Frontotemporal Dementia

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Disclosure

I do not have any financial conflicts of interest to disclose.

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Outline

- Phenotype versus pathology
- FTD syndromes and their core features
- Anatomy, pathology, and management
- Key mimics and diagnostic pitfalls

Some slides were adapted from presentations by Trey Bateman, MPH, MD, VCU

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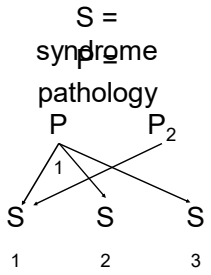
Phenotype vs Pathology

- We diagnose patients based on *syndrome,* not proteins.
- Some phenotypes align closely with specific pathologies, but many do not.
  - i.e. behavioral variant FTD can arise from different pathologies
  - One pathology can present in more than one clinical syndrome



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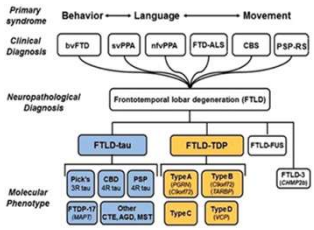
Frontotemporal Lobar Degeneration

FTLD refers to the broad *neuropathologic* category, including the FTD clinical syndromes (bvFTD, svPPA, nfvPPA) and related Parkinsonian tauopathies (PSP, CBS)



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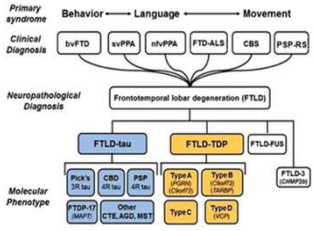
Frontotemporal Lobar Degeneration

- Neuropathologic spectrum defined by abnormal protein aggregates in neurons/glia
- Primarily tau (FTLD-Tau) and TDP-43 (FTLD-TDP), less frequently FUS
- Clinical and pathologic heterogeneity can make diagnosis challenging



(Irwin et al., 2014)

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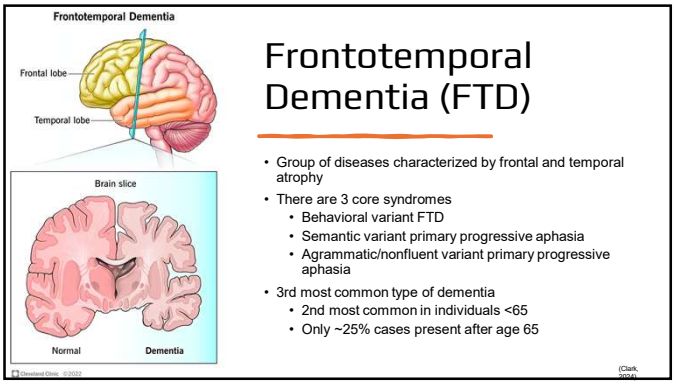

Frontotemporal Dementia (FTD)

- Group of diseases characterized by frontal and temporal atrophy
- There are 3 core syndromes
  - Behavioral variant FTD
  - Semantic variant primary progressive aphasia
  - Agrammatic/nonfluent variant primary progressive aphasia
- 3rd most common type of dementia
  - 2nd most common in individuals <65
  - Only ~25% cases present after age 65

(Clark, 2024)

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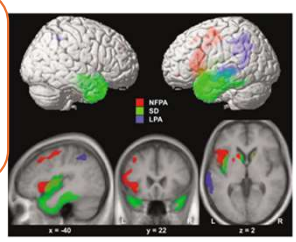
Primary Progressive Aphasias: Focal Onset Diseases

- Semantic dementia: anterior temporal lobe, L >> R
  - There is a R predominant variant
- Non-fluent PPA: Left perisylvian, frontal operculum, dorsal frontoinsular cortex
- Logopenic PPA: Posterior temporal / inferior parietal lobe



(Gorno-Tempini et al., 2004)

Image from Gorno-Tempini et al., 2004

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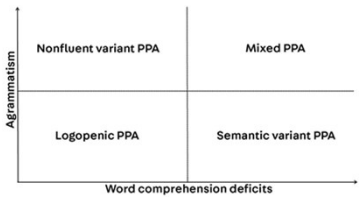
Semantic variant PPA - Clinical

