Clinical Phenotypes of FLTD-TDP Type E Cases

Case #1: Met formal criteria for bvFTD*: simple motor perseverations, "flattening of mood," loss of emotional warmth and empathy, hyperorality, loss of manners and decorum, utilization behavior. Had word finding difficulties, and after ECT for suspected depression prior to diagnosis of FTD was reported as largely uncommunicative. The patient was too impaired for detailed language testing at first visit and could not follow commands consistently. Elemental neurological exam exhibited bradykinesia but not rigidity. No clinical signs of MND reported with normal muscle strength and no fasiculations.

Case #2: Met formal criteria for bvFTD*: loss of manners and decorum, socially inappropriate, impulsive. Cognitive testing revealed executive impairment with minimal memory or visuospatial impairment. Clinical motor neuron disease reported near onset of behavior change.

Case #3: Met formal criteria for bvFTD*: impulsive, loss of manners and decorum, socially inappropriate, complex rituals, hyperorality, apathy. Cognitive testing revealed intact memory but impaired executive function. Visuospatial function was not tested. Later developed comprehension difficulties. No clinical signs of MND reported with normal muscle strength and no fasiculations.

Case #4: Behavioral phenotype with prominent social disorder but not enough information upon review of clinical records to meet full formal bvFTD criteria*: apathy, complex rituals of pacing, simple rituals of "panting," agitation and anxiety per report. The patient was hospitalized in inpatient psychiatry and received ECT treatment for suspected depression with psychosis as the etiology for these symptoms. Subject was reported to have executive difficulty with problems with concentration, attention and social discourse difficulty but formal neuropsychological testing records are not available. No clinical signs of MND reported with normal muscle strength and no fasiculations.

Case #5: Met formal criteria for bvFTD*: complex rituals, social disinhibition, hypersexual behavior, poor empathy. Cognitive testing revealed executive impairments with no spatial or memory impairment. No clinical signs of MND reported with normal muscle strength and no fasiculations.

Case #6: Met formal criteria for bvFTD*: socially inappropriate including approaching strangers, loss empathy, "flat affect," hyperorality with carbohydrate craving, perseverations. Language difficulties near onset consisting of mixed expressive (simplification of grammar) and receptive (difficulty following multi-step commands and difficulty understanding single words with surface dyslexia) features. At first visit there was no spontaneous speech, and only dysarthric one word answers. These language features did not meet formal criteria for a primary progressive aphasia (PPA) syndrome** as there was mixed semantic and non-fluent language features accompanied by a prominent social disorder which precludes a diagnosis of PPA. No clinical signs of MND reported with normal muscle strength and no fasiculations.

Case #7: Rapidly progressive neurologic syndrome, initially developing dysphagia, followed by difficulty walking, difficulty climbing stairs, and multiple falls which eventually required a walker then a wheelchair. Aside from dressing, patient was unable to perform activities of daily living. On examination, subject without frank dementia, able to communicate by writing but nearly anarthric. Multiple apraxias (speech, eye closure, tongue movement, hand movements), Parkinsonism, hypomimia, eye movement abnormalities (absent upgaze and decreased downgaze, impaired smooth pursuit with saccadic intrusion, reduced saccade amplitude with optokinetic strip). No clinical signs of motor neuron disease reported with normal muscle strength and no fasiculations.

*Retrospective review of clinical records according to modern clinical criteria for bvFTD (Rascovsky K, et al. Sensitivity of revised diagnostic criteria for the behavioral variant of frontotemporal dementia Brain. 2011 Sep;134(Pt 9):2456-77).

** Retrospective review of clinical records according to modern clinical criteria for PPA (Gorno-Tempini ML, et al. Classification of primary progressive aphasia and its variants. Neurology. 2011 Mar 15;76(11):1006-14).

