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Clinical Study

Neurocognitive speed associates with frontotemporal lobar degeneration TDP-43 subtypes

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ABSTRACT

Frontotemporal lobar degeneration (FTLD) is pathologically heterogeneous with the TAR DNA binding protein 43 kDa (TDP-43) proteinopathy the most common substrate. Previous work has identified atrophy patterns across TDP-43 subtypes with Type A showing greater frontotemporal and parietal atrophy, Type C predominantly anterior temporal, and Type B predominantly posterior frontal. Despite neuroanatomical correlates of involvement, neuropsychological findings have been inconsistent. The current study utilized broader neurocognitive domains based on aggregated neuropsychological measures to distinguish between subtypes. We hypothesized that patterns of neurocognitive domain impairments would predict FTLD–TDP subtype. Fifty-one patients, aged 38–87, were identified post mortem with pathologically confirmed FTLD with TDP-43. Participants were classified into subtypes A, B, or C. Patients had completed neuropsychological assessments as part of their clinical evaluation. Six cognitive domains were created: Language; Cognitive Speed; Memory; Learning; Visuoperception; and Fluency. Binary logistic regression was conducted. All but three patients could be classified as FTLD–TDP Types A, B, or C: 26 as Type A; nine as Type B; and 13 as Type C. Cognitive Speed scores were associated with Types A and C ($p < 0.001$ and $p = 0.003$, respectively). Impaired performances on the Trail Making Test differentiated Types A and C. Worse Boston Naming Test and Logical Memory (Immediate) ($p < 0.05$) scores also increased the likelihood of Type C phenotype. Findings suggest Cognitive Speed associates with TDP-43 subtypes. Type C also demonstrated language-specific involvement. Differences between TDP-43 subtypes further supports the notion of differences in pathophysiology or topography across these types.

1. Introduction

Frontotemporal lobar degeneration (FTLD) is an umbrella term that encompasses a clinically and pathologically heterogeneous group of overlapping disorders. These disorders are characterized by varying degrees of behavioral, personality, and cognitive changes, as well as aphasia. While the most common form of dementia for those over the age of 65 is Alzheimer's disease, for those under 65, FTLD approaches comparable incidence rates.[1,2]

Neary et al. proposed clinical diagnostic criteria to differentiate three syndromes commonly associated with FTLD.[3] These included behavioral variant frontotemporal dementia (bvFTD), progressive non-fluent aphasia (PNFA), and semantic dementia (SD). Research has continued to evolve our understanding and clinical definition of these syndromes. We now consider possible, probable, and definite bvFTD categories,[4] which has been shown to be more sensitive than the older criteria. Research has also demonstrated that PNFA is not a homogeneous group and that PNFA patients can be reclassified into three different groups: agrammatic primary progressive aphasia; logopenic primary progressive aphasia; and primary progressive apraxia of speech.[5,6]

Pathologic findings in FTLD have evolved over the past two decades. Originally patients with FTLD were divided into those without any identified inclusions (dementia lacking distinctive histology) and those in which inclusions could be identified with silver impregnation. With the advent of immunohistochemistry, the former group was shown to have inclusions that were identified with ubiquitin immunohistochemistry and the latter with tau immunohistochemistry. Hence, dementia lacking distinctive histology became FTLD–ubiquitin (FTLD–U) while the other group became FTLD–tau. More recent research has shed light on the pathological markers that identify and differentiate FTLD–U into two major protein categories: FTLD–TAR DNA binding protein 43 kDa

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(FTLD–TDP) and FTLD–fused in sarcoma (FTLD–FUS). Therefore, FTLD is now separated into FTLD–tau, FTLD–TDP and FTLD–FUS.

Of these, FTLD–TDP is the most common substrate underlying the FTLD spectrum of disorders, and therefore an important entity for researchers to investigate. Further work on FTLD–TDP identified different distributions and morphological features of the TDP-43 immunoreactive inclusions that lead to the identification of four subtypes of FTLD–TDP, Types A–D.[7,8] Within the general population, clinicopathologic studies have shown that the most common FTLD–TDP subtype is FTLD–TDP Type A, accounting for 41% of FTLD–TDP patients, followed by Type B (34%), and Type C (25%)[1,7,9–11] (Fig. 1); Type D is extremely rare. It has been demonstrated that there are important clinicopathological associations between clinical syndromes and histological subtype[7,10] implying that pathologically subdividing FTLD–TDP is important and not arbitrary. FTLD–TDP Type A is associated most commonly with the bvFTD phenotype, as well as mutations associated with progranulin,[10] Type B with C9ORF72 repeat expansions,[12] and Type C with SD.

One of the inherent challenges in the appropriate diagnoses of FTLD is that the relationship between clinical diagnosis, imaging features, and pathology is not well defined. However imaging studies have been completed and have identified distinct patterns of atrophy across TDP-43 subtypes with Type A showing greater atrophy in frontotemporal and parietal regions, Type B showing posterior frontal atrophy, and Type C showing predominantly anterior temporal atrophy.[13] Thus far, studies investigating the neuropsychological profiles of FTLD have revealed modest but inconsistent findings. A review of the literature reveals a multitude of studies that fail to differentiate among the various pathologies that underlie FTLD. Studies investigating the neuropsychological performances reveal arbitrary clustering of neurocognitive domains such as language, executive functioning, and memory, or investigations of specific tests. This is somewhat limiting and potentially contributes to the copious inconsistencies that are reported, further confusing differentiation of the subtypes.

