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Clinical phenomenology and treatment of frontotemporal dementia

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INTRODUCTION

Frontotemporal dementia (FTD) is a common cause of dementia under age 70 years,[1–3] and occurs in 8–17% of cases with dementia in this age group based upon neuropathological series.[4,5] FTD is part of a spectrum of disorders encompassed by the broader entity of frontotemporal lobar degeneration (FTLD) that includes progressive nonfluent aphasia and semantic dementia.[6] FTD is a behavioral syndrome whereas progressive nonfluent aphasia and semantic dementia are syndromes related to deficits in language and semantic knowledge, respectively. FTD, progressive nonfluent aphasia, and semantic dementia share the same spectrum of pathologies but differ clinically due to different lesion sites.[6] The focus of this chapter is to review the neurobehavioral features of FTD, as well as the emerging literature on treatment of FTD. There will also be a brief overview of progressive nonfluent aphasia and semantic dementia.

TERMINOLOGY AND DIAGNOSTIC CRITERIA

The literature on FTLD contains a variety of different terms that have been used to describe the same syndromes.[7] For example, whereas Neary et al. applied the term FTLD to the overarching disorder and FTD to the behavioral presentation,[6] others have used FTD as the broad label and frontal variant FTD (fvFTD) for the behavioral syndrome.[8] Other examples of differences in terminology are temporal lobe variant FTD[9,10] and progressive fluent aphasia[8] for semantic dementia. In addition, primary progressive aphasia has been used to encompass both progressive nonfluent aphasia and semantic dementia.[11] Moreover, Pick complex has been proposed as a term that encompasses all of the preceding syndromes plus corticobasal degeneration, progressive supranuclear palsy and FTD with motor neuron disease. The term Pick complex highlights the clinical and neuropathological overlap among these syndromes.[11,12]

In 1994, the Lund Manchester criteria for FTD were published.[13] Although they were widely used, these criteria essentially comprised a checklist without guidelines defining the number of features required for diagnosis. In 1998, Neary et al. reported a consensus statement which provided an update and extension of the earlier Lund Manchester criteria.[6] Another set of diagnostic criteria was published in 2001 by the Workgroup on Frontotemporal Dementia and Pick's Disease.[14] These criteria use the term FTD to encompass the behavioral syndrome and

the language presentation. In addition, the language presentation includes both progressive aphasia and semantic dementia.

The Neary criteria provide well-defined and detailed descriptions of each of the three syndromes comprising FTLD and are thus well suited for subject selection in research trials. Knopman et al.[15] examined the accuracy of ante-mortem diagnosis of FTLD against neuropathological diagnoses. Their series consisted of 34 cases with pathological FTLD among 433 consecutive patients who underwent autopsy. Ante-mortem diagnosis of FTLD was based on the sum of clinical, neuropsychological and imaging features derived from the criteria presented by Neary et al.[6] The sensitivity was 85% with a specificity of 99%. The approach taken in this chapter will be to use the terminology and classification system proposed by Neary and colleagues, i.e. FTLD as the overarching disorder with FTD, progressive non-fluent aphasia and semantic dementia as the syndromes encompassed by FTLD.[6]

CLINICAL FEATURES

FTD

Based on the Neary criteria (Table 3.1), there are five core diagnostic features required for a diagnosis of FTD. In addition to insidious onset and gradual progression for at least 6 months, these consist of the following early features: loss of insight, decline in social interpersonal conduct, emotional blunting, and impaired regulation of personal conduct.[6]

Loss of insight occurs early in the illness in the setting of relatively well-preserved cognition in areas outside the social cognitive realm. The following is a case example:

> *Case DL:* A high functioning woman developed a significant change in behavior that included a decline in social cognitive function. She was diagnosed with FTD and was informed of this diagnosis by her neurologist. Although DL retained the knowledge that she had been given a diagnosis of FTD, i.e. she recalled being told that she had FTD, she was insistent that she had no problems and that she was fully capable of working. To assess her insight and awareness, her neurologist asked her to participate in role play where she pretended to be an employer who had to make a decision about hiring a man who had been diagnosed with FTD. As was the case with DL, the man felt that he did not have any cognitive or behavioral problems. Thus the

Table 3.1 The clinical diagnostic features of FTD: clinical profile

I. Core diagnostic features
   A. Insidious onset and gradual progression
   B. Early decline in social interpersonal conduct
   C. Early impairment in regulation of personal conduct
   D. Early emotional blunting
   E. Early loss of insight

