Frontotemporal Dementia (FTD) Syndromes

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Outline

- History and epidemiology
- Clinical syndromes
- Pathology & genetics
- Prognosis
- Management

A Brief History (1)

- 1890s Arnold Pick: amnestic aphasia in patients with left temporal atrophy → later he described frontal atrophy cases

- 1912 Alzheimer described silver positive inclusions in such cases “Pick Bodies”
A Brief History (2)

- 1970s Lund and Manchester
  Cases of frontal dementia (DFT)
  Pathology non AD, some Pick bodies

- 1982 Mesulam “Primary progressive aphasia”
  → outpouring of cases of PPA
  Two main forms:
  - Non-fluent
  - Fluent with semantic impairment

A Brief History (3)

- 1994 Consensus criteria for FTD from Lund and Manchester

- 1998 Revision of criteria for frontotemporal lobar degeneration (FTLD)
  Three main subtypes:
  - Behavioural variant known simply as FTD
  - Semantic dementia
  - Progressive non-fluent aphasia

FTD/FTLD Classification

- FTD
  - Behavioural variant
  - Language variants (Progressive aphasia)
    - Progressive non-fluent aphasia (PNFA)
    - Semantic dementia
FTD: Overlaps

- Considerable overlap between FTD and motor neurone disease (MND).
  Typically present with rapidly progressive mixed frontal-aphasic syndrome sometimes with psychotic features and verb processing deficit then develop bulbar MND.
  Bak T et al. Brain 2001, 124, 103-120
- Extrapyramidal features are common.
  Some cases develop severe apraxia → corticobasal degeneration syndrome.
  Also cases with CBD commonly become aphasic.

FTD/FTLD Classification

- FTD/FTLD
- MND
- Behavioural form
- Language form (progressive aphasia)
- Corticobasal degeneration
- Progressive non-fluent aphasia (PNFA)
- Semantic dementia

Causes of Late Onset Dementia

- AD
- Vascular
- DLB
- Other
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Causes of Early Onset Dementia

<table>
<thead>
<tr>
<th>Condition</th>
<th>Prevalence per 100,000</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>81 - 98</td>
</tr>
<tr>
<td>AD</td>
<td>11 - 41</td>
</tr>
<tr>
<td>FTD</td>
<td>4 - 15</td>
</tr>
</tbody>
</table>

City of 4 million → 4,000 EOD

Ratnavalli et al. Neurology 2002, 58

Levels of Classification in FTD

- Clinical syndrome reflects distribution of pathology
- Histopathological syndrome
  - Inclusion based (immunohistology)
  - ± tau; ± ubiquitin etc.

Frontal (Behavioural) Variant
FTD (fvFTD)

- Commonest variant
- Presents with insidious personality and behavioural disturbance
- Loss of empathy, apathy, changes in food preference/appetite, stereotypic and repetitive behaviours, disinhibition, blunting, poor self-care
  (Neuropsychiatric Inventory NPI or Cambridge Behavioural Inventory)
Typical fvFTD Case: J.W. (1)
- Accountant aged 49
- Seen in 1991; No complaints
- Wife:
  - several yrs of odd behaviour
  - Rigid and anti-social
  - Tactless
  - Lack of empathy with children
  - Unwise financial decisions

Typical fvFTD Case: J.W. (2)
- No Family History
- Physical Examination normal
- MMSE 30/30
- Formal Neuropsychology ± unremarkable
  - Poor fluency only
  - WCST 6 categories; memory all normal

Typical fvFTD Case: J.W. (3)
- MRI: normal
- HMPAO-SPECT: mildly abnormal
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Typical fvFTD Case: J.W. (4)
- 1991-1993: little change
- 1994
  - Declining self-care
  - Very stereotyped
  - Anti-social “sexual” behaviours
  - MMSE still 30/30

Typical fvFTD Case: J.W. (5)
- 1995
  - Overeating sweets ++
  - Wt gain 40 lbs
  - Apathetic
  - Occasional incontinence
  - MMSE 30/30
  - MRI and SPECT now abnormal

Typical fvFTD Case: J.W. (6)
- 2000-2004
  - Living alone with support
  - Little conversation
  - Poor self-care
  - MMSE 30 → 26
  - Decline on “frontal” and memory tests
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Neuropsychology in fvFTD

- May be normal
- Memory poor in a third of cases, can be severe
- Fluency (FAS) fairly sensitive but non-specific
- Recent work shows more specific deficits in “theory of mind” and emotion processing

Theory of Mind (ToM)

- Ability to infer the mental state of other people: “mentalising”
- ToM defective in autism
- Imaging and lesion studies implicate OFC and ant cingulate in ToM

