**Title**
Clinico-pathologic features in early vs. late-onset Frontotemporal Dementia



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**Publication Date**
2016

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**Independent Study Project**
**May 1, 2016**

# Clinico-pathologic features in early vs. late-onset Frontotemporal Dementia

## Objectives:

International Consensus Criteria for Behavioral Variant Frontotemporal Dementia (bvFTD) base diagnosis upon the presence of salient behavioral alterations. It may be the case, however, that this presentation is modified with aging such that bvFTD is more difficult to distinguish from Alzheimer's Disease (AD) in those with late age of onset (i.e., ≥65) versus typical early age of onset (i.e., ≤60).

## Project Rationale:

Frontotemporal dementia (FTD) is a progressive neurodegenerative disease in which patients often suffer from prominent behavioral and cognitive symptoms. These behavioral and cognitive changes are in association with marked circumscribed atrophy within the frontal and anterior temporal lobes [1]. Frontotemporal atrophy can be attributed to a range of heterogeneous pathologies including: Pick bodies, hyperphosphorylated tau inclusions, ubiquitin inclusions, and nonspecific superficial cortical neuron loss [2]. Although patients with FTD typically present with personality and behavioral changes, they may also gradually acquire deficits in frontal "executive" functions and/or semantic memory processes essential to language. Visuospatial, constructional, and episodic memory abilities, however, often remain relatively preserved [3]. A variety of disorders that fall under the clinico-pathologic profile for FTD include Pick's disease with or without Pick bodies, familial chromosome 17 linked FTD with Motor Neuron Disease, dementia lacking distinctive histopathology, and corticobasal degeneration. [4]. Together, these disorders encompass FTD and account for approximately 3-20% of all cases of dementia [2].

Amongst the variety of disorders that fall within the umbrella of FTD, each can often be classified into one of two categories: either the behavioral variant of FTD (bvFTD) or primary progressive aphasia (PPA). bvFTD is the most prevalent amongst the FTD disorders accounting for nearly 70% of all FTD cases. Patients typically present with significant alterations in behavior, personality, and executive function, while cognitive functions such as gnosia, praxis and memory remain intact. Pathologically, bvFTD has been associated with symmetrical ventromedial frontal, orbital frontal, and insular atrophy and left anterior cingulate atrophy. [5]

Primary progressive aphasia is a disorder often associated with early temporal lobe atrophy resulting in alterations in a person's abilities to read, write, and speak as well as comprehend language. Clinical criteria were implemented in 2011 allowing for the classification of PPA into three subtypes: nonfluent/agrammatic variant PPA

(PNFA), semantic variant PPA (SD) and logopenic variant PPA (lvPPA). PNFA has the second highest prevalence amongst the FTD disorders and accounts for approximately 25% of all cases. Patients with PNFA display agrammatism and/or laborious speech with relatively intact language comprehension. Semantic dementia (SD) presents in about 20-25% of FTD patients and is characterized by impairment in the ability to comprehend words as well as the ability to name objects and actions. Speech production, however, remains relatively preserved. Lastly, patients with logopenic variant PPA have marked difficulty repeating sentences or phrases. [5]

Clinically, bvFTD and the subtypes of primary progressive aphasia are often difficult to distinguish between due to syndrome overlap that can arise as the diseases progress to more advanced stages. Additionally, FTD also has strong associations with the onset of motor symptoms as 40% of FTD patients also experience motor neuron dysfunction. Disorders that are closely related to FTD include corticobasal syndrome (CBS) and progressive supranuclear palsy (PSP). Patients with PSP and CBS display cognitive and behavioral alterations as well as parkinsonian extrapyramidal symptoms including bradykinesia, abnormal posture, and rigidity. [5]. In this study we will be focusing on the behavioral variant of frontotemporal dementia and the associated clinical syndrome that arises.

During a patient's lifetime, it is often difficult to distinguish between bvFTD and Alzheimer's disease (AD). Both disorders possess an insidious onset and yield a progressive dementia syndrome that can include deficits in executive function and language as well as changes in behavior. As a result of the absence of conclusive biomarkers, diagnosis relies predominantly upon differences in the prevalence of characteristic behavioral disturbances between the two disorders. Thus, the diagnosis of bvFTD requires the evaluation of a patient's presenting clinical syndrome.

In 2011, International consensus criteria were proposed for the clinical identification of bvFTD. The criteria included 5 behavioral features and 1 feature dependent upon neuropsychological evaluation. They include: 1) behavioral disinhibition [e.g. socially inappropriate behavior, loss of manners/decorum, impulsive actions] 2) apathy or inertia 3) loss of sympathy/empathy [e.g. diminished response to other people's needs and feelings, diminished social interest, interrelatedness, or personal warmth] 4) perseverative/stereotyped/compulsive/ritualistic behavior 5) hyperorality and dietary changes [e.g. altered food preferences, binge eating, increased consumption of alcohol or cigarettes, oral exploration or consumption of inedible objects] 6) sparing of memory and visuospatial functions [6]. In contrast, episodic memory impairment is typically the earliest and most prominent aspect of the AD dementia syndrome as opposed to changes in behavior and personality. [4].