Therefore, the current study sought to investigate whether neurocognitive domains derived from previous factor analytic studies can differentiate pathologically confirmed FTLD–TDP phenotypes utilizing neurocognitive domains. We hypothesized that neurocognitive domains and impairment levels would differentiate the FTLD–TDP subtypes.

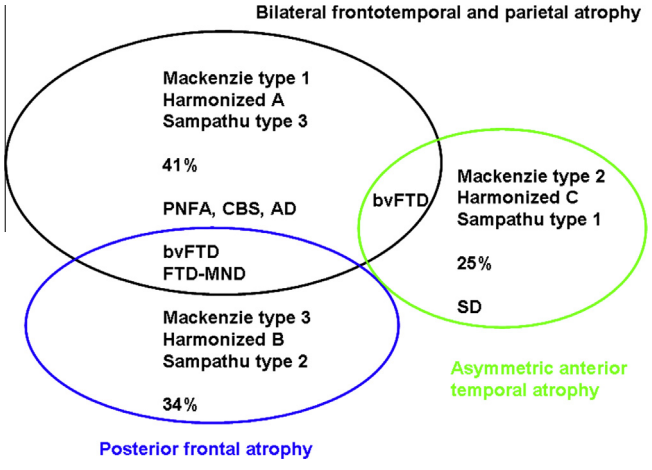

Fig. 1. Diagram showing the clinical diagnoses and patterns of atrophy associated with the three frontotemporal lobar degeneration–TAR DNA binding protein 43 kDa subtypes. AD = Alzheimer's disease, bvFTD = behavioral variant frontotemporal dementia, CBS = corticobasal syndrome, FTD–MND = frontotemporal dementia with motor neuron disease, PNFA = progressive nonfluent aphasia, SD = semantic dementia.

2. Methods

2.1. Participants

Fifty-one patients with antemortem clinical and neuropsychological evaluations and post mortem pathologic diagnosis of FTLD–TDP were identified from the neuropathology files of the Mayo Clinic, Rochester, MN, USA. Participants were classified into TDP-43 subtypes A, B, or C by a neuropathologist (D.W.D.) and neurologist (K.A.J.). All but three patients could be classified as FTLD–TDP Types A, B, or C: 26 as Type A; nine as Type B; and 13 as Type C. Table 1 shows the demographic data for the 51 patients by subtype. Patients with Type A ranged in age from 46 to 87 years; Type B ranged from 38 to 67; and Type C ranged from 53 to 78. Table 2 shows the associations between final clinical diagnoses and subtypes. Clinical diagnoses were based on the most current clinical criteria.

Data for this study were obtained from the first neuropsychological evaluation. The average time from first neuropsychological evaluation to the date of death was 6.5 years (standard deviation = 4.4 years). This study was approved by the Institutional Review Board at the Mayo Clinic.

2.2. Pathologic methods

All patients had neuropathological examinations according to the recommendations of the Consortium to Establish a Registry for Alzheimer's Disease.[14,15] This protocol was utilized based on standard neuropathological practices at the Mayo Clinic. Specifically, all patient samples underwent routine staining methods with hematoxylin and eosin, Bielschowsky silver, and immunohistochemistry to phosphorylated neurofilament, phospho-tau, α-synuclein, β-amyloid, and TDP-43, as previously described. All patients were diagnosed as FTLD–TDP based on published criteria (i.e., TDP-43 and ubiquitin only immunoreactive inclusions).

2.2.1. FTLD-TDP subclassification

Sections of frontal and medial temporal lobe, including hippocampal dentate granule cells, were restained using a DAKO autostainer with TDP-43 (rabbit polyclonal; 1:3000, Protein Tech Group, Chicago, IL, USA) and were reviewed by one neuropathologist (D.W.D.) who sub-classified each sample. The neuropathologist was blinded to clinical data. The harmonized classification scheme was chosen in this study to classify all samples.[16] Samples were classified as Type A if there were moderate to numerous TDP-43 immunoreactive neuronal cytoplasmic inclusions (NCI), as well as thin and short dystrophic neurites predominantly in layer II of neocortex and variable density of pleomorphic NCI in the dentate gyrus of the hippocampus; Type B if there were NCI in the neocortex and dentate

Table 1
Demographic information of patients with frontotemporal lobar degeneration by TDP-43 subtype.

	Type A	Type B	Type C
	n = 26	n = 9	n = 13
Age at evaluation	66.3 (12.30)	54.4 (10.48)	65.1 (7.52)
Education, years	13.8 (2.48)	13.9 (10.48)	12.7 (2.19)
Disease duration, years	7.1 (4.57)	4.5 (4.87)	7.6 (2.42)
Handedness			
Right	92.9%	57.1%	85.7%
Left	7.1%	42.9%	14.3%
Sex			
Male	38.5%	55.6%	38.5%
Female	61.5%	44.4%	61.5%

Data shown as mean (standard deviation) or percentage.