The Frontotemporal Dementias: what we find and what we do

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Fair balance

- No financial or intellectual conflicts

- Pharmacologic interventions discussed in this presentation are “off-label”
Targets

- Introduction and description
- Presentations and problems
- Management
A woman of 42 gradually lost her interests and became inefficient at work. She complained of stomach pains for which no cause could be found. Some months later she began repetitive checking behavior and counting rituals and became progressively untidy and withdrawn. The following year...her memory was impaired and her verbal fluency was poor...she was still fully oriented.

Two years later she was withdrawn, incontinent and mostly mute. She sat swaying and rocking, often singing in a fatuous manner. Marked frontal atrophy and ventricular enlargement were apparent on CT scan. The EEG remained normal.

Lishman, 1998
• An accountant of 40 showed a 2-year decline in efficiency at work and self care, and developed severe compulsive behavior. He would check that the front door was closed up to 10 times per day. A diagnosis of obsessional neurosis was made, though it was noted that insight was lacking. His mood tended to be jovial.

• During the following year he developed child-like behavior with yelps and shouts, and became gluttonous, often stealing from other people’s plates. When seen 4 years from onset new learning was poor but he gave the dates of past events correctly. He was oriented for place and year but was wrong for the month. He performed poorly on proverb interpretation. The EEG was normal, but the CT scan showed severe frontal atrophy.

Lishman, 1998
Frontotemporal lobar dementia (FTLD)

- Primary dementias manifesting progressive disintegration of social cognition:
  - Behavioral dysregulation and antisocial behavior
  - Impoverished emotions and apathetic states
  - Disruption of speech and language
Formal criteria for diagnosis

- Lund-Manchester, 1994
- Neary et al., 1998
- McKhann et al., 2001
- Recent European criteria for Pick’s disease
- Consortium for FTLD
- Consortium for FTD
Features

- Disinhibition
- Apathy/inertia
- Loss of emotional reactivity/interpersonal sensitivity and social judgment
- Stereotypies, perseverations, fixations, compulsions and rituals
- Dysregulation of feeding and sexual behavior
- Aphasias, speech apraxia, logopenia and mutism
Features

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Progressive non-fluent aphasia*

- Hesitations, omissions, word searching, vagueness
- Telegraphic speech and phonemic errors
- Impaired naming, reading, repetition and spelling
- Impaired sentence comprehension
- Speech apraxias
- Early preservation of other cognitive domains

*Or primary progressive aphasia
Semantic dementia

- “My memory is very bad”... “I am forgetting things”... “I can’t remember words”
- Or “I can’t remember the meaning of words”
- Progressive loss of word and object knowledge
- Early anomia and impaired word comprehension
- Regularization errors in spelling
- Behavioral impairments are common
• A teacher of 58 developed dysnomia and decline in spelling ability, comprehension of reading and conversation, and singing ability. He also had impaired attention, planning and organization, along with declining self-care, child-like behavior and altered social habits (he had eaten some meals with his fingers). He developed anxiety. Two years into the illness, a neurologist suspected early dementia. MMSE score 27 points and the neurological exam was normal. Brain MRI showed temporal lobe atrophy.

• On formal neuropsychological testing 3 years later the MMSE score was 28, and he had impaired memory and learning. He had marked dysnomia, made grammatical and spelling errors, and drew a poor copy of a complex figure. When seen in our clinic, his partner described impulsive, obstinate and gluttonous behavior. His memory was poor, as were word and sentence comprehension. He scored 29 on the MMSE. Other testing was negative, including SPECT scan of the brain.

From the JHH FTD clinic
Other clinical signs

- Appearing in the moderate stages of illness
- Echolalia and mutism
- Incontinence
- Mannerisms, stereotypies and echopraxia
- Apraxias - e.g. dressing apraxias
- Environment dependence and utilization behavior
- Parkinsonism - akinesia, rigidity and tremor
- Pyramidal signs (in FTD-MND)
Differential diagnosis

- Alzheimer disease
- Vascular dementia
- Psychiatric disorders - bipolar disorder, major depression, OCD
- A variety of “young onset” dementias - for an excellent discussion of this subject: Sampson EL, Warren JD and Rossor MN. Young Onset Dementia. Postgrad Med J 2004; 80:125-139
Phenotypic diversity

- Diversity in FTLD of **character**, **pathology**, **genetics** and **tempo of evolution**
- Phenotypic variation occurs within kindreds
- Variety contributes to nosological confusion