II. Supportive diagnostic features
   A. Behavioral disorder
      1. Decline in personal hygiene and grooming
      2. Mental rigidity and inflexibility
      3. Distractibility and impersistence
      4. Hyperorality and dietary changes
      5. Perseverative and stereotyped behavior
      6. Utilization behavior
   B. Speech and language
      1. Altered speech output
         a. Aspontaneity and economy of speech
         b. Press of speech
      2. Stereotypy of speech
      3. Echolalia
      4. Perseveration
      5. Mutism
   C. Physical signs
      1. Primitive reflexes
      2. Incontinence
      3. Akinesia, rigidity, and tremor
      4. Low and labile blood pressure
   D. Investigations
      1. Neuropsychology: significant impairment on frontal lobe tests in the absence of severe amnesia, aphasia, or perceptuospatial disorder
      2. Electroencephalography: normal on conventional EEG despite clinically evident dementia
      3. Brain imaging (structural and/or functional): predominant frontal and/or anterior temporal abnormality

role play involved DL having to make a decision about hiring someone who was essentially in the same situation as she was in. DL enquired whether she would have access to information that the applicant had FTD and was advised that she would be given this information.' The examiner then asked DL whether she would hire the applicant. She responded 'no' and explained that she would not hire him because he had FTD and indicated that this disorder could affect his ability to work. At the end of the role play, DL was asked to 'be herself' again. The examiner then asked whether she was able to work. She replied 'Well yes I am'.

This case example indicates a marked lack of DL's insight and awareness of her deficits in relation to herself at an early point in her illness. In contrast, there is strikingly preserved awareness of the impact of FTD when applied to someone else. This illustrates that she had sufficient knowledge and understanding of FTD to know that this disorder can affect a person's ability to work. Thus DL's belief that she is capable of working is a true lack of insight into her own deficits as opposed to a lack of knowledge about the effects of FTD.

Decline in social interpersonal conduct refers to breaches of social etiquette that represent a change from previous behavior. Examples include a decline in manners and social graces, disinhibition, violation of interpersonal space, and antisocial behavior.[6] The following are case examples of a decline in social interpersonal conduct in patients with FTD:

Case RJ: A man in his 50s showed a change in behavior that initially manifested with stealing two toy airplanes from a gift shop. He subsequently continued to take other people's possessions. Other problems included poor hygiene. He also took a shower while wearing his pajamas. In addition, he started to eat food from garbage cans. When asked about this latter activity, RJ noted that he was discriminating about the food that he took from the garbage. He said that he ate the 'good' food. He was aware that others thought it 'highly abnormal' that he was eating food from garbage cans and that 'it looked bad'. However, he felt that there was nothing wrong with what he did.

Case SM: A previously shy woman started to approach strangers on the street and tried to give them hugs and kisses. After being admitted to hospital for assessment, she approached other patients and staff in the same way.

Case LT: A woman who had developed inappropriate behavior was asked to write a sentence during a mental status exam. She wrote 'I love you' to the examiner by drawing a picture of an eye, a heart, and a ewe.

Emotional blunting refers to emotional shallowness with unconcern, loss of emotional warmth, indifference to others, and a loss of empathy and sympathy.[6] Empathy refers to an awareness of the feelings of others, whereas sympathy refers to sharing these feelings. The following description by the wife of a patient with FTD (Case HR) illustrates an example of emotional blunting. In response to the examiner's question about her husband's emotions she replied: 'The changes in how he behaves are that he has become quite emotionally detached ... He is still quite happy to see people. He will give me a hug and everything else but there is no real feeling attached anymore.'.

Impaired regulation of personal conduct refers to changes spanning the spectrum of inactivity, passivity, inertia, pacing, wandering, increased talking and laughing, sexuality, singing, and aggression.[6]

In addition to the core diagnostic features required for a diagnosis of FTD, patients may show features such as stereotypic behavior, utilization behavior, and hyperorality. Stereotypic behavior includes repetitive activities such as clapping and singing, as well as routines such as repeatedly walking along fixed routes. Utilization behavior refers to the unrestrained exploration of objects in the environment by grasping and using them.[16] Hyperorality includes overeating, food fads, and oral exploration of objects. The following excerpts from a conversation between Case HR, referred to above, and his wife illustrate features of hyperorality:

Wife: What have you taken to doing in terms of going into other people's rooms?
Case HR: Nothing.

Wife: Oh come on, what have you been doing?
Case HR: No nothing.
Wife: Remember that day when I came in and found an empty box of cookies in your room?
Case HR: Yah.
Wife: Where did you get that?
Case HR: I don't know.
Wife: Oh yes you do. What's the name of the man's room where you took it?
Case HR: No. I don't know. I just took it.
Wife: That's right.
Examiner: So you did take the cookies?
Wife: And ate them all.
Case HR: And ate them all.

