Motor function decline correlates with behavioral impairment in *C9orf72* mutation carriers

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Expansion mutations in the *C9orf72* gene are associated with clinical presentations of amyotrophic lateral sclerosis (ALS), frontotemporal dementia (FTD), and mixed ALS-FTD features.¹ Clinical phenotypes in neurodegenerative disorders have been attributed to the progression of degeneration along specific networks, implying that different networks produce symptoms of ALS and FTD. In a longitudinal study of *C9orf72* expansion carriers, we found that the ALS Functional Rating Scale (ALSFRS-R) declined in patients meeting the criteria for ALS or ALS-FTD, and the Frontal Behavioral Inventory (FBI) worsened in patients meeting the criteria for FTD/dementia or ALS-FTD.² To explore whether degeneration affects motor, cognitive, and behavioral domains differentially, we examined correlations between changes in ALSFRS-R scores, FBI scores, and cognitive measures over a 6-month period in *C9orf72* carriers.

Methods

All patients or legal representatives gave written informed consent for the Institutional Review Board-approved protocol (NCT01925196). Fifty participants with *C9orf72* mutations were enrolled in the study, with scheduled 6- and 18-month follow-ups at the National Institutes of Health Clinical Center.² At enrollment, 31 participants met the revised El Escorial criteria for ALS (mean age 56.8 ± 8.6 years, 64.5% men), of whom 7 also met the international consensus criteria for behavioral variant FTD (theaftd.org/wp-content/uploads/2018/03/Table-3-International-consensus-criteria-for-behavioural-variant-FTD.pdf) and were classified as “ALS-FTD”. Three men and 1 woman had FTD or dementia (mean age 63.6 ± 7.4) alone. Fifteen participants were asymptomatic (mean age 43.3 ± 9.7 years, 20% men). Motor function was assessed with the ALSFRS-R. Behavioral function was assessed using the FBI-ALS version,³ a caregiver interview rating the severity of behavioral changes not caused by physical limitations, with subscores for negative behaviors and disinhibition. Items confounded by a patient’s motor limitations were not rated (e.g., aphasia in anarthric patients), and scores were expressed as percentage of total possible points. Higher FBI scores indicate more severe behavioral impairment. Cognitive measures included trails, fluency, sorting, and 20-question subtests from the Delis-Kaplan Executive Function System⁴ and the Mattis Dementia Rating Scale (DRS-2),⁵ which assesses attention, initiation, construction, conceptualization, and memory. ALSFRS-R scores were obtained on 50 patients at enrollment, whereas 40 patients completed cognitive testing and 38 patient caregivers completed the FBI at the 6-month follow-up. Because most participants returning at 18 months were asymptomatic, only changes from enrollment to the 6-month time point were analyzed. One patient with ALS met the criteria for FTD at the follow-up. Pearson correlations were calculated with adjustment for covariates of age, education, and interval (IBM SPSS Subscription v.1.0.0.1072).

Data availability

The data will be submitted to a repository (neurobank.org) as participants complete study NCT01925196.

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Results

Higher scores on the FBI, indicating greater impairment, were correlated with a decline in the ALSFRS-R between enrollment and 6-month follow-up ($r = -0.519$, $p = 0.048$), particularly among patients with ALS (figure 1A, red symbols) or ALS-FTD (green symbols). Negative behavior FBI subscores increased mostly in patients with ALS and ALS-FTD, whereas disinhibition FBI subscores increased in patients with FTD (figure 1B). The most frequently affected items were apathy (e.g., loss of interest in friends), inflexibility, and loss of insight in patients with ALS; asponaneity, logopenia, and perseveration in patients with ALS-FTD; and impulsivity, irritability, and aggression in patients with FTD/dementia. Changes in scores of trails, sorting, fluency, and 20-question subsets were not correlated with changes in the ALSFRS-R. A weak

correlation between declining ALSFRS-R scores and worsening DRS-2 Initiation subscore was found ($r = 0.407$, $p = 0.028$).

Discussion

In this natural history study of patients with a *C9orf72* gene mutation, we found that behavioral impairment increased as motor function declined. This was because of worsening of negative behavioral scores in patients with ALS or ALS-FTD, in contrast to greater disinhibition subscores in patients with FTD alone. Negative items affected by physical disability were not included in scores. Most cognitive tests were not correlated with ALSFRS-R scores, but accurate assessment of some tasks in the cognitive batteries, for example, fluency, was limited by motor disability. Additional limitations of this study are the small sample size because of the relative rarity of *C9orf72* mutation carriers and dropout of more rapidly progressing patients longitudinally.

Pathologic studies have led to the proposal that degeneration spreads in a rostral-caudal pattern from the medial frontal cortex in FTD⁶ and in a corticofugal pattern from the motor cortex in ALS.⁷ Our data suggest that disease progression affects both motor and behavioral networks in *C9orf72* mutation carriers. This correlated decline in behavioral and motor function measures has implications for selection of outcome measures in clinical trials. The ALSFRS-R alone may be insufficient to follow disease impairments in patients with ALS. However, our analysis is based on a relatively small sample of *C9orf72* carriers. Further studies are needed to better understand whether interventions can affect behavioral, cognitive, and motor manifestations independently.

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Disclosure

The authors report no disclosures relevant to the manuscript. Go to Neurology.org/N for full disclosures.

Figure Six-month changes in clinical measures

(A) Decline in the ALS functional rating scale correlates with increased total scores on the ALS version of the FBI³ over 6 months in *C9orf72* carriers ($r = -0.519$, $p = 0.048$, line). Items confounded by a patient's motor limitations (e.g., aphasia and incontinence) were not included; thus, FBI scores are expressed as percentage of total possible points. Patients with ALS (red symbols) and ALS-FTD (green symbols) exhibited a greater decline in both scores than asymptomatic carriers (black symbols) and patients with dementia (blue symbols). Negative changes in FBI scores reflect the caregivers' rating of behavior as less severe than that at enrollment. (B) Changes in FBI subscores for negative behaviors and disinhibited behaviors between enrollment and 6-month follow-up. Changes were more prominent in negative behavior scores for patients with ALS (red) and ALS-FTD (green) and in disinhibited behavior scores for patients with FTD/Dementia (blue). ALS = amyotrophic lateral sclerosis; FBI = Frontal Behavioral Inventory; FTD = frontotemporal dementia.

Appendix Authors

Name	Location	Role	Contribution
Shreya Gandhi, MD	George Washington University Hospital Current location: University of Pennsylvania	Author Neurology Resident Rotator	Interpreted the data and drafted the manuscript
Jennifer Farren, RN	NINDS, NIH	Author Research Nurse	Major role in data acquisition and critical review of the manuscript
Mary Kay Floeter, MD, PhD	NINDS, NIH	Author Principal investigator	Project conception, statistical analysis of the data, and manuscript revision

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