<table>
<thead>
<tr>
<th>FTD</th>
<th>CBD</th>
</tr>
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<tbody>
<tr>
<td>Primary aphasias</td>
<td>PSP</td>
</tr>
<tr>
<td><strong>FTD-MND</strong></td>
<td>AGD</td>
</tr>
<tr>
<td>Primary prosopagnosia</td>
<td>NIFID</td>
</tr>
<tr>
<td>Hippocampal sclerosis dementia*</td>
<td>IBMPFD</td>
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</table>

*Blass et al., 2004 and Hatanpaa et al., 2004*
Epidemiology

• 5 - 10% of all dementia cases
• 50:50 sex distribution
• Usually develops between ages 45 - 65
  • Range 21 - 85
  • Onset peaks in 6th decade (avg. 53 - 58)
• Familial in up to 40% of cases

Bird et al., 2003; Neary et al., 2005
Epidemiology

- AD:FTD ratio close to 1:1 below age 60
- Average duration of illness is 6 - 8 years
  - Shorter (~3 years) in FTD-MND and NIFID
- Slow progression has also been reported (longest 22 years)

*Bird et al., 2003; Neary et al., 2005*
Genetics

- Autosomal dominant in familial cases
- FTDP-17: 40+ MAPt gene mutations
- FTD-U: progranulin gene mutations
- IBMPFD: VCP gene mutations
- FTD-3: CHMP2B gene mutations
- FTD-9: IFT74 gene? mutation
Pathological appearance of the brain in a case of Pick’s Disease: “knife’s edge” atrophy of the frontal lobe; thinning of the cortical ribbon, white matter pallor and atrophy of the caudate head

Adapted from Graff-Radford and Woodruff, 2007
Histological changes: microvacuolation in the upper layers of the cerebral cortex

Adapted from Neary et al., 2005
Histological changes: ubiquitinated intraneuronal inclusions

Adapted from Neary et al., 2005
Histological changes: intraneuronal Pick bodies

Adapted from Neary et al., 2005
Histological changes: neurofibrillary tangles in a case of FTDP-17

Adapted from Neary et al., 2005
Clinical syndromes and FTLD pathology

- Clinical syndromes are associated to varying degrees with tau+ or TDP-43 inclusions
- A majority manifest ubiquitinated TDP-43

Figure adapted from Knibb et al., 2006
Von Economo neuron (VEN) swelling and dysmorphism in FTD

Adapted from Seeley et al., 2006
FTD-associated tau pathology in von Economo neurons (VENs)

Adapted from Seeley et al., 2006
Evaluation

- History - proxy interview is essential!
- “Bedside” cognitive assessment: MMSE, mMmSE (3MS), verbal fluency tasks, CDR, clock drawing, digit span, and Trail Making Test (parts A and B)
- Formal neuropsychological testing
- Brain imaging
- EEG
- CSF analysis
MMSE score by dementia status

Source: Onyike, CU. Unpublished data from the Maryland Assisted Living Study
• A technician of 55 had difficulty finding words, which in a few years evolved to dysfluency, repetitiousness, stereotypies and echolalia. He is a bit forgetful. In the last year, work efficiency deteriorated due to his poor comprehension, reasoning, planning and completion, and lately he has been on disability leave. He approaches strangers indiscriminately. He is childlike, impulsive and unfeeling. He insists on the same TV shows. He is restless. He has eaten out of a serving bowl, and will jump the queue at the grocery store. He has become abrupt in manner, and he is restless - he bikes every day, swims many laps and runs 6.5 miles each day. His wife feels that his perception of tiredness is impaired. He “volunteers” at a local nursing home, making the rounds with the maintenance crew all day long. His wife, formerly an OR nurse, is chief of safety operations in a large local hospital. Their 23-year-old son, a professional magician and waiter, lives in another city.

• On examination he was pleasant and proper. Depression was not evident, and he did not have euphoria, psychosis or paranoia. Speech was mildly non-fluent. Verbal fluency was impaired. MMSE 29 (3MS 96). Brain MRI showed right temporal atrophy.

From the JHH FTD clinic
Cognitive testing in FTD

- MMSE score may be normal!
- Executive dysfunction ++
- Disorders of fluency and semantics
- Impairments of insight, emotion perception and processing, and social judgment
- Relative sparing of immediate memory, topographical orientation and higher-order visual perception
# Language disturbance in early FTD

