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FRONTOTEMPORAL DEMENTIA CLASSIFICATION AND NEUROPSYCHIATRY

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Abstract

BACKGROUND—Frontotemporal dementia (FTD) is a syndrome encompassing the clinical expression of frontal or temporal lobe degeneration. The many clinical phenotypes of FTD include primary progressive aphasia and a more common frontotemporal degeneration with less marked language alteration but significant behavioral changes.

SUMMARY—This paper describes the clinical progression of neuropsychiatric symptoms among 62 predominantly behavioral presentations and 30 language presentations of FTD. Disinhibition and depression became common for both subject groups over the course of illness. Significantly more cases presenting with behavioral changes had apathy and disinhibition.

CONCLUSIONS—Language presentations of FTD had longer latency to onset of distinct neuropsychiatric changes but eventually converge with the phenotype initially affected with behavioral change. Clinicians should anticipate such neuropsychiatric changes, prepare families for the course of illness in patients with either clinical presentation, and treat symptomatically with psychotropic medications to help families cope with behaviorally disturbed patients.

Keywords

frontotemporal dementia; neuropsychiatry; Pick's disease; primary progressive aphasia; semantic dementia

Frontotemporal dementia (FTD) is a non-Alzheimer's type of dementia syndrome accounting for as many as 16% of dementia cases that go to autopsy (1). Frontotemporal dementia is a category of dementias encompassing numerous neurodegenerative disorders with a predilection for frontal or temporal lobes. Changes in the frontal lobes cause loss of organizational skills, impulsivity, poor judgment, marked changes in personality, and loss of

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language ability. Most cases are referred to as “Pick's disease,” although most patients do not have specific phenotype pathology at autopsy. Criteria for the diagnosis of FTD are listed in Table 1. The first two generations of diagnostic criteria (2,3) created expectations for neuropathological findings that have not been met. The recent recommendations from the Work Group on Fronto-temporal Dementia and Pick's Disease (4) simplify the clinical diagnostic categories to emphasize the postmortem neuro-pathological diagnoses.

SAMPLE CASE 1 ILLUSTRATES A BEHAVIORAL PRESENTATION OF FTD

A.B. was a 71 year old, right-handed woman with chief complaints of behavioral and memory problems. She had onset at age 68 years of disinhibition, impulsivity in many areas, including spending money, flattened affect, and voracious appetite. As an example, she disrobed in public if feeling too hot.

A.B. had developed a new ritualistic behavior: on daily walks with her dog; she felt compelled to touch a particular tree. As the disease wore on, she began to peel bark off the same tree. Memory and concentration problems later developed. She had difficulty with learning and maintaining new appointments, handling complex tasks such as managing a checkbook, and cooking. Several years into illness, she had falls and urinary incontinence.

Past medical history was remarkable for heavy alcohol use for 20 to 30 years, including an arrest for “driving under the influence” and regular diazepam use, but discontinuation of both substances did not improve her cognition or behavior. A half-sister had Alzheimer's disease late in the eighth decade of life.

On examination three years into illness, the patient was awake, alert and attentive but with flat affect. She displayed utilization behavior (picking up items and using them although it was inappropriate during her medical appointment) and perseverations. Her speech had decreased output and limited responses and then declined to mutism in the 5th year of illness. Mini-Mental State Examination (MMSE) score 3 years into illness was 25/30. Abbreviated Boston Naming Test score was 13/15. The patient had decreased category and letter word fluency: 6 animals/min; 4 F-words/min. Digit span forward was normal (6), but the patient took 1 full minute to name months of the year in reverse and could not do it accurately. Memory testing with the 10-item auditory verbal learning test revealed a learning curve 3,4,5 word recollection over three trials; spontaneous recall of 4/10 words after a delay; and 10/10 word recognition, consistent with a retrieval type of memory deficit, as opposed to the amnesic disorder characteristic of Alzheimer's disease. Visuospatial testing revealed disorganization on copying three-dimensional sketches, but the patient copied overlapping pentagons and simple geometric shapes well.

On neurologic examination, she had motor impersistence, brisk but symmetric deep tendon reflexes, and a marked grasp reflex bilaterally.