- Semantic = general, abstract knowledge including facts, concepts, and word-meaning
- The sound of the word is no longer associated with the word's meaning
  - i.e. what a "dog" is
- Speak fluently
  - Sometimes no language disorder is obvious
- Can affect nonverbal semantics
  - Semantic dementia
  - Face recognition (prosopagnosia)



(Clark, 2024)

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Semantic variant PPA: Clinical

- Unable to recognize famous faces, animals, objects
- May provide lengthy, fluent replies without errors in speech or grammar
- May bluntly ask questions about common words
  - i.e. "what is mood?"
- Single-word repetition intact

(Clark, 2004)

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Semantic Dementia: Diagnostic Criteria

Core Features
- Impaired confrontational naming and single-word comprehension
  - Especially low-frequency words

At least 3 of 4
- Impaired object knowledge
- Surface dyslexia/dysgraphia → Knight, Broad, Sew, Colonel
- Spared repetition and grammar
- Spared motor speech

- Imaging supported: ATL

(Gorno-Tempini et al., 2011)

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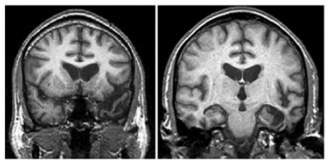
Semantic Dementia: Anatomy

- Anterior temporal lobe
  - Semantic "hub" – integrates meaning across sensory & language networks
- Always bilateral, but usually left >> than right
  - Right temporal variant exists
    - Odd, flat, rigid personality, emotionally distant (if you *really* don't understand 'kindness'…)



Images from Hodges JR, Davies RR, Patterson K. Semantic Dementia. In: Miller BL, Boeve BF, eds. *The Behavioral Neurology of Dementia*. New York, NY: Cambridge University Press; 2009.

(Hodges et al., 2009)

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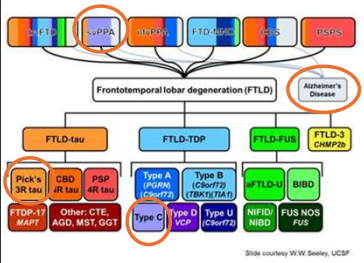
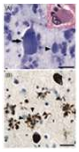
Semantic Dementia: Pathology



TDP-43: Most common pathology (69%)

Alzheimer's disease (25%)

Pick bodies: a specific type of tauopathy seen on histology (6%)



Circumscribed, cytoplasmic tau inclusions.
A: H&E stain
B: immunohistochemistry (tau)

(Grossman, 2010)

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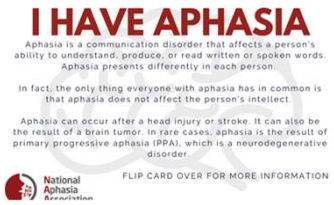
Semantic Dementia: Demographics and Management



- Average age 60, survival 8-9 years (range 2-19 years)
- Management
  - Explanation card
  - SLP
  - No value in AChE / Memantine
  - SSRI / Trazodone / low-dose antipsychotics for neuropsychiatric symptoms

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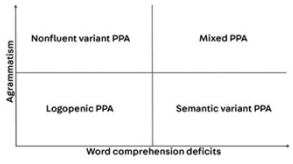
Nonfluent variant PPA: Clinical

- Agrammatism *or* difficulty with fluency
- Agrammatism - "telegraphic speech"
  - Omission of grammatical affixes / function words
  - May struggle with comprehension, esp complex sentences (passive voice)
- Disorders of fluency
  - Effortful, halting speech, sound distortions
  - Writing may be preserved
  - Swallowing issues, drooling can be seen



(Clark, 2024)

