CASE STUDIES IN BEHAVIORAL NEUROLOGY: FOCUS ON FRONTOTEMPORAL DEGENERATION

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HOW DO YOU DIAGNOSE THE FTDs?

1. Is there a history of an **acquired behavioral disturbance in middle or late life**, i.e., an insidious change from their prior pervasive pattern of behavior?
2. If behavioral, does it involve **socioemotional behavior**?
3. If cognitive, is there disproportionate **"executive" dysfunction**?
4. If suspect PPA, do the language and speech changes correspond to one of the **PPA syndromes**?
5. Is there **biomarker** support?

PART A: Clinical Critiera

Table 1. International Frontotemporal Dementia Consensus (FTDC) Criteria for behavioral variant FTD (adapted from Rascovsky et al., 2011).

I. Neurodegenerative disease
A. Patient must show progressive deterioration of behavior and/or cognition by observation or history

II. Possible bvFTD
Three of the following behavioral/cognitive symptoms must be present:
A. Early behavioral disinhibition
B. Early apathy or inertia
C. Early loss of sympathy or empathy
D. Early perseverative, stereotyped or compulsive/ritualistic behavior
E. Hyperorality and dietary changes
F. Neuropsychological profile: executive/generation deficits, relative sparing of memory and visuospatial functions

III. Probable bvFTD
All of the following symptoms must be present:
A. Meets criteria for possible bvFTD
B. Exhibits significant functional decline (by caregiver report or functional scales)
C. Imaging consistent with bvFTD (i.e. frontal and/or anterior temporal atrophy on CT or MRI or frontal hypoperfusion or hypometabolism on SPECT or PET)

IV. bvFTD with definite FTLD pathology
Criterion A and either Criterion B or C must be present to meet criteria
A. Meets criteria for possible or probable bvFTD
B. Histopathological evidence of FTLD
C. Presence of a known pathogenic mutation

V. Exclusionary criteria for bvFTD
Criteria A and B must be answered negatively for any bvFTD diagnosis. Criterion C can be positive for possible bvFTD but must be negative for probable bvFTD
A. Pattern of deficits is better accounted for by other non-degenerative nervous system or medical disorders
B. Behavioral disturbance is better accounted for by a psychiatric diagnosis
C. Biomarkers strongly indicative of Alzheimer's disease or other neurodegenerative process

The FTDC diagnostic criteria for bvFTD allows for variable symptom presentations. The criteria for probable bvFTD are based on the presence of at least three behavioral features plus demonstrable functional decline and associated brain structural and/or functional changes. The classification of bvFTD with definite FTLD pathology is based on combined features of the clinical syndrome and evidence of a pathogenic mutation or FTLD histopathology. In a large, multicenter study, these FTDC criteria were significantly more sensitive (86% to 53%) than previously established criteria; however, the FTDC criteria continue to miss many frontotemporal degeneration variants, particularly in early stages of the disease, and may need to be significantly revised. Examples of variants are described in this case series on frontotemporal degeneration.

Table 2. Clinical-Pathological Features of PPA (adapted from Rascovsky and Grossman, 2013)

Clinical Features	Anatomy	Pathology
Nonfluent/ Agrammatic (na-PPA)	Effortful, halting speech Speech sound errors Simplified grammar Impaired syntax comprehension Apraxia of speech	L inferior frontal insula and anterior temporal; FTD-Tau (70%)
Semantic Dementia (sv-PPA)	Poor confrontational naming Impaired single-word comprehension Poor object / person recognition	L (+/-R) anterior temporal FTD-TPD-43 (80%)
Logopenic-Phonological (lv-PPA)	Impaired repetition (multi-syllable words) Impaired single word retrieval	L posterior temporal and parieta AD (70%)

Since the seminal initial case descriptions by Mesulam in 1982, the clinical classification of progressive aphasias has expanded into 3 distinct syndromes, all of which are predicated on language disturbances being the predominant early clinical manifestations. The two syndromes most commonly associated with FTD are semantic variant (sv-PPA) and nonfluent / agrammatical (na-PPA), whereas the logopenic-phonologic variant of PPA is most commonly associated with AD.(Gorno-Tempini et al., 2011) Although these syndromes have distinctive clinical and anatomical correlations, the underlying pathological substrates are variable. LV-PPA is the newest and most controversial of the PPAs, and is sometimes referred to as the “language variant” of AD.

