)	14.9 (2.3)	15.6 (2.7)	15.2 (2.5)	15.4 (2.5)	16.1 (3.0)	16.6 (2.6)	16.2 (2.7)	15.8 (2.9)	16.2 (2.6)	15.5 (3.0)	0.091
MAPT (%)	88 (31.8)	3 (9.7)	3 (17.6)	22 (8.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (6.7)	
C9orf72 (%)	94 (33.9)	14 (45.2)	6 (35.3)	35 (13.5)	5 (25.0)	7 (70.0)	0 (0.0)	2 (2.6)	0 (0.0)	1 (1.3)	0 (0.0)	1 (6.7)	
GRN (%)	63 (22.8)	4 (12.9)	4 (23.5)	9 (3.5)	0 (0.0)	0 (0.0)	3 (4.8)	0 (0.0)	1 (10.0)	2 (2.6)	0 (0.0)	2 (13.3)	
Any known mutations	249 (89.9)	21 (67.7)	13 (76.5)	70 (26.9)	5 (25.0)	7 (70.0)	4 (6.3)	3 (3.8)	1 (10.0)	3 (3.9)	0 (0.0)	4 (26.7)	
MoCA total score	27.3 (2.3)	23.8 (4.7)	24.5 (3.3)	17.9 (7.2)	17.0 (6.3)	21.2 (7.4)	19.5 (7.0)	16.3 (6.3)	12.6 (5.9)	22.0 (5.1)	20.6 (5.5)	15.2 (9.6)	<0.001
FAQ total score	0.1 (0.7)	3.5 (5.2)	3.0 (5.2)	18.9 (8.7)	20.1 (8.6)	8.8 (9.4)	9.6 (10.3)	13.6 (7.4)	13.7 (10.6)	12.3 (8.9)	17.2 (7.8)	15.8 (8.4)	<0.001
NPI-Q total score	1.1 (2.1)	6.5 (4.8)	9.6 (6.8)	11.1 (6.9)	10.2 (5.7)	3.8 (4.4)	4.1 (4.1)	9.6 (6.3)	2.8 (3.3)	4.9 (4.1)	6.0 (4.8)	11.6 (6.0)	<0.001
UPDRS total score	0.0 (0.0)	2.3 (3.4)	0.3 (0.9)	4.5 (9.3)	6.9 (9.0)	4.8 (4.3)	7.7 (10.1)	1.5 (3.5)	0.6 (1.8)	23.2 (15.1)	29.0 (14.2)	5.4 (6.0)	<0.001
Global CDR	0.0 (0.0)	0.4 (0.3)	0.4 (0.2)	1.2 (0.7)	1.4 (0.8)	0.7 (0.5)	0.7 (0.7)	0.9 (0.5)	0.8 (0.5)	0.8 (0.6)	0.9 (0.7)	1.0 (0.6)	<0.001
Global CDR plus NACC FTLD	0.0 (0.0)	0.6 (0.2)	0.5 (0.1)	1.6 (0.7)	1.7 (0.8)	1.0 (0.8)	1.1 (0.7)	1.3 (0.6)	1.2 (0.6)	1.0 (0.6)	1.5 (0.8)	1.5 (0.7)	<0.001
CDR-SB	0.0 (0.0)	1.5 (1.2)	1.1 (0.8)	6.7 (3.9)	7.3 (4.3)	3.2 (3.1)	3.2 (3.7)	4.6 (2.7)	3.9 (3.1)	3.8 (3.2)	5.8 (3.8)	6.4 (3.5)	<0.001
CDR plus NACC FTLD-SB	0.0 (0.0)	2.1 (1.6)	2.1 (1.2)	9.2 (4.9)	9.7 (5.2)	4.2 (3.8)	5.2 (4.6)	6.9 (3.5)	5.6 (3.8)	4.9 (3.8)	7.4 (4.5)	7.9 (4.7)	<0.001
LANG	0.0 (0.0)	0.2 (0.3)	0.1 (0.2)	0.8 (0.8)	1.0 (0.8)	0.4 (0.3)	1.5 (0.7)	1.3 (0.6)	1.4 (0.6)	0.6 (0.6)	0.9 (0.7)	0.4 (0.6)	<0.001
BEHAV	0.0 (0.0)	0.4 (0.5)	0.9 (0.4)	1.7 (0.7)	1.5 (0.7)	0.7 (0.8)	0.5 (0.6)	1.1 (0.7)	0.3 (0.4)	0.4 (0.5)	0.8 (0.7)	1.1 (1.0)	<0.001

The genetic data refer 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.

Values in table are mean (standard deviation).