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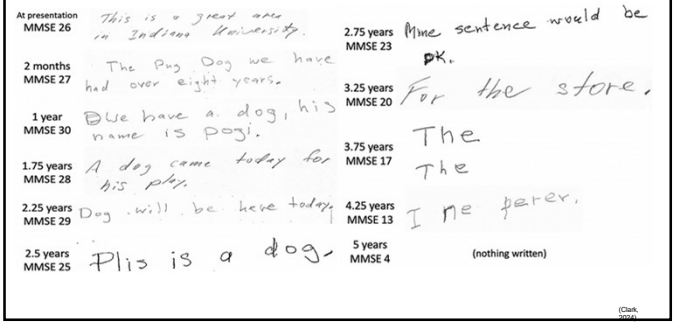
nfvPPA: Clinical



(Clark, 2024)

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Non-fluent variant PPA: Diagnostic Criteria

- Core: either agrammatism **or** apraxia of speech
  - Sometimes both, sometimes only one
- At least 2/3
  - Impaired comprehension of syntactically complex sentences
  - Spared single-word comp
  - Spared object knowledge
- Imaging: Left posterior frontal atrophy on MRI / hypometabolism on PET

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nfvPPA: Anatomy

- Left posterior frontal region and anterior insula
  - Areas supporting speech production and grammar
  - Bilateral involvement common
    - Right should give you more prosodic challenges

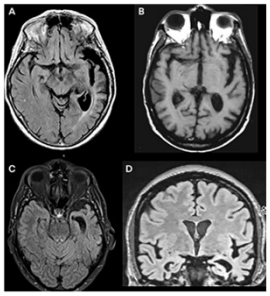

Image from Clark, 2024

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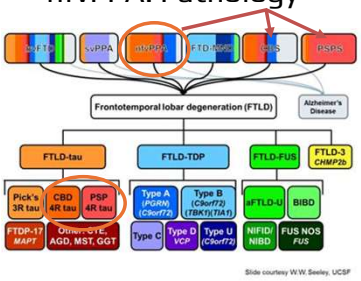
nfvPPA: Pathology



Tauopathy most common
- Overlap with CBD and PSP (4R-tau)
- May develop motor symptoms later in course

AD and TDP-43 much less common

(Grossman, 2010)

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nfvPPA: Demographics and Management

- Avg. age 60, survival ~ 7 years
  - But varies widely
- SLP
  - Augmentative communication
- Symptomatic treatment of neuropsychiatric symptoms
  - SSRIs
- Watch for Parkinsonian syndromes

(Grossman, 2012)

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bvFTD: Clinical

- Must be *progressive*
- Possible
  - ≥3/6 of the following:
    - Behavioral disinhibition
    - Apathy/inertia
    - Early loss of sympathy/empathy
    - Early OCD-like behavior
    - Hyperorality/dietary changes
    - Neuropsych profile with EF deficits
      - Sparing of memory, VS
- Probable
  - Meets criteria for possible

    +
  - Functional decline

    +
  - Structural or functional evidence of frontal and/or anterior temporal involvement

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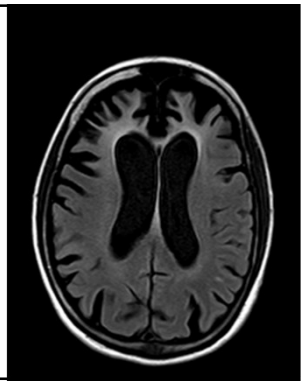
bvFTD: Anatomy

- OFC, ACC, anterior insula, and anterior temporal cortices
  - Often R>L, but symmetry is not uncommon
- Some correspondence between regions of atrophy and clinical syndromes
  - Apathy – medial frontal regions esp ACC
  - Disinhibition – R>L, OFC, anterior insula
  - Executive deficits – dorsolateral frontal cortex
  - Changes in eating – right insula or OFC



(Clark, [illegible])

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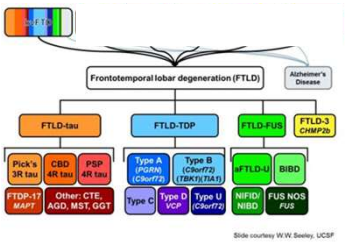
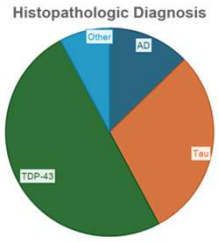
bvFTD: Pathology