PART B: Clinical Assessment

The clinical assessment of bvFTD requires A. tests of executive cognition; B. evaluation of social cognition and behavior; and C. a neurological examination with assessment for motor sterotypies, extrapyramidal signs, and evidence of motor neuron disease.. In contrast to Alzheimer’s disease (AD), where standard cognitive screening tests are generally useful for identifying and staging purposes, cognitive symptoms are often not the main clinical manifestations of bvFTD. Moreover, the cognitive exam focuses on frontally-mediated executive functions, which can be difficult to test in the clinic or at the bedside. Suspect executive deficits when there is a history of apathy or decreased goal-oriented behavior, disinhibition, poor reasoning, or impaired judgment and insight.

Judgment reflects the presence or absence of logic and reasoning. Along with information management, judgment and reasoning account for a large part of "intelligence." It is difficult to test a patient's judgment; responses to questions such as "what would you do if you saw a fire in a theater?" are unreliable. Judgment is best assessed by examples or observations of behavior from the patient's daily life of personally and socially appropriate goals, strategies, and procedures. Impaired insight or diminished awareness and understanding of illness is often seen with frontal dysfunction.

A. Clinical or Bedside Executive Tests:

1. Working memory tasks, eg, digit reversal/subtractions, months backwards, and digit ordering
2. Complex attentional task (sustaining, shifting, dividing) such as digits span and Trailmaking A
3. “Reactive flexibility” tasks such as Trailmaking-B; evidence of perseveration
4.* Verbal fluency or word list generation, e.g., “F” words and categories
5.* Tests of response inhibition, e.g., Go No-Go test, anti-saccades
6. Design fluency, such as the Five-Point Test

7.* Simple motor programming tasks such as alternate tapping
8.* Luria programming tasks such as written programs and the fist-edge-palm test
9.* Abstraction on idioms and proverbs
10. Environmental dependency e.g. echolalia, echopraxia, or utilization behavior

*The Frontal Assessment Battery (FAB) is a test battery that can be administered in a few minutes and covers 5 executive tests (see asterisks above), along with testing for the frontal grasp reflex (Dubois et al, 2000).

Working memory involves holding information online, while it is manipulated or processed. Aspects of working memory include the maintenance of online posterior representations, manipulation of representations: select, amplify some, ignore others, and inhibition of unattended/irrelevant information, perseveration, immediate gratification. The common tests for working memory involve reversing digits or "WORLD" backwards and simple serial subtraction tasks. When performed in a forward direction, these tests also assess complex attention.

Many of the other executive cognitive tasks reflect aspects of strategic planning, or the formulation of attainable goals, the steps and program to meet these goals, the motivation to follow-through, and the ability to monitor and self-correct along the way. Related functions include set-switching and the ability to program motor sequences. Motor programming tasks include reproduction of a simple rhythm that the examiner taps out of the table. The Luria written task involve copying alternating programs such as a series of "m" and "n" letters, continuing the pattern to the end of the page. Another test of motor programming involves the Luria Fist-Edge-Palm Hand Sequence. The examiner first demonstrates this task before asking the patient to reproduce it at least six times without error.

Other executive tasks involve set maintenance on verbal and design fluency tasks and response inhibition tests. In addition to the word-list generation tasks noted during language testing, there is a decline in the number of free form designs/minute or "design fluency." One way to evaluate response inhibition is to have the patient must copy a pattern, such as spiral loops, continuing the pattern to the end of the page. The Go No-Go Test also assesses response inhibition: 1st set: Subject copies Examiner (1 or 2 taps); 2nd set: new rule- Examiner taps 1x → Subjects taps 2x; Examiner taps 2x → Subject doesn't tap.

The ability to abstract is disturbed in many patients with frontal-systems disease. The examiner asks the patient to interpret similarities, idioms, and proverbs. Patients with brain lesions often respond with concrete interpretations. Examples of similarities include orange-banana, table-chair, and a watch-ruler. Common idioms include the meaning of "broad-minded," and "warm-hearted." Examples of proverbs include relatively familiar ones such as "People who live in glass houses shouldn't throw stones." Unfamiliar proverbs are preferable, since their interpretation requires novel ways of thinking.

