An update on frontotemporal dementia

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Outline of the talk

1. Background
2. Clinical syndromes
3. Pathology
4. Genetics
5. Biomarkers
6. Clinical trials
7. Support for patients and families
1. Background
Epidemiology

• Second most common young onset degenerative dementia

• Prevalence
  – 10-20 per 100,000 (ages 45-64)

• Incidence
  – 3-4 per 100,000 (ages 45-64)
Increasing interest in FTD over the years

Number of papers on FTD in Pubmed

1990: 18
1992: 22
1994: 28
1996: 46
1998: 69
2000: 107
2002: 202
2004: 255
2006: 292
2008: 341
2010: 426
2012: 460
2014: 568
FTD is a heterogeneous disease

Genetics
- MAPT
- GRN
- C9ORF72
- VCP
- FUS
- CHMP2B

Pathology
- Tau
- TDP
- FUS
- Ubi
- UPS

Clinical syndromes
- bvFTD
- PNFA
- SD
- CBS/PSP
- MND/ALS
2. Clinical presentation
Disorders commonly overlap with each other
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- SD
- bvFTD

UCL
Splitting the progressive aphasias

• Traditionally 2 subtypes
  – SD = ‘fluent’ aphasia
  – PNFA = ‘nonfluent’ aphasia

• Problem: PNFA very mixed
  – Agrammatism
  – Motor speech impairment: ‘apraxia of speech’
  – Anomia
  – Word-finding pauses

• New classification splits “nonfluent” patients into PNFA and LPA
PNFA

- ‘Motor’ speech impairment
- Can be very slow and misdiagnosed as functional
- Agrammatism
- May develop CBS/PSP
- More anterior atrophy

- Underlying pathology is FTLD: tau >> TDP-43

LPA

- Hard to characterise as ‘fluent’ vs ‘nonfluent’
- Word-finding difficulties
- Motor speech/grammar normal
- More posterior atrophy

- Underlying pathology AD
3. Pathology
Frontotemporal lobar degeneration (FTLD)

**Tau-positive**
- 4R
  1. CBD
  2. PSP
  3. AGD
  4. GGT
- 4R +/- 3R
- 3R
  5. MAPT mutations
  6. Pick’s disease

**Ubiquitin-positive, tau-negative (FTLD-U)**
- FTLD-TDP
  7. Type A
  8. Type B
  9. Type C
  10. Type D
  11. Other
- FTLD-FUS
  12. aFTLDU
  13. NIFID
  14. BIBD
- FTLD-UPS
  15. CHMP2B mutations
Pathology – the helpful parts

• Commonest pathologies
  – TDP ~ Tau >> FUS

• Some clear associations:
  – PSP syndrome very commonly PSP pathology
  – SD most commonly TDP type C
  – FTD-MND most commonly TDP type B
  – V young onset sporadic disease (<40) associated with FUS pathology
  – AD pathology: ?10-20% of bvFTD; PPA (LPA most and ?<5% of SD and PNFA)
Pathology – the unhelpful parts

- No one-to-one correlations

- CBS can have multiple pathologies including most of the tau types and TDP type A

- PNFA more commonly tau pathology if there is a motor speech disorder but variable

- bvFTD has very variable pathology
4. Genetics
Genetics of FTD

- Up to 50% of patients with FTD describe a family history of a dementia

- But… a smaller number have an autosomal dominant inheritance (~a third)

- And variable across clinical syndromes
Genetics of FTD

- Which are the genes involved in FTD?

- **1998** – Microtubule-associated protein tau (*MAPT*)
- **2004** – Valosin-containing protein (*VCP*)
- **2005** – Charged multivesicular body protein 2B (*CHMP2B*)
- **2006** – Progranulin (*GRN*)
- **2008** – TAR-DNA binding protein (*TARDP*)
- **2009** – Fused-in-sarcoma (*FUS*)
- **2011** – Chromosome 9 open reading frame 72 (*C9orf72*)
- **2012** – Sequestosome 1 (*SQSTM1*)
When and what to test?

- **On family history**
  - Autosomal dominant family history commonly present… but not always

- **On clinical syndrome:**
  - bvFTD/FTD-MND > PNFA > CBS >> PSP >> SD
  - bvFTD: any of the genes (C9orf72 if delusions)
  - FTD-MND: C9orf72
  - PNFA: GRN >> C9orf72
  - CBS: MAPT > GRN mutations
  - PSP syndrome: rare cases of MAPT mutations
When and what to test?

• Imaging pattern can be helpful

• No clear pattern for C9orf72 expansions
C9orf72 – a brief overview

- Hexanucleotide GGGGCC repeat disorder
- Minimum pathogenic repeat length unclear (?20-30). Usual repeat length 100’s/1000’s
- Abnormal repeat translated into dipeptide repeat proteins which appear to be toxic species
- Clinical presentation usually FTD (bvFTD >> PNFA), ALS or both. Odd delusions and hallucinations can be present.
- Unusual presentations reported:
  - “HD-like”, “PD-like”, DLB, MSA, CBS, cerebellar ataxia
  - OCD, ‘schizophrenia’, ‘bipolar disorder’
- Imaging v. variable – may involve thalamus and cerebellum
- Very variable prognosis: a couple of years to >20
Risk of genetic mutation

- bvFTD
  - autosomal dominant family history: chance of finding a known mutation is ~90%
  - with a single young onset (<65) first degree relative: risk is ~60%
  - with a single older onset (>65) first degree relative: risk is ~25%
  - no known family history: risk is ~10%

- PPA: risk is <5%
  - This is mostly in patients with PNFA
  - SD: risk is <1% (0 in UCL cohort)

- CBS: risk is 1%
- PSP: risk is <0.5%
When and what to test?

• Next generation sequencing will allow us to test all the genes at the same time (apart from C9orf72).

• But… multiple variants in same person – what’s pathogenic?

• Some people carry double mutations e.g. in C9orf72 and GRN
5. Biomarkers
How useful is …

• CSF?
  – Exclude AD pathology
  – NB: raised tau NOT a marker of tau pathology

• PET scan?
  – FDG-PET – no large advantage over volumetric MRI; less knowledge about variability in different subtypes
  – Amyloid (e.g. AV45/Florbetapir) – will become available to help exclude AD pathology in very specific circumstances
  – Tau (e.g. AV1451) – experimental and unlikely to be available soon

• DaTscan?
  – Probably not
6. Clinical trials
Current trials in FTD

- TauRx: methylene blue
- Forum: HDAC inhibitor for GRN mutations
6. Support for patients and families
Rare dementia support

frontotemporal dementia

[FTDSG] SUPPORT GROUP
(formerly Pick’s Disease Support Group)

familial frontotemporal dementia

[ fFTD ] SUPPORT GROUP
www.ftdsupport.org
Distinguishing FTD from Alzheimer’s disease using brain imaging

Researchers in Sydney, Australia have been investigating an area deep in the brain called the striatum. Their work suggests that this area and the way it is connected to other areas of the brain could be used as a new marker to help work out whether someone has FTD or Alzheimer’s disease. We have a [...]

Continue Reading →

What causes people to

October 5, 2015

October 7, 2015
Summary and the future

• FTD still a clinical diagnosis supported by neuroimaging

• Poor clinico-pathological correlation

• Genetic testing worth doing in certain circumstances

• Biomarkers still in very early stages

• Therapeutic trials now starting: 2 already running and more planned
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