In addition to the behavioral and cognitive distinctions that exist between two diseases, FTD is generally associated with an earlier age at onset than is AD. The majority of FTD cases occur within the fourth and sixth decades of life, while AD

generally presents after the sixth decade of life. There are, however, a number of FTD patients who present with a later age of onset that is more similar to that of AD patients. It has been suggested that there may be differences in the clinical manifestations between patients with early/typical vs. late-onset FTD, with those presenting later in life more closely resembling AD patients than typical FTD. A recent study observed that memory loss may be more prominent within late-onset FTD patients while behavioral changes are less obvious [7]. Neuropathologically, the majority of late-onset FTD patients within this same study displayed prominent hippocampal sclerosis and less severe cortical lobar atrophy [7]. These findings suggest that patients presenting with late-onset FTD might often be misdiagnosed with AD due to similar ages of onset, the presence of more severe memory impairment (memory is usually spared in FTD) as well as the absence of the salient behavioral symptoms that are strongly emphasized within the international consensus criteria used to diagnose bvFTD.

The purpose of this study is to examine the effect of age at onset on the clinical manifestations (according to the features listed within the international consensus criteria) in patients with autopsy confirmed FTD. The frequency of these features listed within the criteria will be compared between autopsy confirmed FTD and AD patients who will be matched on the basis of education, age at onset, and level of dementia at initial evaluation (measured by MMSE and DRS). We expect that patients with late-onset FTD (age 65 and older) will display clinical manifestations more closely resembling their age matched AD population than the patients with typical early-onset FTD (60 years of age or younger) will match their matched AD population. This would serve to highlight that the international consensus criteria may be less effective for the diagnosis of patients who present with late-onset FTD.

**Methods:**

I examined electronic databases and patient charts provided by the ADRC to identify patients that have been pathologically confirmed to have FTD via autopsy. Once I found my sample of 30 autopsy-confirmed FTD patients, I then used additional databases to identify necessary demographic information such as MMSE scores, age at onset, age at initial evaluation, gender, DRS scores, and levels of education. Once this information was gathered, I then matched each FTD patient with an autopsy confirmed AD patient who had a similar level education level, age at onset, and level of dementia at evaluation. 1 AD patient was matched for each 1 FTD patient for a total of 30 FTD and 30 AD patients.

I then reviewed each patient's medical chart at initial ADRC evaluation, which consisted of clinical and laboratory records, detailed narrative histories (as provided by knowledgeable informants; e.g. spouse or close family member of the patient), psychiatric symptom questionaires, and comprehensive physical neurological and neuropsychological evaluations. In reviewing the charts, I assessed for either the presence or absence of five of the six features listed within the International Consensus Criteria: 1) behavioral disinhibition (e.g. socially

inappropriate behavior, loss of manners/decorum, impulsive actions) 2) apathy or inertia 3) loss of sympathy/empathy (e.g. diminished response to other people's needs and feelings, diminished social interest, interrelatedness, or personal warmth) 4) perseverative/stereotyped/compulsive/ritualistic behavior 5) hyperorality and dietary changes (e.g. altered food preferences, binge eating, increased consumption of alcohol or cigarettes) oral exploration or consumption of inedible objects). Features were considered to be present if they were stated within the narrative and absent if the feature was stated as not present within the narrative or when no statements regarding the features were made.

After all of the autopsy confirmed FTD and AD patients within the sample were examined for the presence of the FTD criteria features, I then compared the prevalence of symptoms between early-onset FTD and early-onset AD and late onset-FTD and late-onset AD.

