Putative Pathologic Correlates of Neurodegeneration in an Autopsy Series of FTLD-TDP Type C

Allegra Kawles, Yasushi Nishihara, Nathan Gill, Alex Feldman, Hui Zhang, Margaret E. Flanagan, M.-Marsel Mesulam, Changiz Geula, Eileen Bigio, Qinwen Mao, Tamar Gefen

Mesulam Center for Cognitive Neurology and Alzheimer's Disease, Feinberg School of Medicine, Northwestern University, Chicago, IL

Abstract

**Background.** The TDP-43 type C pathologic form of frontotemporal lobar degeneration (FTLD-TDP-C) is characterized by the presence of immunoreactive TDP-43 short and long dystrophic neurites (DNs), neuronal cytoplasmic inclusions (NCIs), and neuronal loss and gliosis (NL/G). Autopsy data show a tight correlation between FTLD-TDP-C cases and either behavioral variant frontotemporal dementia (bvFTD) or the semantic variant of primary progressive aphasia (PPA-S), offering the opportunity to study the putative correlates of neurodegeneration in clinical dementia syndromes. Here, we report regional distributions of pathologic TDP-43 and the extent of NL/G in cortical and subcortical regions in FTLD-TDP-C cases, and investigate the relationship between FTLD-TDP-C pathologic inclusions and NL/G.

**Methods.** Twenty-six cortical and subcortical regions were immunostained with a phosphorylated TDP-43 antibody and evaluated for long DNs, short DNs, and NCIs in ten cases with FTLD-TDP-C (PPA-S N=7; bvFTD N=3). NL/G was assessed using hematoxylin-eosin stained sections. Specimens were obtained from the Northwestern Alzheimer Disease Center. TDP pathology and NL/G were graded using a semiquantitative 5-point scale. We calculated a “neuron-to-inclusion” score (TDP-C mean score – NL/G mean score) for each region per case to assess the relationship between the extent of FTLD-TDP-C pathology vs NL/G.

**Results.** Distribution heat maps showed that long DNs were most abundant in the left superior temporal and inferior parietal gyri, and inferior frontal gyri bilaterally. The amygdala, caudate, and putamen were heavily affected. Interestingly, NL/G was most severe in bilateral temporal poles, amygdala, and trans/entorhinal cortices, and not necessarily the cortical regions most heavily affected by TDP-43. At both group and individual levels, linear mixed models showed that regions with the lowest “neuron-to-inclusion” score (little pathology and high neuronal loss) differed significantly from those with high “neuron-to-inclusion” scores (abundant pathology and preserved neuronal densities) across all three TDP markers (p<0.01).

**Conclusion.** In cases with FTLD-TDP-C, there is extensive TDP-43 pathology and NL/G in both cortical and subcortical regions. There appears to be an inverse relationship between the extent of TDP-positive inclusions and NL/G, which may reflect a process whereby inclusions disappear as their associated neurons are lost. Future studies will aim to investigate the mechanistic basis of this phenomenon to better understand the putative substrates of neurodegeneration in clinical dementia syndromes.