

Review article

Frontotemporal dementia: clinical and therapeutic features

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INTRODUCTION

In 1982, Arnold Pick described cases of cognitive deterioration, notably in the language, associated with focal brain atrophy or circumscribed to the temporal and frontal lobes. He therefore challenged the existing dogma at that time, in which the process of brain degeneration would be invariably diffuse.¹ In 1911, Dr. Alois Alzheimer (1864-1915) described the histopathological status related to these patients, pointing the absence of senile plaques and neurofibrillary tangles, and the presence of neuronal inclusions (later called “Pick bodies”) and swollen cells (later called “Pick cells”).¹

However, during the 20th century, these patients with frontotemporal lobar degeneration were generically referred to as patients with dementia, being often diagnosed with Alzheimer disease (AD).² In 1994, two major research groups from Lund, Sweden, and Manchester, England proposed clinical and neuropathological criteria for the diagnosis of frontotemporal dementia (FTD).³ With regard to the neuropathological criteria, it has been recognized that only part of the individuals with FTD (25%) show the typical findings of Pick bodies and cells according to the original description. The most commonly observed pattern is the microvacuolar (60%), characterized by neuronal loss and microvacuolar degeneration. For the rest of the patients (15%), there is a concomitance of pathological findings of microvacuolar degeneration and motor neuron disease.^{2,3} In clinical terms, it has been suggested that, besides FTD, the status of semantic dementia and nonfluent progressive aphasia would be clinical manifestations of the frontotemporal lobar degeneration.⁴

The establishment of the criteria for the diagnosis of FTD^{3,4} allowed the wide recognition of this condition in several parts of the world. A recent epidemiological study in Catanduva (São Paulo, Brazil) carried out by Herrera et al.,⁵ found a 7.1% prevalence of dementia in individuals over 65 years. The AD was responsible for 55.1% of cases; vascular dementia (VD) for 9.3%; and AD associated with VD for 14.4%. The FTD and dementia with Lewy bodies were responsible for 2.6 and 1.7% of cases, respectively. Epidemiological studies carried out in Brazilian university

services found values similar to those obtained in this community study, identifying the FTD as the second main cause of degenerative dementia.⁶

Since the behavioral symptoms are very prominent in FTD, these patients are often initially assessed by psychiatrists, who must recognize this clinical entity. Therefore, the aim of the following study is to discuss the clinical characteristics of FTD, as well as the perspectives of the pharmacological therapy. In order to do so, we surveyed the literature related to FTD, initially based on review articles over the past 5 years at MEDLINE database, and later original articles cited in these references, whenever they were considered relevant for our objective.

Clinical characteristics of FTD

FTD is mainly manifested in the presenium, between 45 and 65 years of age, and it occurs in the same proportion in men and women. The family history of dementia is seen in half of cases, which suggests a major role of genetic factors in the development of FTD.^{2,7}

FTD is characterized by a significant change in personality and behavior, with relative preservation of the cognitive functions praxis, gnosis and memory^{3,4} (table 1). Visuospatial skills are also intact. Language in its turn is progressively affected, and there might be difficulties in the understanding and verbal expression, with reduction in fluency or even mutism. The FTD diagnosis is not made or there is a late diagnosis, once memory is preserved at the disease onset, and the change of this function is requested by the syndromic diagnosis of dementia, according to the criteria of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV),⁸ which give too much emphasis on cognitive deficits.^{9,10} The psychiatrist plays a major role in the early recognition of FTD, because the behavioral and personality changes are very significant. The complaints are often brought about by family members, since most patients ignore their changes in personality, behavior and social conduct. Therefore, the development of these symptoms in the presenium should be a warning for the diagnosis of FTD.^{9,10}

Table 1 - Criteria for the clinical diagnosis of FTD according to the Consensus of the American Academy of Neurology (AAN) of 1998⁴

Change in personality and inadequate social conduct are the dominant characteristics at the onset and during the disease progression. Functions of perception, spatial ability, praxis and memory are intact or relatively well preserved.

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;
- 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. asponaneity 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. Sphincteric incontinence;
3. Akinesia, rigidity and tremor (Parkinsonian syndrome);
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 or conventional electroencephalography despite clinical evident dementia;
3. Brain imaging (structural and/or functional): predominant frontal and/or temporal abnormality.

III. Supportive diagnostic features (common to other frontotemporal lobar degeneration syndromes):

- A. Onset before 65 years, positive family history of similar disorder in first-degree relatives;
- B. Bulbar palsy, muscular weakness and fasciculations (associated motor neuron disease present in a minority of patients).