Structural neuroimaging showed bifrontal atrophy. Single-photon emission computerized tomography (SPECT) scan of brain showed bifrontal hypoperfusion (see Figure 1).

SAMPLE CASE 2 ILLUSTRATES THE LANGUAGE PRESENTATION

Investigators agree that subjects with the language presentation have acquired progressive language deficits that dominate other cognitive deficits in severity, at least at the onset of cognitive impairment (5-17).

C.D. was a 68-year-old, right-handed man with chief complaint of word-finding problems. He had onset at age 59 years of difficulty with speech output. His family became alarmed when he was unable to lead prayers at a Jewish holiday dinner.

C.D.'s nonfluent speech worsened from little spontaneous output to stereotypic speech, "I don't know," and relative mutism over 9 years. He withdrew from most activities, but it is difficult to tell whether this was because of the inability to communicate verbally or due to his moderate apraxia. In the 9th year of illness, he developed bowel and bladder incontinence and severe bruxism, but he still answered yes-no questions by nodding or shaking his head appropriately most of the time.

On examination, C.D. was awake, alert and attentive but with flat affect and was almost entirely nonverbal. He chewed gum constantly to avoid damaging his teeth with bruxism. He could not state his full name. He could neither participate in an MMSE nor point to pictures when given verbal cues. The patient was able to copy overlapping pentagons until seven years into illness. He had severe ideomotor apraxia nine years into illness.

On neurologic examination, C.D. developed flattening of the right nasolabial fold, decreased right armswing when walking, bilateral grasp reflex, and right extensor plantar response (Babinski sign) in the seventh year of illness.

Structural neuroimaging showed left frontal atrophy greater than right. Serial SPECT scans showed that hypoperfusion was based at first in the left frontal lobe but then affected right frontal lobe significantly (see Figure 2).

We monitor the neuropsychiatric symptoms of our subjects with both presentations of FTD regularly. This report is the first to compare the frequency of neuropsychiatric disturbances in behavioral versus language presentation groups of FTD.

METHODS

This sample includes cases identified from 1989 to 2000 at the UCLA Frontotemporal Dementia Clinic, the Harbor-UCLA Neurobehavior Clinic, and the UCSF Memory Disorders Clinic. We diagnosed subjects with behavioral or language presentation according to the criteria listed in Table 1, after mental status testing and neurologic examination, as in the Consortium to Establish a Registry for Alzheimer's Disease protocol. Structural and functional neuroimaging-indicating more pathology in dominant frontal or temporal lobe supported the diagnosis of non-Alzheimer's FTD but was not available for all subjects. Two subjects had evidence of cerebral infarction on magnetic resonance imaging (MRI) brain but the aphasia was progressive over time and the SPECT abnormalities could not be explained by stroke alone. Geschwind et al. previously reported the autopsy-confirmed diagnostic

accuracy of FTD subjects identified through the UCLA Alzheimer's Disease Center at over 90% (18).

Demographic data about the subject and caregiver responses to the Neuropsychiatry Inventory (NPI) (19) were recorded. The NPI was repeated annually if subjects were available for follow-up.

We defined onset age as the earliest age at which the first symptoms were reported by either subject or caregiver. Histories of present illness provided data on behavioral changes at onset of illness, while the NPI supplied data specifying presence of apathy, dysphoric depression, and disinhibition. The NPI was performed on initial presentation to the clinic specializing in dementia and annually if the subject followed up at the clinic.

We compared the behavioral and language presentation groups using chi-squared testing to explore differences in gender and frequency of neuropsychiatric symptoms at onset and later in the course of illness among the three diagnostic groups. T-tests compared mean ages at onset, mean educational levels, and time from onset of first symptom to diagnosis.

RESULTS

Among our sample of 62 patients with behavioral and 30 with language presentations, the two groups share similar gender distributions and mean levels of education. Non-White subjects constituted 4.8 to 6.7% of each FTD subgroup.

Mean age at onset of illness was significantly lower in behavioral presentation (μ 58 years, $t = -2.8$, two tailed $P = 0.006$), but language presentation subjects also had early onset ages (64 years). Time from onset of symptoms to diagnosis varied widely and did not differ significantly among the diagnostic groups. Childhood history of learning disorder was uncommon among all diagnostic categories.