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<th></th>
<th>FTD</th>
<th>PNFA</th>
<th>SD</th>
</tr>
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<tbody>
<tr>
<td>Fluency</td>
<td>✓</td>
<td>↓↓</td>
<td>✓</td>
</tr>
<tr>
<td>Speech apraxia</td>
<td>-</td>
<td>++</td>
<td>-</td>
</tr>
<tr>
<td>Errors</td>
<td>-</td>
<td>Phonemic</td>
<td>Semantic</td>
</tr>
<tr>
<td>Naming</td>
<td>✓</td>
<td>↓↓</td>
<td>↓↓</td>
</tr>
<tr>
<td>Repetition</td>
<td>✓</td>
<td>↓↓</td>
<td>✓</td>
</tr>
<tr>
<td>Reading</td>
<td>✓</td>
<td>✓</td>
<td>Surface dyslexia*</td>
</tr>
<tr>
<td>Written sentence</td>
<td>✓</td>
<td>Telegrammatic</td>
<td>✓</td>
</tr>
<tr>
<td>Spelling</td>
<td>✓</td>
<td>↓↓</td>
<td>Surface dysgraphia†</td>
</tr>
<tr>
<td>Verbal fluency</td>
<td>↓↓</td>
<td>Letter &lt;&lt; category</td>
<td>Letter &gt;&gt; category</td>
</tr>
<tr>
<td>Social behavior</td>
<td>↓↓</td>
<td>✓</td>
<td>↓↓</td>
</tr>
</tbody>
</table>

*Difficulty reading irregularly spelled words, along with regularization errors
†Regularization errors in spelling, for example colonel spelled as “curnal” and soldiers “solgers”
Coronal (top) and axial (below) views of brain imaging in selected cases of presenile dementias: From top left, viewing from left to right: MRI, TI, Alzheimer disease; MRI, TI, semantic dementia; MRI, TI, Frontotemporal dementia; MRI, FLAIR, paraneoplastic limbic encephalitis; CT, frontal meningioma; MRI, TI, the lacunar state; MRI, FLAIR, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL); MRI, FLAIR, new variant Creutzfeldt-Jakob disease.

Adapted from Sampson et al., 2003.
Neuroimaging in the differential diagnosis of FTLD: MRI and PET imaging in a case of FTLD, showing anterior temporal atrophy and hypoperfusion
Neuroimaging in the differential diagnosis of FTLD: PET imaging in a case of FTLD, showing anterior temporal hypoperfusion.
Clinical management
A retiree of 71 was seen with his wife, whose main complaint was his compulsive hoarding -- so extreme it had crowded their home and was causing marital tension. He had developed anxiety and amnesia several years earlier, and was first treated for depression. After a year he underwent neuropsychological testing, and his impaired verbal and visual memory and abstract reasoning and prompted a diagnosis of Alzheimer disease from his neurologist. Soon his lifelong collecting, learned from his mother, evolved into compulsive hoarding and prompted a referral to a psychiatrist. Psychotherapy and antidepressants were vigorously applied, to no avail, and the hoarding escalated. Their home eventually was so cluttered that they were no longer able to use the basement, attic, living room, dining rooms, and all but one of five bedrooms. Attempts by his wife to clean out the clutter elicited angry outbursts, threats of suicide and flight for several days. He perceived the situation as a contest of wills.

He had no abnormalities of mood, ideation or percept. Despite a tendency to ramble, he conversed effectively. He underestimated the extent of his memory impairment. MMSE score was 24. He acknowledged collecting, but felt that his problem was boredom. He accused his wife of using dementia as a means to win control of their home, and railed at the erosion of his role in the home.
A psychologist of 51 was seen with his wife, who complained of his emotional aloofness, gross errors of judgment in parenting and driving, disinhibited behavior and irrepressible spending. The family was on the verge of bankruptcy and he seemed unaware of this and indifferent to his wife’s complaints. He came reluctantly and threatened divorce. His MMSE score was 28. His talk was “somewhat tangential”. Abstraction was mildly impaired, and insight and judgment were also impaired. He did not have any language impairments, and he performed well on verbal fluency tasks. Recent memory was good, though imperfect, and fund of general knowledge seemed impaired (the test asked of him to name presidents of the US in reverse order – he named three and then was confused). The neurological exam was normal.

On follow-up a month later, he had been offered a promotion at work. Things were not going as well at home, as the children had been affected by his illness – his daughter, 14 at the time, seemed distant, and his son, 10 at the time, was struggling in school. The results of diagnostic tests were reviewed, the notable finding being elevation of AST and ALT. Brain MRI and SPECT were normal.
A minister and stockbroker of 58 has had FTD for some 5 years. He is cared for at home, and his wife, committed and very resourceful, would continue. She recognizes that their daughter, now 13, needs more of her attention. At last visit his apathy and inertia had become marked. He speaks little (and only in reply), and is much more difficult to direct - which reflects his declining comprehension and know-how. He is still playing tennis and ping-pong. Gluttony is extreme, with gorging and lack of satiety, and he puts inedible objects in his mouth. He also shakes his head frequently.