IV. Diagnostic exclusion features (common to other frontotemporal lobar degeneration syndromes):

A. Based on history and clinical status

1. Abrupt onset with ictal events;
2. Head trauma related to onset;
3. Early, severe amnesia;
4. Spatial disorientation;

5. Logoclonic, festinant speech;
6. Myoclonus;
7. Corticospinal weakness;
8. Cerebellar ataxia;
9. Choreoathetosis.

B. Investigations

1. Brain imaging: predominant postcentral structural or functional deficit; multifocal lesions on CT or MRI;
2. Laboratory tests indicating brain involvement of metabolic or inflammatory disorder such as multiple sclerosis, syphilis, AIDS and herpes simplex encephalitis.

V. Relative diagnostic exclusion features (common to other frontotemporal lobar degeneration syndromes):

- A. Chronic alcoholism;
 - B. Sustained hypertension;
 - C. History of vascular disease (e.g., angina, claudication).
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The functional division of the frontal lobe into three distinct areas – orbital, medial and dorsolateral –, which constitute parallel and segregated circuits with subcortical structures, allows an explanatory approach of the FTD symptoms.¹¹⁻¹³ In this sense, the orbital lesion would be associated with disinhibition, impulsiveness and antisocial and stereotyped behaviors. Stereotyped or ritualistic behaviors may take different forms, from simple motor and verbal stereotypes, such as repeating gestures and words frequently, to complex routines, which include changes in eating habits, with an increase in oral ingestion and preference for sweet foods.^{3,4} The frontomedial lesion is correlated with apathy, passiveness, loss of motivation and tendency to social isolation.

Depressive symptoms might be present. As there is a progression of the degenerative process to the

convexity of the frontal lobe and consequent dorsolateral dysfunction, executive dysfunctions start to occur.

According to the prevalence of frontal area lesions by the focal degenerative process, there could be different clinical types of FTD, namely disinhibited, apathetic and stereotyped.² Nevertheless, in practice there is a large superposition between these clinical subsyndromes. For example, Caixeta & Nitrini,¹⁴ assessing 10 cases of FTD, observed a repetitive or stereotyped behavior in all of them, disinhibition prevailing in six and apathy in four patients. Also, five out of the six disinhibited patients presented deficit syndrome characterized by a reduction in discourse production, life and affective repertoire. Interestingly, disinhibited patients exhibited lower scores than apathetic patients in neurological tests.¹⁴

On neurological examination, patients with FTD may also show primitive reflexes, such as hand grasping and suction, which are signs of cortical release. More rarely, there may be signs of motor neuron disease (amyotrophic lateral sclerosis), which include muscular weakness, amyotrophy and fasciculation.²

Neuroimage examinations tend to show atrophy of frontotemporal lobes. However, in the early stages of FTD, such structural changes may not be evident.¹⁵ In these cases, the single photon emission computed tomography (SPECT) may reveal hypoperfusion in frontal areas (mainly ventromedial) and/or temporal (mainly anterolateral). It is a more sensitive examination to help in the diagnosis of FTD.¹⁶

As previously said, besides FTD, which represents more than 70% of cases, two other clinical conditions are manifestations of frontotemporal lobar degeneration.⁴ The first one is the semantic dementia, also called temporal variant of FTD, responsible for around 15% of cases. Patients with semantic dementia present a progressive degeneration of verbal comprehension and of the recognition of objects and people (agnosia), with great difficulty to name them. Nonetheless, the grammatical and phonological structure of patients' discourse remains intact. Behavioral changes tend to be less prominent than in FTD.^{4,10} The other manifestation of the frontotemporal lobar

degeneration is the nonfluent progressive aphasia, marked by a progressive reduction in verbal fluency, discourse with phonological and syntactic errors and anomia.^{4,17} In this case, the behavioral changes are also less intense.

The main differential diagnosis of FTD is with AD, which is responsible for more than half of dementia cases. Patients with AD seek for medical help complaining of memory changes, visuospatial functions or other cognitive functions.¹⁸ The behavioral and/or personality changes occur later. In patients with FTD, the behavioral changes take place early, whereas cognitive functions are relatively preserved in the early stages of the disease.

The differential diagnosis with VD, which may also affect frontotemporal structures, is based on the history (sudden onset and fluctuating course, presence of vascular risk factors or history of strokes) and on the clinical examination (presence of focal motor signs) and neuroimage examination (single or multiple infarctions, diffuse white matter injury). From the neuropsychological point of view, patients with VD show a predominant subcortical standard of dementia, characterized by deficits in executive functions, which include planning of acts and thoughts, self-regulation and mental flexibility.