Other abnormal behaviors include mental rigidity and inflexibility, distractibility and impersistence, and a decline in hygiene and grooming. Although the consensus criteria published by Neary et al. list early severe amnesia as an exclusion,[6] Hodges et al.[17] found that amnesia may be the dominant presenting symptom in a study of pathologically proven cases with FTD. In contrast, visuospatial and perceptual symptoms were absent in their series. This is in keeping with spatial disorientation as an exclusion feature in the Neary criteria.

Neuropsychological assessment

The early behavioral changes in FTD may be due to lesions in orbitomedial frontal systems.[18] This concept is supported by neuropathological data showing early involvement of orbital cortex in FTD. Broe et al.[19] staged severity of atrophy in patients with FTD who were selected from a neuropathological series of cases with dementia. They grouped the FTD cases into four stages of severity. Stage 1 represented the earliest changes and was characterized by atrophy in the orbital and superior medial frontal cortex and hippocampus. The concept that orbital pathology underlies the initial clinical manifestations of FTD suggests that standard neuropsychological tests are likely to be ineffective for detecting early FTD. The vast majority of these neuropsychological measures are sensitive primarily to dorsolateral frontal function and do not adequately assess orbitofrontal cortical function.[18,20] For assessment of early FTD, this suggests a need for the development of clinical neuropsychological measures that are sensitive to orbitofrontal system deficits.

The object alternation task, a measure of working memory for objects and ability to shift sets, is an example of an experimental test that is sensitive to orbitofrontal damage[21] and that may be adaptable for clinical use. The object alternation task is sensitive to ventrolateral-orbitofrontal (inferior frontal convexity and orbital surface) lesions in nonhuman primates[22–25] and has been validated as being sensitive to ventrolateral-orbitofrontal and medial frontal lesions in humans.[21] The neuroanatomical regions involved include Brodmann areas 10, 24, 32, and 47, and possibly 11. The object alternation task is one of the few neuropsychological tests of orbitofrontal function in humans. Freedman et al.[26] administered this task to patients with FTD and found significant impairment in this group. The sensitivity to differentiating FTD from controls was 93% at a cut-off of 23 errors. Specificity was 51%.

Tests of social cognition, such as measures of Theory of Mind (ToM), may also prove useful in the assessment of patients with FTD. ToM refers to the awareness of other people's minds and the ability to make inferences about the mental states of others.[27–30] An example of a ToM test is the first order false belief task.[31,32] A typical false belief task involves a scenario where two people are in a room (person A and B). Person A puts an object somewhere while person B watches. Person B then leaves the room. After person B leaves, person A moves the object. Person B then returns. The false belief question to the subject is 'Where does person B think that the object is?'. To answer correctly, the subject must take the perspective of person B who has a false belief of where the object is. Other ToM tasks include recognition of faux pás,[33,34] detection of deception,[30] and the Reading the Mind in the Eyes Test.[35,36]

ToM has been studied in patients with focal brain lesions and FTD. Stone et al.[33] found that patients with bilateral orbitofrontal lesions showed deficits in the ability to recognize a faux pas. Stuss et al.[30] found that patients with medial frontal lesions, particularly right ventral, were impaired on detection of deception. These

studies suggest a role for orbital and medial frontal systems in the mechanisms underlying ToM and suggest that tests of ToM may be useful in defining deficits in FTD. In support of this concept, Gregory et al.[36] studied ToM in patients with FTD and found significant deficits as measured by performance in false belief tasks, detection of faux pas, and the Reading the Mind in the Eyes Test.

Progressive nonfluent aphasia and semantic dementia

Progressive nonfluent aphasia is associated with asymmetric atrophy, affecting primarily the left frontotemporal lobes, whereas semantic dementia is associated with bilateral atrophy that is most marked in the anterior temporal lobes, with the middle and inferior temporal neocortex predominantly affected.[6] The atrophy in semantic dementia is commonly asymmetric.[37] Diagnostic criteria for progressive nonfluent aphasia and semantic dementia have been published by Neary et al.[6] Features of progressive nonfluent aphasia include insidious onset and gradual progression, nonfluent spontaneous speech, agrammatism, phonemic paraphasias, anomia, stuttering speech, poor repetition, alexia and agraphia. There is early preservation of word meaning. Behavioral characteristics of FTD may emerge as the disease progresses.