On examination, he was inert and indifferent. He stared at the examiner the entire time. His expression was dull and unchanging. He was not depressed, anxious or psychotic. He spoke very little, only in reply and after a delay, in single words or short phrases that conveyed little literal answers and no ideas. Once echolalia was observed. Earlier he stepped on the examiner’s foot impulsively. He fiddled with objects on the table. He blew his nose repeatedly when he spotted the box of tissues (the box was removed to stop this). During cognitive testing he tried to eat the examiner’s pen, biting off a piece as it was pried from his mouth. Given one minute, he could not name one animal. His MMSE score was 9.
General principles of dementia care

- Supervision and basic needs
- Management of the environment
- Carer resources
- Respite and residential care
- Psychotherapeutic interventions
- Pharmacologic interventions
- Genetic counseling
Clinical care for a young-onset dementia

- Illness education
- Establishment of decision-making processes
- Counseling and social support for the carer
- Adjustment to (or preparation for) loss of income
- Attending to children and parenting issues
- Identification of respite care resources
# Neurotransmitters in FTLD

<table>
<thead>
<tr>
<th>Neurotransmitter</th>
<th>Effect</th>
</tr>
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<tbody>
<tr>
<td>Serotonin</td>
<td>Decreased postsynaptic receptor density and binding; and loss of neurons in the raphe nuclei.</td>
</tr>
<tr>
<td>Dopamine</td>
<td>Loss of presynaptic terminals in the striatum; transporter reduction in the basal ganglia.</td>
</tr>
<tr>
<td>Norepinephrine</td>
<td>Possible neuron dysfunction and losses in the locus cereleus.</td>
</tr>
<tr>
<td>Acetylcholine</td>
<td>No abnormalities.</td>
</tr>
</tbody>
</table>

Huey et al., 2006
## Pharmacologic agents in FTLD

<table>
<thead>
<tr>
<th>Drug Type</th>
<th>Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trazodone</td>
<td>Irritability, disinhibition, insomnia</td>
</tr>
<tr>
<td>SSRIs</td>
<td>Depression, irritability, disinhibition, impulsions and compulsions</td>
</tr>
<tr>
<td>Neuroleptics</td>
<td>Irritability, agitation, aggression</td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>Agitation, aggression</td>
</tr>
<tr>
<td>Stimulants</td>
<td>Distractibility, restlessness, apathy, depression</td>
</tr>
<tr>
<td>Dopamine agonists</td>
<td>Apathy</td>
</tr>
<tr>
<td>Mirtazapine</td>
<td>Insomnia, restlessness, irritability</td>
</tr>
<tr>
<td>Amantadine</td>
<td>Inattention/distractibility, disorganization, perseverations</td>
</tr>
<tr>
<td>α2-antagonists</td>
<td>✓ ?</td>
</tr>
<tr>
<td>Memantine</td>
<td>✓ ??</td>
</tr>
<tr>
<td>Anticholinesterases</td>
<td>Not indicated</td>
</tr>
</tbody>
</table>
Standard of care in 2007

- Clinical interview, *with interview of proxy*
- Neurological examination and cognitive testing
- Laboratory testing, brain CT/MRI ± PET, ± EEG, ± CSF analysis
- Proxy/carer involvement in all aspects of care
- Supervision + environmental interventions as needed
- Active management of childcare and employment issues
- Empirical and trial-and-error pharmacotherapy
- Carer resources - support, information and advocacy
Genetic testing*

- A three generation pedigree is recommended
- Carefully characterized case histories
- Pathologic confirmation of diagnosis is critical
- Pre- and post-testing counseling essential for predictive testing
- Enrollment of the family in follow-up
Resources

- The Johns Hopkins Hospital Frontotemporal Dementia Clinic
  410-502-2981
- Chiadi Onyike, MD, MHS
- Brian Appleby, MD
- Mary Anne Wyle, RN
- Susan Newhouse, LCSW-C
- Support group
  - Contact: Susan Newhouse
  - 1850 York Road, Suite D, Timonium Maryland 21093
Resources

• Association for Frontotemporal dementias at [www.ftd-picks.org](http://www.ftd-picks.org)

• Websites at JHH, UCSF, the Mayo Clinics several other universities, and the NIH

• SOME EXCELLENT BOOKS:
  - *What if it is not Alzheimer’s: A Caregiver’s Guide to Dementia* - Lisa and Gary Radin, editors
  - *The Banana Lady and Other Stories of Curious Behavior* - Andrew Kertesz
  - *The 36 Hour Day* - Nancy Mace and Peter Rabins
Thanks

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- The Mackeys
- Our patients and families!