On the neuropsychological evaluation of patients with mild FTD, there was impairment only in gambling tasks and reversal learning tasks.¹⁹ These patients presented a normal performance in an extensive battery of memory and executive function tests, such as recognition memory, work memory, planning and control of the focus of attention.¹⁹ In a comparative study of patients with FTD, semantic dementia and AD involving language tests, patients with semantic dementia had a worse performance than those with FTD in the Boston naming test and in the verbal fluency test. Patients with FTD were worse than those with AD only in the verbal fluency test.²⁰ Therefore, we conclude that several neuropsychological screening tests, which are originally developed to screen the cognitive deficits present in AD, especially memory, fail to identify the FTD.¹⁰ On the other hand, tests like the gambling test, reversal learning and language tasks might be useful in the differential diagnosis of FTD.²⁰

Interestingly, in gambling tests, patients with FTD showed an intact ability for probabilistic judgements, but adopted an excessive risk behavior when making decisions. However, it is not about inhibitory lack of inhibitory control and premature responses, since patients take more time than controls thinking about their decisions. This risk behavior may be related to the lack of insight about the consequences of the behavior itself, and thus be associated with sociopathic tendencies seen in FTD.^{19,21} Individuals with different orbitofrontal structural lesions also present a disadvantageous performance in gambling tasks.²² Patients with FTD in their turn showed a perseverative behavior in the reversal learning task, in which previously reinforced stimuli became neutral, i.e., they maintained the standard of responses according to the previous learning.¹⁹ Individuals with brain injuries affecting the orbitofrontal cortex also show impairment in reversal learning tasks.²³ Together, these studies suggest that assessment tests of orbitofrontal functions are quite sensitive in the FTD identification.

Specific neuropsychiatric inventories to identify FTD have also been developed, with a focus on behavioral changes, such as the Neuropsychiatric Inventory and the Frontal Behavioral Inventory.²⁵

Pharmacological therapy of FTD

The current therapeutic approach of neurodegenerative diseases is essentially based on the strategy of neurotransmitter replacement.^{18,26} As opposed to what occurs in other primary dementias, such as in AD and in dementia with Lewy bodies, neurochemical studies did not show changes in the cholinergic system in FTD.²⁷ Therefore, the acetylcholinesterase inhibitors used in the treatment of these primary dementias did not benefit patients with FTD.^{2,28,29}

Changes in the serotonergic system are found in different clinical conditions that manifest apathy/depression or disinhibition/impulsiveness.³⁰ Serotonergic deficits were also found in patients with FTD, in which these behavioral disorders are striking.³¹ It is interesting to note that studies on the serotonergic modulation of the prefrontal cortex function indicate that this

neurotransmitter affects the tasks related to the orbitofrontal part selectively, such as the gambling task and the reversal learning task, which are also those in which patients with FTD showed a most significant impairment.^{21,32} A series of open studies showed therapeutic efficacy of serotonergic drugs, remarkably the selective serotonin reuptake inhibitors, to control the behavioral symptoms of FTD.^{28,29,33} Nonetheless, Deakin et al.³⁴ did not verify any benefit of a selective serotonin reuptake inhibitor, the paroxetine, in doses up to 40 mg/day, in a double-blind placebo-controlled study involving 10 patients with FTD. Although such discrepancy may be due to methodological reasons, it is important to highlight that, in the study by Deakin et al.,³⁴ the paroxetine was used for only 6 weeks, whereas in the open studies it was used for more than 3 months. This is a major issue, since it was demonstrated that the selective serotonin reuptake inhibitors affect the serotonergic function in the orbital prefrontal cortex after 8 weeks of use, but not after 3 weeks.³⁵ Therefore, several weeks of training may be needed before achieving the desired therapeutic effect in FTD, as well as in the obsessive-compulsive disorder, which is a condition that also involves serotonergic and orbital prefrontal cortex disorder. That is why other controlled clinical tests must be performed to evaluate the real efficacy of serotonergic drugs to control the behavioral symptoms of FTD.

The role of the dopaminergic dysfunction in FTD is controversial, once there are both positive³⁶ and negative results.²⁷ Behavioral disorders, particularly disinhibition and aggressiveness, that expose the patient or their caretakers to risks, may be controlled with dopaminergic antagonists or antipsychotic drugs.^{28,29} In this case, the current tendency is to preferentially use the atypical antipsychotic drugs.²⁹ It has been proposed that even the dopaminergic agonists, such as the bromocriptine, may improve certain dimensions of the frontal cognitive functioning.²⁸ However, it is stressed that the dopamine is related, above all, to the modulation of executive functions, such as work memory, planning and attention control, and to the dorsolateral aspect of the prefrontal cortex, which are less implicated in FTD, but may be affected later in the disease progression.³² More systematic studies are thus needed to confirm the therapeutic benefit of dopaminergic drugs in FTD.