Semi-quantitative TDP-43 Pathology Scores

Estimated semi-quantitative TDP-43 pathology scores across brain and spinal cord regions are provided. The amount of TDP-43 pathology appeared to be dependent on tissue preservation, length of fixation, and technical variability between immunohistochemistry runs, particularly given the generally light staining of GNFIs and grains which sometimes required optimization of anti-TDP-43 antibody dilutions. Despite these caveats, estimated pathology scores reflecting the density of TDP-43 inclusions are listed as 0=absent, rare, 1=low density, 2=moderate density, 3=high density, N/A=not available. In some areas such as the hippocampal dentate gyrus and brainstem, GFNI scores reflect total neuronal inclusion burden which included compact NCIs.

Case	Pathology	Frontal Cortex	Anterior Cingulate	Temporal Cortex	Parietal Cortex	Motor Cortex	Occipital Cortex
1	*GFNI*	2	2	2	1	2	0
	Grains	2	2	2	1	2	0
	Oligo	3	2	1	2	2	0
2	*GFNI*	3	3	3	3	2	Rare
	Grains	2	1	1	2	Rare	0
	Oligo	3	2	3	2	3	Rare
3	*GFNI*	3	2	2	1	2	0
	Grains	2	2	2	1	2	0
	Oligo	3	2	2	2	2	0
4	*GFNI*	2	2	2	2	1	0
	Grains	3	2	2	2	1	0
	Oligo	2	2	2	2	1	Rare
5	*GFNI*	2	1	2	1	2	0
	Grains	1	1	1	1	2	0
	Oligo	1	1	1	1	1	0
6	*GFNI*	2	3	2	2	2	0
	Grains	3	3	2	2	Rare	0
	Oligo	1	2	1	1	2	Rare
7	*GFNI*	Rare	N/A	1	1	N/A	0
	Grains	1	N/A	1	2	N/A	0
	Oligo	Rare	N/A	Rare	Rare	N/A	0

Case	Pathology	Amygdala	Hippocampus	Striatum	Globus Pallidus	Thalamus
1	*GFNI*	3	2	2	1	2
	Grains	2	0	2	3	2
	Oligo	3	Rare	1	2	2
2	*GFNI*	3	3	2	2	3
	Grains	2	0	1	2	Rare
	Oligo	2	Rare	1	3	1
3	*GFNI*	2	3	2	0	2
	Grains	2	2	2	1	Rare
	Oligo	1	1	1	Rare	1
4	*GFNI*	2	2	3	1	1
	Grains	Rare	2	2	1	1
	Oligo	2	1	1	2	Rare
5	*GFNI*	3	3	1	1	1
	Grains	3	2	1	1	1
	Oligo	2	2	Rare	1	1
6	*GFNI*	3	3	3	1	2
	Grains	2	1	1	2	1
	Oligo	1	2	1	2	1
7	*GFNI*	2	2	2	1	2
	Grains	1	1	1	1	2
	Oligo	1	Rare	Rare	Rare	Rare

Case	Pathology	Substantia Nigra	Midbrain	Pons	Medulla	Cervical Spinal Cord	Cerebellum
1	*GFNI*	3	2	0	3	2	0
	Grains	2	2	2	2	1	0
	Oligo	Rare	2	1	Rare	1	0
2	*GFNI*	3	2	3	3	1	0
	Grains	2	1	1	1	0	0
	Oligo	1	1	1	Rare	1	Rare
3	*GFNI*	1	0	2	2	3	0
	Grains	1	0	1	2	1	0
	Oligo	0	1	1	2	1	0
4	*GFNI*	3	2	Rare	1	3	0
	Grains	2	2	1	2	0	0
	Oligo	Rare	1	1	Rare	1	0
5	*GFNI*	Rare	Rare	Rare	1	2	0
	Grains	1	1	1	1	Rare	0
	Oligo	0	1	1	1	1	0
6	*GFNI*	Rare	2	Rare	2	1	0
	Grains	1	1	1	2	0	0
	Oligo	1	1	Rare	1	2	Rare
7	*GFNI*	Rare	Rare	0	Rare	N/A	0
	Grains	2	2	2	1	N/A	0
	Oligo	0	1	Rare	Rare	N/A	0