Semantic dementia is characterized by loss of meaning for words and impaired recognition of faces and objects. An example of loss of word meaning is illustrated by the following excerpts from an interview with a patient who has semantic dementia:

Examiner: Point to the watch.
Case BW: Point to my watch? I forget what is the watch, what is the watch?
Examiner: Point to the ceiling.
Case BW: Point to the ceiling, what is the ceiling? Is the ceiling here?
Examiner: There is a ceiling here, could you point to the ceiling?
Case BW: No, I don't know.

Other features of semantic dementia include insidious onset and gradual progression, fluent, empty spontaneous speech, semantic paraphasias, preserved ability to match or reproduce simple line drawings, and preserved single word repetition. Patients are able to read and write to dictation orthographically regular words, i.e. words with direct sound-to-letter correspondence, but are commonly impaired with orthographically irregular words, i.e. words that do not have direct sound-to-letter correspondence. Examples are reading 'mild' to rhyme with 'build' and writing 'flight' as 'flite'. This deficit in reading is called surface dyslexia and the writing deficit is referred to as surface dysgraphia. Features of FTD may emerge as the illness progresses.[38]

TREATMENT

Although several drugs have been tested in FTD, only four have been studied in double-blind placebo-controlled trials: idazoxan,[39] trazodone,[40] paroxetine,[41] and galantamine.[42] Significant benefit has been reported with idazoxan and trazodone in FTD. In contrast, a decline in performance was found with paroxetine. Galantamine produced benefit in primary progressive aphasia.

Idazoxan is an alpha-2 adrenoreceptor antagonist. Alpha-2 receptors act as presynaptic autoreceptors to inhibit noradrenaline (norepinephrine) release. Blockade may therefore increase noradrenaline. Idazoxan was tested using a single case cross-over design. There was improvement in tests of frontal lobe function, i.e. Tower of London, verbal fluency for category and sustained attention.[39] Trazodone was studied using a cross-over design in doses of 150–300 mg daily. There was significant benefit on the NPI total score with improvement in eating disorders, agitation, irritability, and depression/dysphoria. Thirty-one subjects were initially treated and 26 subjects completed the trial.[40] In the paroxetine trial, a cross-over design was used. Assessments were carried out at a dose of 40 mg daily. There were 12 subjects initially. Two withdrew before being tested on the drug. There are complete data for 6 of the remaining 10 subjects. The results showed a significant decline in performance on reversal learning and delayed pattern recognition, as

well as decline on paired associate learning that neared significance.[41]

Galantamine was studied in FTD and primary progressive aphasia at a dose of 16 or 24 mg per day. Patients were treated for 18 weeks and then entered a 4-week double-blind placebo-controlled withdrawal phase. Thirty-six subjects completed the open-label phase and 34 completed the double-blind phase. A significant benefit was found in patients with primary progressive aphasia in the placebo-controlled withdrawal phase on the Clinical Global Impressions. In addition, the Aphasia Quotient of the Western Aphasia Battery remained stable in the active treatment group, whereas the placebo group showed a decline.[42]

In addition to the above double-blind placebo-controlled trials, several other studies have been carried out in FTD. The drugs tested include lithium plus fluoxetine,[43] lithium plus paroxetine,[43] SSRIs (selective serotonin reuptake inhibitors),[44–47] l-deprenyl,[48] moclobemide,[49] methylphenidate,[50] piracetam,[47] donepezil,[51] and rivastigmine.[51,52] There was benefit in all cases except piracetam. Although improvement has been reported for SSRIs,[44–47] including paroxetine,[45,47] the double-blind placebo-controlled trial of paroxetine showed a decline in function on this medication.[41]

In addition to treatment of FTD with medication, there is an important role for nonpharmacological interventions.[53–55] These typically include environmental, behavioral and psychosocial strategies.[53] Research is needed to demonstrate the efficacy of these approaches in FTD in well-designed clinical trials.

CONCLUSIONS

FTD is being increasingly recognized as a common cause of dementia, particularly in patients under 70 years of age. Although there are well-defined criteria for FTD, and its related disorders that are encompassed by FTLD, progressive nonfluent aphasia and semantic dementia, there is a need for consensus on uniform terminology that can be applied across research studies and clinically. In addition, improved cognitive assessment tools are required to aid in early diagnosis of FTD. This includes the development of clinical neuropsychological measures that are sensitive to orbitofrontal lesions that may underlie the initial clinical manifestations of FTD. Also, with the emergence of pharmacologic treatment studies for FTD, there is an important need to develop consensus on standards for therapeutic trials. These include standards for diagnostic criteria, severity measures, outcome measures, and experimental design.[56] Finally, the relation between FTD and disorders such as motor neuron disease,[57–59] corticobasal degeneration,[60] and progressive supranuclear palsy[60] needs to be further defined.

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