In terms of therapeutic approach specifically oriented to the pathophysiological process subjacent to the FTD, interventions that inhibit the aggregation of the tau protein may be promising in the future. It is important to highlight that the pathological aggregation of the tau protein seems to be related to the pathogenesis of several neurodegenerative diseases, generically called tauopathies, which include AD, FTD, corticobasal degeneration and progressive supranuclear palsy.³⁷⁻³⁹

ILLUSTRATIVE CLINICAL CASE AND DISCUSSION

Patient A., 56 years old, male, married, retired engineer. The patient was referred to our service with history of depression for 2 years, showing no clinical improvement with the antidepressant treatment with tricyclics and selective serotonin reuptake inhibitors.

According to the patient, since retirement about 2 years ago, he was dismayed, with no interest in taking part in any work or ludic activity, presenting a tendency to become socially isolated. However, he denied having feelings of sadness, negative ideas or ideas about death. Even with the antidepressant treatment, he denied clinical improvement. According to his wife, besides these symptoms, A. started to show a disinhibited behavior in a social environment, mainly characterized by jocosity, even directed to people he was not familiar with. This often caused embarrassing situations, which A. did not recognize as such, representing a significant change in the patient's personality, who had always been discrete and shy. A. also changed his eating habits, by increasing the water intake and giving preference to sweet foods. He repeatedly used stereotyped words and gestures, such as drumming his fingers on the table. The patient's previous medical and family histories were not relevant.

The clinical-neurological examination did not show focal neurological signs. In the cognitive screening test – the Mini-Mental State Examination⁴⁰ –, A. adequately performed all tasks, punctuating the total score. He also performed the clock drawing test correctly. The patient invariably developed a copious discourse, but with logical ideas and a tendency to minimize the behavioral changes related by his wife. Sometimes he seemed to be more disinhibited, making fun

of his condition. It should be mentioned that A. always carried a plastic glass of water, which he often drank, saying that he “was very thirsty”.

The hematological, biochemical and serological screening tests did not show any changes. The neuropsychological screening, including evaluations of general intelligence, language, memory, visuoconstructive skills and executive functions, showed a poor performance of the patient only related to executive functions and in the gambling task. The brain magnetic resonance showed bilateral hypotrophy of frontal and temporal lobes. The SPECT showed frontotemporal hypoperfusion.

The case reported illustrates the development of FTD, in which symptoms of apathy and social retraction may initially suggest a depressive syndrome. Nevertheless, the presence of striking changes in personality – in this case, in the form of disinhibition –, associated with lack of insight, clearly indicates a demential process. The occurrence of stereotyped behaviors and hyperorality reinforces the hypothesis of frontotemporal impairment. The Mini-Mental State Examination and the clock drawing test are not able to early identify the cases of FTD.¹⁰ In this sense, a detailed neuropsychological evaluation was performed. It showed impairment in assessment tests of the frontal lobes functions, mainly of the orbitofrontal (decision making) and dorsolateral areas (executive dysfunction) and preservation of the other cognitive functions. The neuroimage examinations corroborated the FTD diagnosis by showing a frontotemporal impairment. With regard to the therapy, the use of different antidepressants, including the selective serotonin reuptake inhibitors, was not efficient in the control of the symptoms of apathy or disinhibition manifested by the patients, which stresses the difficulty of the pharmacological approach to the FTD.

CONCLUSION

In the FTD, there is a striking change in the patient’s behavior and personality, with relative preservation of the cognitive functions traditionally assessed for the diagnosis of dementia, particularly the memory. Psychiatrists thus play a major role in the recognition of this type of

dementia. Therefore, when treating individuals in the presenium with behavioral changes or with early onset depressive syndromes, they must be aware to the diagnosis of FTD.

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ABSTRACT

Frontotemporal dementia is a major cause of dementia in the presenium. It is characterized by significant changes in behavior and personality, while cognitive functioning as assessed by traditional psychometric tests is relatively preserved. Thus, many patients present to the psychiatrist because of the prominence of behavioral symptoms, such as apathy, disinhibition, perseverative or

stereotyped behaviors. Rational treatment for frontotemporal dementia is currently limited. The behavioral symptoms are controlled mainly with selective serotonin reuptake inhibitors.

Keywords: *Frontotemporal dementia, taupathy, clinical features, therapeutic.*

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