Patient vs. Control Performance on ToM and Physical Cartoons

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Emotion Judgement

Morphed faces: 100% disgust to 100% anger

Lough, Neuropsychologia

Atrophy in fvFTD:
Orbitofrontal and Medial Cortex

Hodges et al., Brain 1992, 115, 1783–1806

Semantic Dementia (SD)

- Selective impairment of semantic memory causing severe anomia, impaired spoken and written word comprehension, impoverished fund of general knowledge
- Relative preservation of other aspects of language output and comprehension notably syntax and phonology
- Preservation of perceptual skills and non-verbal problem solving
- Relatively preserved autobiographical and day-to-day memory

Hodges et al., Brain 1992, 115, 1783–1806

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Typical SD Case: D.V. (1)
- 65 year-old man, skilled craftsman
- 24 months word finding difficulty and “loss of memory for words”
- Impaired comprehension of word meaning
- Intact everyday activities
- Good day-to-day memory

Typical SD Case: D.V. (2)
Change in naming errors

<table>
<thead>
<tr>
<th></th>
<th>dog</th>
<th>horse</th>
<th>zebra</th>
<th>kangaroo</th>
<th>eagle</th>
</tr>
</thead>
<tbody>
<tr>
<td>1998</td>
<td>√</td>
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<tr>
<td>2001</td>
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</table>

Typical SD Case: D.V. (3)
Comprehension in SD

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Perirhinal Cortex: a Key Region?

Normal
Perirhinal (blue) and Entorhinal cortex (red)

Semantic Dementia


VBM Correlation with Semantic Deficit in Mixed FTD-SD Group (n=20)
- Strong correlation with anterior temporal lobes


Brain Basis of Concept Knowledge?

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Laterality

<table>
<thead>
<tr>
<th>Loss of “word Memory”</th>
<th>Person recog’n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Impaired comprehension</td>
<td>Loss of insight</td>
</tr>
<tr>
<td>Lf predominant cases</td>
<td>Social cognition</td>
</tr>
<tr>
<td>N = 36</td>
<td>N = 11</td>
</tr>
</tbody>
</table>

Word-Picture Matching: Faces Vs. Animals

Progressive Non-Fluent Aphasia (PNFA)

- Speech dysfluent, halting, distorted
- Phonological errors
  - /elec-trick-ery (electricity)
- Grammatical errors
- Impaired sentence comprehension
  - If the lion ate the tiger, who was left?
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Progressive Non-Fluent Aphasia (PNFA)
- Orobucal apraxia common
- Behavioural changes unusual
- Overlaps with corticobasal degeneration (CBD)

Distribution of atrophy: SD vs. PNFA

- All PPA patients vs. control
- Each clinical group vs. control

FTD Genetics: tau Mutations
- Up to a third have a positive history, if you include dementia, Parkinson’s and MND
- 50+ families with various tau gene (chromosome 17q21) mutations, but overall < 10% of those with familial FTD have a tau mutation

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**FTD Genetics: Non-tau**

- Linkage to Chr 17q21 in some families without tau mutation, no tau histopath
- Recent discovery of Chr 3 endosomal ESRCT III complex in Danish family, plus one unrelated UK case
- FTD-MND linked to Chr 9, two loci, no gene found yet

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**Pathology of FTD:**

**Histological Subtypes**

- Tau-positive
  - Classical Pick bodies (3R)
  - ‘CBD’ (glial tau) (4R)
  - AGD (4R)
  - Other FTDP-17
- Ubiquitin-positive
- Neurofilament
- Lacking distinctive features; now very few cases

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**Relationship between pathology and clinical syndrome**

- n=61 pathologically confirmed FTD in Sydney-Cambridge series
- Clinical CBD = 7/9 tau +ve CBD pathology
- PNFA = most have tau +ve Pick Bodies
- MND-FTD = 9/9 ub +ve “MND dementia”
- SD = 4/9 also have ubiquitin +ve (MNDI) inclusions
- fvFTD (n=26) pathology unpredictable

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Pathological Basis of SD

- Consecutive cases clinically diagnosed semantic dementia with pathology
- n=18
- Categorized by histopathology
- Distribution of pathology (semi-quantitative, 0...+++)


Histopathology in SD

- 13 cases: ubiquitin inclusions
  - 3 cases: Pick bodies
  - 2 cases: tangles, plaques (AD)
    - One atypical MRI

Survival from Symptom Onset

- Age onset symptoms 58.5±8
- Age at diagnosis 61.5±7
- Age at N. Home entry 63.1±8
- Age at death 65.6±8

Hodges JR et al. 2003 Neurology 61, 42
Management

- Multidisciplinary team
- Genetic screening and counselling
- Behaviour modification: psychological and drug therapies
- Information and support
  - Pick's Disease Support Group
    www.pdsg.org.uk
  - FTD Carer Support Group (Cambridge)
    www.ftdcarers.org.uk