Table 2 lists the frequency of neuropsychiatric symptoms in our sample. NPI data were available for only 48 of the behavioral presentation subjects. All subjects with language presentation had NPI data. Two of the 62 behavioral subjects had the motor neuron variant of FTD and earned the designation of "behavioral" because behavioral change was the initial symptom of illness. As expected from the diagnostic criteria, significantly fewer subjects with language presentation had neuropsychiatric symptoms at the onset of illness and over the course of illness. All but one of the behavioral presentation subjects developed behavioral disturbances within 2 years of manifesting cognitive dysfunction. Despite differences in initial presentation, the mean time to onset of first behavioral disturbances among subjects with positive NPI scores was similar for both groups. Over time, language presentation FTD subjects developed behavioral changes, although apathy and disinhibition occurred much more frequently among subjects with behavioral presentation ($P < 0.001$).

DISCUSSION

Subjects with behavioral presentation FTD had earlier onset of illness and earlier occurrence of behavioral disturbances than subjects with language presentation but neuro-psychiatric

profiles for both presentations of FTD tended to converge by late stages of illness. Behavioral changes have not been reported widely in other case reports of PPA. Six of Kertesz' 16 PPA cases developed hyperorality, utilization behavior, aggressiveness, emotional flatness, and bizarre obsessive behavior, but timing of onset relative to aphasia was not reported (20). A case report on a Dutch man with semantic dementia described onset at age 50 and disinhibition as the only behavioral change 9 years into course of illness (12). Behavioral changes occurred most consistently in our behavioral presentation group, but depression, apathy, and disinhibition occurred with high frequency in both groups. As expected by the diagnostic criteria, more subjects with language presentation maintain normal behavior patterns in the first half of the illness than those with the behavioral presentation. The few subjects with language presentation who had severe behavioral disturbances manifested them fairly early in the course of illness. This may allow the clinician to inform family members of the expected course of illness, in the context of a 7 to 10 year survival with FTD.

These conclusions are based on cross-sectional data in which subjects had been followed over a range of 0 to 10 years into illness. Examination of longitudinal data might provide more complete prognoses and elicit risk factors for developing changes over time. The power of this type of study would be increased by autopsy-confirmed diagnoses.

SUMMARY

The most recently recommended clinical classification of FTD divides cases on the basis of neural systems most markedly impaired at presentation: behavior or language. Although disinhibition and other socially disruptive behaviors are not frequently seen early in the course of the primary progressive aphasia or the motorically affected cases of FTD, depression, apathy, and disinhibition should be anticipated in most patients.

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Figure 1.
Sample case 1 with behavioral presentation of frontotemporal dementia: 3D reconstruction of HMPAO SPECT scan of brain shows bifrontal hypoperfusion.

Figure 2.
Sample case 2 with language presentation of frontotemporal dementia: 3D reconstruction of HMPAO SPECT scan of brain shows left greater than right hypoperfusion, but right sided abnormality increased from Year 7 of illness (A) to Year 8 (B).