Slide courtesy W.W. Seeley, UCSF



Data from Perry DC, Brown JA, Possin KL, et al. Clinicopathological correlations in behavioural variant frontotemporal dementia. *Brain*. 2017;140(12):3329-3345. doi:10.1093/brain/awx254

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bvFTD: Management

- Higher caregiver stress/depression compared with AD
  - Education, non-pharmacologic interventions
- AVOID cholinesterase inhibitors (can induce delirium, worsening of behavior)
  - Also, evidence that memantine does not help
- SSRIs/Trazodone: disinhibition, impulsivity, irritability, compulsive behaviors
- Amphetamines/amantadine: apathy
- Anticonvulsants (carbamazepine, lamotrigine): problematic sexual behaviors
- Topiramate: Hyperorality
- Antipsychotics: severe behavioral symptoms; monitor for Parkinsonism

(Tsai & Boxer, 2014)

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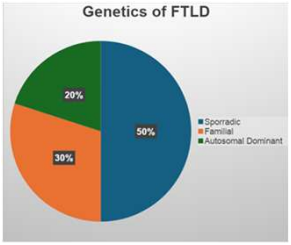
Genetics of FTD

- Sporadic (50%)
- Familial (30-40%)
  - ~40% (!) have some fam hx of dementia, ALS, Parkinson disease
- Autosomal dominant (10-20%)
  - 3 genes
    - MAPT
    - GRN
    - C9orf72
- Slightly younger age of onset in familial cases (53 vs 58 years)



(Clark, 2014)

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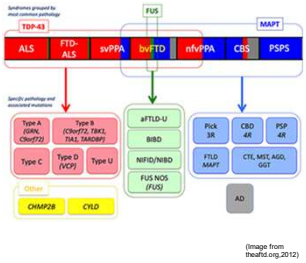
C9orf72

- Chromosome 9
- TDP-43 pathology
- Most common hereditary form
  - 5-20% of all cases
  - Familial FTD, ALS, FTD-MND
  - bvFTD most common
- More psychotic features (esp delusions)
- Parkinsonism may arise later in course
- Associated with greater frontal atrophy



(Image from theaftd.org,2012)

(Clark, 2014)

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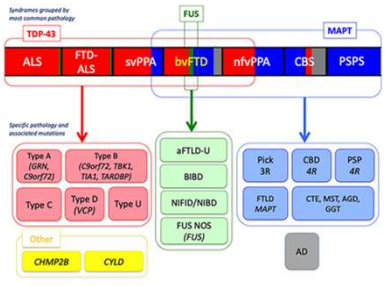
Progranulin (*GRN*)

- Chromosome 17
- TDP-43 pathology
- 5-10% of all FTD cases
- bvFTD > nfPPA, lvPPA
  - Occasionally PCA
- Tends to present with more apathy
- Associated with very asymmetric atrophy



(Clark, 2014)

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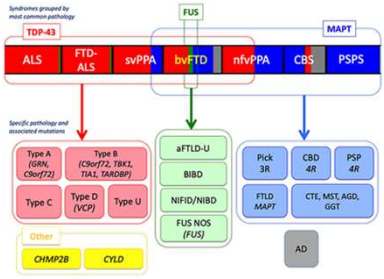
Microtubule associated protein tau (*MAPT*)

- Chromosome 17
- Tau pathology
- 5-10% of all FTD cases
- Younger age of onset than *GRN* or *C9orf72* (avg 49.5)
- bvFTD >> PPA, PSPS, CBS
  - FTD with Parkinsonism (FTDP-17)
  - Tend to have more disinhibition
- Associated with greater temporal atrophy



(Clark, 2024)

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What's on the differential?