Abbreviations: AD, Alzheimer's disease; CBS, corticobasal syndrome; CDR-SB, sum of the boxes score of the six domains of the CDR; CDR plus NACC FTLD-SB, sum of the boxes score of the six domains of the CDR plus the behavior/comportment and language domains; CN, clinically normal; FAQ, Functional Activity Questionnaire (higher score = more impairment); lpvPPA, logopenic variant primary progressive aphasia; MoCA, Montreal Cognitive Assessment (higher score = less impairment); nfvPPA, non-fluent/agrammatic variant primary progressive aphasia; NPI-Q, Neuropsychiatric

Inventory-Questionnaire (higher score = more impairment); PSP-RS, Progressive Supranuclear Palsy Rating Scale (higher score = more impairment); svPPA, semantic variant primary progressive aphasia; UPDRS, Unified Parkinson's Disease Rating Scale motor subtest (higher score = more impairment).

*Comparisons simultaneously made among all diagnostic groups using the Kruskal-Wallis test.

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Table 2.

The MCI and FTLD participants who were rated global CDR = 0

Case	Diagnostic group	Global CDR	Global CDR plus NACC FLTD	BEHAV	LANG	CDR-SB	CDR plus NACC FTLD-SB
1	MCI-beh	0	0.5	1	0	0	1.0
2	MCI-beh	0	0.5	0.5	0	0	0.5
3	MCI-beh	0	0.5	0.5	0	0.5	1.0
4	MCI-beh	0	0.5	1	0	0	1.0
5	MCI-beh	0	0.5	0.5	0	0.5	1.0
6	MCI-cog	0	0.5	0	0	0.5	0.5
7	MCI-cog	0	0.5	1.0	0.5	0	1.5
8	MCI-cog	0	0.5	0	0.5	0.5	1.0
9	MCI-cog	0	0.5	0.5	0.5	0.5	1.5
10	MCI-cog	0	0.5	0	0	0.5	0.5
11	MCI-cog	0	0.5	0	0	0.5	0.5
12	MCI-cog	0	0.5	0	0.5	0.5	1.0
13	bvFTD	0	1	1	0	2.0	3.0
14	bvFTD	0	0.5	0.5	0	0	0.5
15	svPPA	0	1	0.5	2	0	2.5
16	nfvPPA	0	1	0.5	2	0.5	3.0
17	nfvPPA	0	2	0	3	0.5	3.5
18	nfvPPA	0	0.5	0	1	0.5	1.5
19	nfvPPA	0	1	0.5	2	0.5	3.0
20	nfvPPA	0	1	0	2	0	2.0
21	nfvPPA	0	0.5	0	1	0	1.0
22	nfvPPA	0	0.5	0.5	1	0	1.5
23	nfvPPA	0	0.5	0.5	1	0.5	2.0
24	nfvPPA	0	0.5	0.5	1	0	1.5
25	nfvPPA	0	0.5	0	0.5	0	0.5
26	nfvPPA	0	0.5	0	1	0	1.0
27	nfvPPA	0	0.5	0	1	0.5	1.5
28	nfvPPA	0	0.5	0	0.5	0	0.5

Abbreviations: BEHAV, behavior/comportment/personality; bvFTD, behavioral variant frontotemporal dementia; CDR-SB, sum of the boxes score of the six domains of the CDR; CDR plus NACC FTLD-SB, sum of the boxes score of the six domains of the CDR plus the behavior/comportment and language domains; FTLD, frontotemporal lobar degeneration; LANG, language; MCI, mild cognitive impairment; MCI-beh, mild behavioral change; MCI-cog, mild cognitive impairment; nfvPPA, non-fluent/agrammatic variant primary progressive aphasia; svPPA, semantic variant primary progressive aphasia.

Table 3.

Interrater reliability study

A. Demographic and clinical data	
Age at visit (mean ± SD)	52.3 ± 12.0
Sex (male:famale)	21:19
Education in years (mean ± SD)	15.6 ± 2.0
Race	100% white
Diagnosis	N (%)
CN	20 (50.0%)
MCl-beh,	4 (10.0%)
MCl-cog	5 (12.5%)
bvFTD	8 (20.0%)
nfyPPA	1 (2.5%)
AD	1 (2.5%)
ALS	1 (2.5%)

B. Weighted kappa and ICC statistics

Description	**Estimate**	**Lower 95% CL**	**Upper 95% CL**
Weighted Kappa for global CDR plus NACC FTLD	0.842	0.723	0.960
Weighted Kappa for global CDR	0.843	0.715	0.971
ICC for CDR plus NACC FTLD sum of boxes	0.947	0.873	0.983
ICC for CDR sum of boxes	0.945	0.855	0.983

Abbreviation: AD, Alzheimer's disease; bvFTD, behavioral variant frontotemporal dementia; CL, confidence level; ICC, intraclass correlation; MCI-beh, mild behavioral change; MCI-cog, mild cognitive impairment; nfvPPA, non-fluent/agrammatic variant primary progressive aphasia.