Table 1

Evolution of Criteria for the Clinical Diagnosis of Frontotemporal Dementia

Lund and Manchester Criteria (3)—1994	Summary of Neary Criteria (2)—1998	Work Group on Frontotemporal Dementia and Pick's Disease (4)—2001
Insidious onset with gradual progression (unlike vascular dementia)		
No evidence of possible or probable Alzheimer's disease or stroke in dominant frontal lobe to explain the deficits below		
At least two of the following:	Three separate lists to describe each prototypic clinical syndrome:	The development of behavioral or cognitive deficits manifested by early and progressive change in either:
<ul style="list-style-type: none">• Early decline in social interpersonal conduct and personal awareness, that could manifest as early emotional blunting, early loss of insight or decline in personal hygiene and grooming• Abnormal oral behaviors• Mental rigidity and inflexibility• Mood change	<div>1 Frontotemporal dementia—Character change and disordered social conduct are the dominant features initially and throughout the disease course. Instrumental functions of perception, spatial skills, praxis, and memory are intact or relatively well preserved.</div> <div>2 Progressive nonfluent aphasia—Disorder of expressive language is the dominant feature initially and throughout the disease course. Other aspects of cognition are intact or relatively well-preserved.</div> <div>3 Semantic dementia—Semantic disorder (impaired understanding of word meaning and/or object identity) is the dominant feature initially and throughout the disease course. Other aspects of cognition, including autobiographic memory, are intact or relatively well-preserved.</div>	<div>1 Personality, characterized by difficulty in modulating behavior, often resulting in inappropriate responses or activities or</div> <div>2 Language, characterized by problems with expression of language or severe naming difficulty and problems with word meaning, causing significant impairment in social or occupational functioning and representing a significant decline from previous level of function.</div>
Plus at least one of the following:		
<ul style="list-style-type: none">• Frontal executive dysfunction• Absence of visuospatial deficit, at least from early-moderate stage of illness• Reduction of speech		
Supportive features which are generally detected in patients in moderate to end-stages of illness include:	Supportive features include list in first column.	
<ul style="list-style-type: none">■ Onset before age 65 y■ Positive family history■ Motor neuron disease■ Difficulty with generation of speech■ Early emergence of primitive reflexes■ Early incontinence■ Late akinesia, rigidity or tremor■ Low and labile blood pressure		

Diagnostic exclusion features:

- Abrupt onset with ictal events
- Head trauma related to onset

Substance-induced conditions, delirium, and psychiatric diagnoses are not primary etiologies for the above.
Neuropathological diagnoses:
Tau-positive inclusions

Lund and Manchester Criteria (3)—1994	Summary of Neary Criteria (2)—1998	Work Group on Frontotemporal Dementia and Pick's Disease (4)—2001
<div><div>■ Early, severe amnesia</div><div>■ Spatial disorientation</div><div>■ Logoclonic, festinant speech with loss of train of thought</div><div>■ Myoclonus</div><div>■ Corticospinal weakness</div><div>■ Cerebellar ataxia</div><div>■ Choreoathetosis</div></div>	<div>Relative diagnostic exclusion features:<div><div>■ Typical history of chronic alcoholism</div><div>■ Sustained hypertension</div><div>■ History of vascular disease (e.g., angina, claudication)</div></div></div>	<div><div>❑ With 3-repeat insoluble tau: Pick's disease, FTD with parkinsonism related to Chromosome 17, familial and sporadic FTD</div><div>❑ With 4-repeat insoluble tau: corticobasal ganglionic degeneration, progressive supranuclear palsy, FTD with parkinsonism related to Chromosome 17, familial and sporadic FTD</div><div>❑ With a mixture of 3- and 4-repeat insoluble tau: neurofibrillary tangle dominant dementia, FTD with parkinsonism related to Chromosome 17, familial and sporadic FTD</div></div> <div>or</div> <div>Neither tau-positive inclusions nor insoluble tau</div> <div><div>❑ ± motor neuron disease-type inclusions: frontotemporal lobar degeneration ± motor neuron disease, familial and sporadic FTD</div></div>

Table 2

Demographics and Neuropsychiatric Symptoms of Subjects with Frontotemporal Dementia

	Behavioral Presentation (n = 62)	Language Presentation (n = 30)
Female	51.6%	47%
Mean years education, SD	14.6, 3.4	14.5, 3.0
Mean onset age (y, SD)	58, 9.1 *	64.7, 9.8
Mean delay to diagnosis in years, SD (range)	5.4, 3.1 (1–33)	3.6, 1.9 (0.5–9)
Behavioral disturbance as initial symptom	68.9% *	36.7%
Dysphoric depressive symptoms at onset	23%	30%
Developed dysphoric depressive symptoms over course of illness	32.3%	43.4%
Mean yrs. to first behavioral disturbance, SD (range)	0.84, 2.0 (0–33)	1.3, 2 (0–10)
Subjects without behavioral changes	0	23.3% **
Apathy	89.6% of 48 **	56.7%
Disinhibition	68.8% of 48 **	53.3%

Some data were missing for 24 of the subjects with behavioral presentation.

*
= $P < .01$

**
= $P < .001$