- bvFTD is degenerative with average lifespan ~ 8 years.
- Symptoms overlap with other diagnoses, some degenerative, others not

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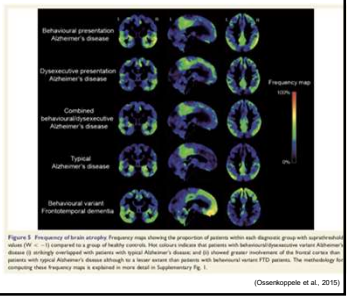
Frontal/Behavioral variant AD

- Basically, it's AD that can mimic bvFTD
- Hence the pathologic AD that shows up in bvFTD cohorts



(Ossenkoppele et al., 2015)

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Table 3 **Key clinical and neuroimaging features of behavioural/dysexecutive variant Alzheimer's disease**

Clinical features	Typical Alzheimer's disease	Behavioural/dysexecutive variant Alzheimer's disease		Behavioural variant FTD
Phenotype	Memory-predominant	Behavioural-predominant	Dysexecutive-predominant	Behavioural
Genetic predisposition				
APOE ε4 positive	Frequent (~60%)[a]	Frequent (59.5%)	Intermediate (40.0%)	Rare (<20%)[b]
Clinical				
Age-at-onset	Late-onset	Early-onset	Early-onset	Early-onset
First symptom	Cognitive (memory)	Cognitive > behavioural	Cognitive (executive)	Behavioural
Cognition				
Episodic memory	Impaired	Impaired	Relatively spared	Typically spared
Executive function	Relatively spared	Impaired	Impaired	Impaired
Behaviour	Relatively spared	Impaired	Mostly spared	Impaired
MRI				
Atrophy pattern	Medial temporal and temporoparietal lobes	Temporoparietal cortex	Temporoparietal cortex	Frontal and anterior temporal lobes

(Ossenkoppele et al., 2015)

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The FTD phenocopy syndrome

- Non-progressive or very slowly progressive bvFTD-like picture
- May represent psychiatric illness, marital discord, untreated sleep apnea, or indolent genetic variants (*C9orf72)*
- Possible versus probable are important distinctions that reflect certainty

(Kipps et al., 2010)

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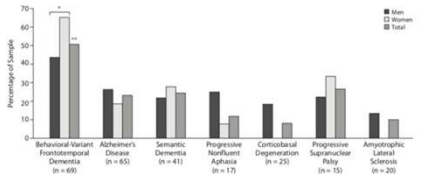
Psychiatric misdiagnosis is common

Figure 1. Rates of Psychiatric Diagnosis Within Each Neurodegenerative Disease[a]



[a]Percentage of patients given a psychiatric diagnosis for symptoms that eventually led to a neurodegenerative disease diagnosis, separated by gender.
*$P < .05$ for comparison of rates of psychiatric diagnosis in men versus women with behavioral-variant frontotemporal dementia.
**$P < .01$ for rates of psychiatric diagnosis in patients with behavioral-variant frontotemporal dementia compared to patients with other forms of neurodegenerative disease.

Esp. bvFTD

Women > men

(Woolley et al., 2011)

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Table 3. Initial Symptoms Leading to Preliminary Psychiatric Diagnosis[a]

Neurodegenerative Disease	Psychiatric Diagnosis	Initial Symptoms
Behavioral variant frontotemporal dementia	Bipolar disorder	Social withdrawal and lack of empathy
	Bipolar disorder	Euphoria, alternating mood, dietary changes, lack of judgment
	Bipolar disorder	Euphoria, disinhibition, impulsivity, alternating mood, compulsive behaviors
	Bipolar disorder	Lack of judgment, disinhibition, compulsive behaviors, euphoria
	Bipolar disorder	Euphoria and hobby changes
	Bipolar disorder	Disinhibition, impulsivity, mental rigidity
	Schizophrenia	Sexual disinhibition, impulsivity, stealing, repetitive speech
	Schizophrenia	Apathy, social withdrawal, poor hygiene, compulsive behaviors
	Major depressive disorder	Heavy drinking
	Major depressive disorder	Profound apathy
	Major depressive disorder	No empathy for wife's breast cancer
	Major depressive disorder	Apathy and lack of empathy
	Major depressive disorder	Apathy and social withdrawal
	Major depressive disorder	Lack of empathy and apathy
	Major depressive disorder	Lack of empathy and lack of insight
	Major depressive disorder	Profound apathy
	Major depressive disorder	Apathy, anhedonia, and social withdrawal
	Major depressive disorder	Lack of empathy, dietary changes, anhedonia, poor hygiene
	Major depressive disorder	Apathy, social withdrawal, and anhedonia
	Major depressive disorder	Lack of judgment and compulsive behaviors
	Major depressive disorder	Cognitive problems
Semantic dementia	Bipolar disorder	Disinhibition, compulsive behaviors, impulsivity
	Major depressive disorder	Apathy, emotional distance, loss of sexual interest
	Major depressive disorder	Memory deficits, dietary changes, insomnia
	Major depressive disorder	Severe lack of empathy
	Major depressive disorder	Memory deficits
Alzheimer's disease	Bipolar disorder	Slight disinhibition and anxiety
	Major depressive disorder	Memory difficulties and mood disturbance
	Major depressive disorder	Reduced speech and movement
	Major depressive disorder	Memory difficulties and mood disturbance
	Major depressive disorder	Memory deficits and stealing
	Major depressive disorder	Memory deficits and disorientation