B. Language Evaluation

The clinical assessment of PPA builds on the standard aphasia evaluation of fluency, comprehension, and repetition. As part of a recent standardized battery designed to assess FTD, the National Alzheimer Coordinating Center (NACC) has assembled a battery of language assessments that are designed specifically to help discern the various subtypes of PPA. This battery includes a letter fluency test, word reading (regular / irregular), semantic word-picture matching, semantic associates test, Northwestern Anagram test, a test of grammatical knowledge, noun and verb naming, and sentence repetition and reading.

C. Evaluation of Social Cognition and Behavior:

Social cognitive tests focus on Theory of Mind with a range of tests: Reading the Mind in the Eyes, Faux Pas, and Sarcasm/irony assessments. These tests are difficult to administer in the usual clinical setting, because they usually require the presentation and subsequent interpretation of social scenarios.

The evaluation of social cognition primarily involves a careful history and behavioral observations. The examiner needs collateral history from the family or caregiver. The history provides the most important information regarding personality change with decreased goal-directed behavior, disinhibition, and apathy and disengagement. The examiner asks specific questions on a social cognitive questionnaire and observes for comparable behavior:

Has there been a change in personality or behavior?

1.* Is the patient less engaged; less motivated or apathetic compared to before?
2.* Is the patient socially inappropriate or disinhibited? Has he/she violated social or legal norms? Loss of manners; crude language; poor grooming; private behaviors in public; criminal acts?
3. Does he/she fail to respond to social cues? Continues talking or interrupting; violates personal space
4.* Does he/she have poor impulse control? Impulsive; rash or careless actions; e.g.; gambling, stealing, giving out personal information
5.* Is he/she less concerned about the feelings and emotions of others (loss of sympathy or empathy)? Poor response to others' needs, feelings or distress; hurtful comments; coldness; decreased social interest
6.* Are there changes in dietary or altered food preferences? Hyperoral; binging; food fads; carbohydrate craving; increased use of alcohol, cigarette or chewing gum
7.* Perseverative; stereotyped or compulsive behavior? Simple repetitive movements such as tapping, clapping, rubbing, scratching, picking, smacking/pursing lips; complex rituals such as checking, counting, cleaning, hoarding; repetitive trips to the bathroom; speech stereotypies

Clinical screening questionnaires such as the Neuropsychiatric Inventory – Questionnaire (NPI-Q) offer a standardized informant based reporting of core bvFTD symptoms (see asterisks above).(Kaufer et al, 2000) Caregiver distress ratings also provide a measure of clinical significance associated with each symptom that can help determine and prioritize interventional strategies.

Other specific scales and inventories for the assessment of bvFTD include:
DAPHNE-6 and DAPHNE-40
Frontal Behavioral Inventory (FBI)
Frontal Systems Behavioral Scale (FrSBe)
Frontotemporal Behavioral Scale (FBS)
Social Norms Questionnaire (SNQ)
Socioemotional Dysfunction Scale (SDS)

PART C: BIOMARKERS ARE SUPPORTIVE FOR FTDS

1. Structural MRI may show regional atrophy
2. FDG PET disclose regional hypometabolism
3. Connectomics, both structural and functional, can disclose specific involvement of callosal, cingulate, uncinate, and other fasciculi as well as the Salience Network on rsFMRI
4. CSF studies can show normal beta-amyloid, total tau and phospho-tau with decreased neurofilament levels and alterations in C9RAN and progranulin in genetic cases
5. Genetic testing for MAPT, C9orf72, and progranulin (new, upcoming gene TBK1)

PART D: Treatment Considerations
There are currently no approved drug treatments for FTD; treatment is empirical and focused primarily on controlling irritability, compulsive behaviors (e.g. over-eating) and repetitive motor behaviors with serotonergic agents (trazadone and SSRIs). Cholinesterase inhibitors are generally not helpful to FTLD patients, and may exacerbate agitation. A multicenter placebo-controlled study of memantine in bvFTD showed consistent effect on neuropsychiatric or other symptoms. PPA syndromes may benefit from aggressive speech-therapy although few speech-language therapists have a lot experience with PPA. Providing caregiver education and support and referring the family for appropriate legal counsel are often the most helpful therapeutic interventions.

Key References
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