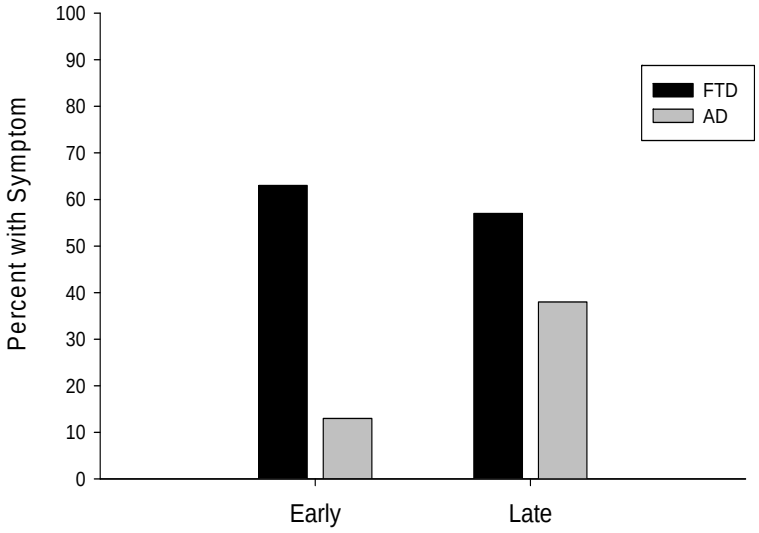
**Results:**

In comparing the 60 matched FTD and AD patients, there was no statistically significant difference between the two groups with regards to age of onset, gender, MMSE, DRS or level of education. In the early-onset condition (n=32), a higher percentage of FTD than AD patients exhibited Loss of Sympathy or Empathy (63% vs 13%), Perseverative, Stereotyped or Compulsive/Ritualistic Behavior (63% vs 6%), and Hyperorality and Dietary Changes (50% vs 0%) (all p's <.01). In contrast, there was no significant difference in the percentage of FTD and AD patients exhibiting any of these behavioral symptoms in the late-onset condition (n=28), although Apathy was greater in bvFTD than AD in both conditions.

**Table 1** Demographic and clinical features (mean ± SD)

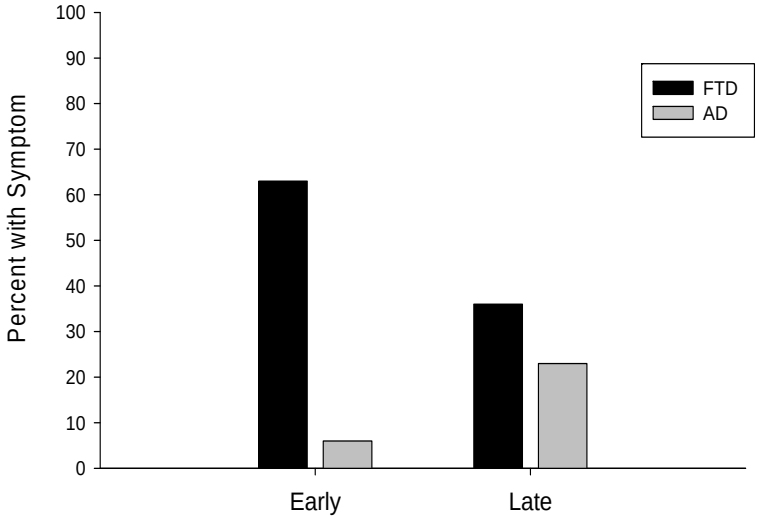
| | FTD | | AD | | |
|---|---|---|---|---|---|
| | n | Mean ± SD | n | Mean ± SD | p Value |
| Age-at-onset, y | 30 | 63 ± 8 | 30 | 63 ± 9 | 0.94 |
| Gender (M:F) | 30 | 19:11 | 30 | 20:10 | 0.79 |
| Education level, y | 30 | 14 ± 4 | 30 | 14 ± 3 | 0.82 |
| Initial MMSE score | 26 | 23 ± 4 | 30 | 22 ± 5 | 0.47 |
| Initial DRS score | 29 | 104 ± 22 | 28 | 111 ± 19 | 0.19 |