[a]Categorization of initial symptoms leading to a preliminary psychiatric diagnosis for 32 patients whose medical charts contained appropriate documentation.

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FTD vs PPD Checklist

- Ducharme et al. (2018). The Frontotemporal Dementia versus Primary Psychiatric Disorder (FTD versus PPD) Checklist: A Bedside Clinical Tool to Identify Behavioral Variant FTD in Patients with Late-Onset Behavioral Changes. *J Alzheimers Dis*

- 17 items
- ≥11: specificity 93.9%, sensitivity 71.1%, PPV 89.2% for dx of bvFTD
- ≤8: specificity 91.3%, sensitivity 77.3%, 396 PPV 92.7% for PPD
- 9–10: indeterminate

(Ducharme et al., 2019)

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Clinical Items	Yes	No
Part A (No = 1)		
Was the patient self-referred?		
Is there a past history of mood, anxiety, psychotic, or personality disorder?		
Is the patient emotionally distressed (dysphoria, anxiety) by the current situation?		
Is the patient expressing guilt, self-blame, or suicidal thoughts?		
Is the main complaint of the family that the patient has anger problems?		
Is the patient aware of or concerned about cognitive or behavioral changes?		
Are the cognitive or behavioral symptoms fluctuating?		
Is the patient showing interest in learning about FTD?		
Does the patient understand what FTD is?		
Is the patient reporting more severe disability that expected based on clinical and cognitive examination?		
Is there a legal or compensation issue associated with the case?		
Are the patient and/or relatives upset or doubtful if told they might not have FTD (as opposed to expressing relief, joy, etc.)?		

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Part B (Yes= 1)	Yes	No
Is there a 1st degree family history of FTD or ALS?		
Are there language related complaints?		
Are there stereotypical or simple repetitive behaviors?		
Are there changes in food preferences?		
Are there abnormalities on elemental neurologic examination (including eye movements, parkinsonism)?		

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Biomarkers/Diagnostic Studies

- Available biomarkers for FTD are currently limited and nonspecific
- Neurofilament light chain (Nfl)
  - Can be detected in blood or CSF
  - Non-specific; signals neuroaxonal loss from neurodegeneration
  - Can help differentiate FTD from PPD
- FDG-PET can be useful in ambiguous cases
- Neuropsychological evaluation
- Genetic testing can help with establishing a diagnosis
  - Ethical and legal concerns, requires careful consideration
  - Support from genetic counseling is helpful

(Clark, 2024)

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In summary,

- FTD has 3 core syndromes: bvFTD (most common), nfvPPA, & svPPA
  - CBS and PSPS on FTD spectrum, monitor for emerging motor symptoms (esp in nfvPPA)
- Diagnostically challenging due to the heterogeneous neuropathology, lack of specific biomarkers, and phenotypic overlap with psychiatric conditions
- Definite diagnosis only possible through genetic testing
  - Consider hereditary form in any patient with a suggestive family history
- Levels of Nfl (serum or CSF) can be helpful in differentiating between psychiatric disease (also FTD vs PPD checklist)
- Cholinesterase inhibitors can worsen symptoms
- Serotonergic medications are the main mode of treatment

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