Loss of Empathy or Sympathy

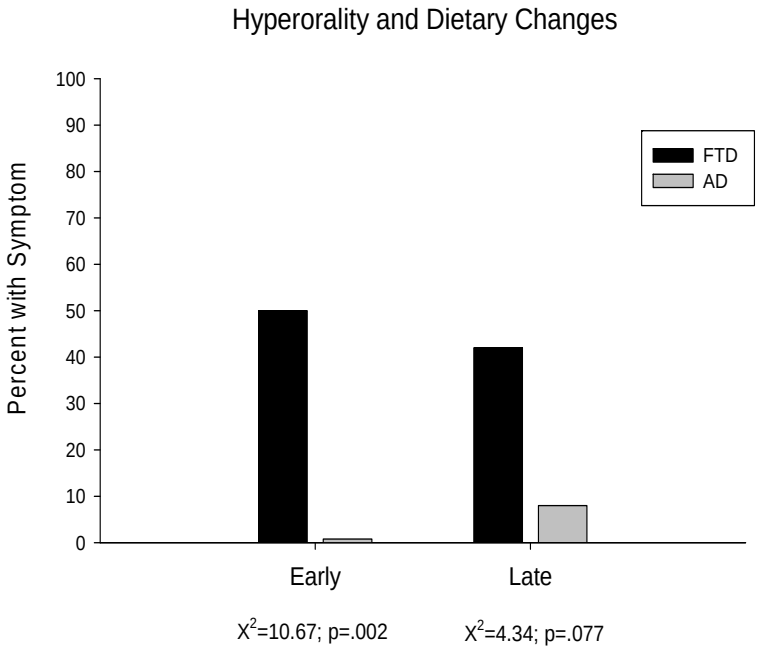


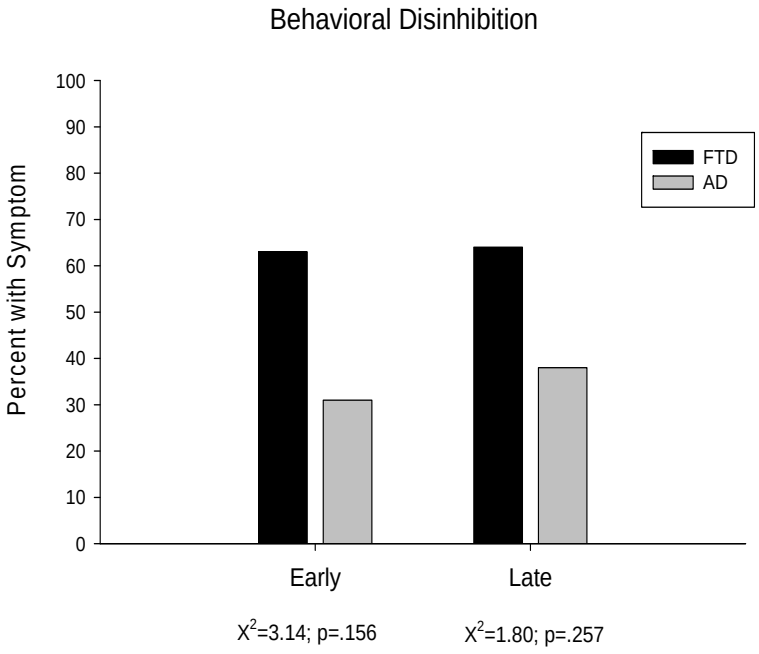

$X^2$=8.53; p=.009 $X^2$=.94; p=.449

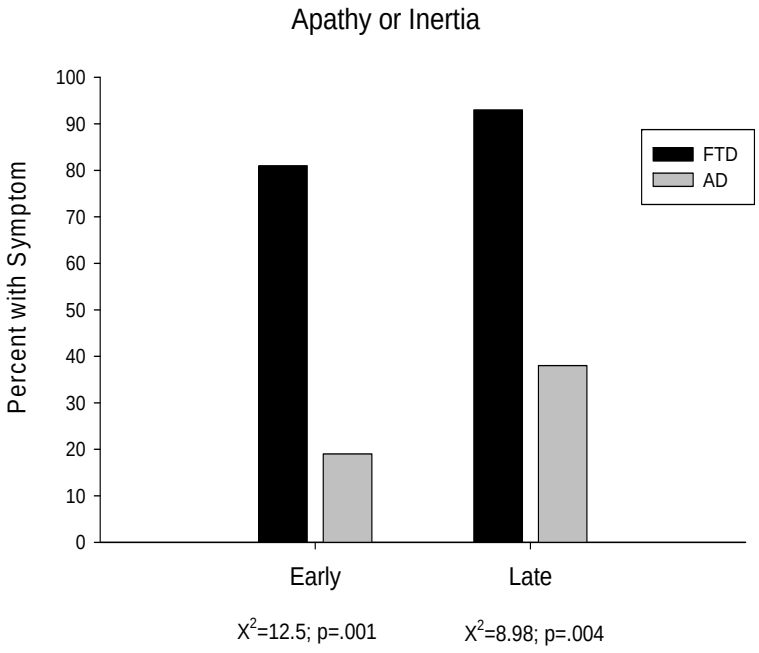
Perseverative, Stereotyped or Compulsive/Ritualistic Behavior




$X^2$=11.2; p=.002 $X^2$=.52; p=.678


Hyperorality and Dietary Changes
Percent with Symptom
100
90
80
70
60
50
40
30
20
10
0
FTD
AD
Early
Late
X2=10.67; p=.002
X2=4.34; p=.077


Behavioral Disinhibition
Percent with Symptom
100
90
80
70
60
50
40
30
20
10
0
FTD
AD
Early
Late
X2=3.14; p=.156
X2=1.80; p=.257




**Conclusion:**

Current diagnostic criteria for bvFTD are less effective at distinguishing the disorder from AD in those with late age of onset (e.g., ≥65) than early age of onset (age ≤60). Patients with late-onset FTD may be more likely to be misdiagnosed as having AD as a result of these patients generally displaying less salient behavioral features as well as presenting at ages of onset more typical for AD than FTD. Support from other biomarkers (e.g., functional imaging, CSF biomarkers) may be particularly important in differentiating FTD from AD in patients presenting after the age of 65.

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