Young Onset Dementia – A New Horizon

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Young onset dementia - definition

- Defined as onset of dementia prior to age 65
- Alzheimer's disease is the most common cause at any age
- Higher prevalence of familial AD cases especially below age 50
- Frontotemporal dementia (FTD) second most common cause
- Other causes: stroke, prion disease, autoimmune disease and cancer related rapidly progressive dementias, and rare conditions

Alois Alzheimer descr case in 1906 of Auguste D from Frankfurt Asylum.

Alzheimer’s disease

- Insidious onset and progressive decline

"Typical" presentation of AD

<table>
<thead>
<tr>
<th></th>
<th>Normal</th>
<th>Pre-clinical</th>
<th>Prodromal</th>
<th>dementia</th>
</tr>
</thead>
<tbody>
<tr>
<td>duration</td>
<td>~30 yrs</td>
<td>~5 yrs</td>
<td>~9-10 yrs</td>
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</table>

Typical progression of cognitive impairment:
- Episodic memory
- Semantic memory
- Attention (frontal) & visuospatial

Reflects pathological spread (esp. NFTs):
- Medial temporal
- Temporal neocortex
- Other multimodal association cortex

"Atypical" presentation of AD

- Frontal variant AD – executive deficits
- Progressive aphasia: anomic or logopenic (hesitant)
- Posterior cortical atrophy:
  - Occipito-temporal: “what” pathway (object, face, word)
  - Bi-parietal: dorsal “where” pathway (location)
- Primary visual cortex (visual variant AD) – cortical blindness
- Congophilic angiopathy – lobar haemorrhages
- Younger onset also can have movement disorders (myoclonus)

18FDG-PET - Quantitative analysis using NeuroStat 3D SSP in AD

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*Initial main features are focal/late episodic memory, atypical in young age onset, course AD here may be accompanied by incidental pathologies – CAA, vascular, Lewy bodies, etc

Galton et al Brain 2000;123:484-498

More likely in younger onset AD than typical amnestic presentation

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Familial AD – genetics of YOD

- Autosomal dominant transmission (both males & females affected and can pass onto their offspring). Present 30’s or older.
- Gene mutations present in ~40% of all EOAD (<1% of all AD)
- 3 commonest genes cause increased production of amyloid
  - Presenilin 1 gene (~50%) on ch 14, gamma-secretase protein, mutations increase toxic amyloid species; Presenilin 2 gene (ch1)
  - APP gene (amyloid precursor protein) on ch 21 gene (cf Down syn trisomy 21 leads to increased gene dosage effect)
- Amnestic or atypical features – language, behavioural, psychiatric, myoclonus, seizures, spastic paraparesis, parkinsonism, ataxia
- Negative family history does NOT exclude FAD

Fronto-temporal Dementia (FTD) - Prevalence

- Second commonest cause young-onset dementia after AD
- Prevalence: 15 per 100,000 population aged 45-64 years (UK studies)
- Australia: 45-64 persons are ~25% of population (5.7/22.9M), total of 860 cases (range 400-1550)
- Exact figures not known for older adults (probably commonly misdiagnosed)

Classifying FTD - Clinical syndromes

- “FTD” vs “FTLD”
- MND
- Behavioural form (bvFTD)
- Language form
  - Progressive Aphasas (PPA)
- Non-fluent (PNFA, nfvFTD)
- Semantic dementia (svFTD)
- Corticobasal degeneration

bvFTD - FDG-PET

53 year old female with 18 months of worsening personality change, repetitive behaviours, marked reduction in speech Neuropsychology identified language and executive dysfunction worse than memory impairment.

FrPaasso FDG-PET

FTD - Clinicoanatomical Correlations

- Dorsolateral Frontal Cortex: executive functions, working memory
- Temporal Cortex Names, faces, face recognition (right)
- Emotion Processing
- Motivation
- Behavioural Regulation
- Social Cognition

Behavioural variant FTD: Revised Criteria

- Clinical features (persistent, recurrent, not single events)
  - Disinhibition* (socially inappropriate, loss of manners, rash, careless)
  - Apathy/inertia
  - Loss of sympathy/empathy
  - Perseverative, stereotypic or ritualistic behaviour*
  - Hyperorality and dietary changes*
  - Neuropsychological - executive/generative deficits
- No other explanation: major psychiatric illness, TBI, strokes, infections, etc

POSSIBLE: ≥3 of above EARLY in course
PROBABLE: + Progression & MRI, SPECT or PET changes
DEFINITE: + Pathological confirmation or Genetic mutation

Symptom checklists are helpful clinically - Cambridge Behavioural Inventory: www.ftdrg.org
Primary Progressive Aphasia

Semantic variant (SD)
- Word comprehension defects
- Anomia
- Fluent speech
- Repetition normal
- Cannot define words

Logopaenic aphasia (LPA)
- Word finding pauses++
- Anomia
- Loss of prosody
- Agrammatism
- Phonemic paraphasias
- Apraxia of speech

Non-fluent variant (PNFA)
- Effortful speech, groping
- Agrammatism
- Anomia
- Phonemic paraphasias
- Apraxia of speech

svFTD - Coronal MRI views
- Normal
- Early AD
- SD
- SV-FTD - 100% abnormal; L temporal lobe

Classifying FTD - Genetics/Familial FTD
- Single gene (Mendelian) disease
- Autosomal Dominant Pedigree
- Up to 30% positive family history if include MND
- Peak onset 60s, many older.
- High risk (2 or more affected relatives) much rarer. May be 10% genetic overall. Single genes more common.
- More a genetic disorder than AD.

Genetics of FTD
- Gene mutations present in ~80% if have autosomal dom pattern, so much more common than in Alzheimer’s disease
- 3 commonest genes have different mechanisms
  - C9ORF72 gene on ch 9 – commonest, esp if MND/psychosis
  - Ch 17 – closely located MAPT (tau) and Progranulin genes
- Negative family history does NOT exclude FAD (ascertainment...)
- svFTD much more commonly genetic than language variants (especially semantic variant)
- Caregiver support - burden is higher than AD due to behaviours
- Minimal research addressing models of care (eg ABC)
- Legal capacity issues, driving tests
- Genetic counseling (asymptomatic relatives)
- Medications - rarely used to Rx depression, psychosis, agitation
- Research trials:
  - FTD registry, brain-banking, genetic testing
  - Anti-tau therapies in phase 1 and II trials (including at ECDC)
  - TDP-43 therapies under development

Picture naming in SD over time

<table>
<thead>
<tr>
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<tr>
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<td>✓</td>
<td>creature</td>
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<tr>
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<td>✓</td>
<td>horse</td>
<td>creature</td>
</tr>
<tr>
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<td>koala</td>
<td>Australian</td>
<td>creature</td>
</tr>
<tr>
<td>eagle</td>
<td>pidgeon</td>
<td>bird</td>
<td>DK</td>
</tr>
</tbody>
</table>

Word definitions:
- Violin: “What’s a violin?”
- Caterpillar: “Is that a kind of cat?”
11C-PiB PET in different dementias

PiB detects Aβ in fibrillar plaques - not Aβ oligomers

Rowe CR et al Neurology 2007; 68:1718

Other causes of YOD

Stroke
- Stroke is associated with strategic infarctions impairing specific cognitive functions, or perhaps more slowly progressive mimic of AD (usually in older patients).
- Vascular disease appears to accelerate AD clinical symptoms.

Prion diseases
- Creutzfeldt-Jakob causes a rapidly progressive dementia with myoclonic jerks (stimulus sensitive), EEG and CSF changes. Currently not reversible.

And numerous rarer conditions...
- eg. cancer and lymphoma are associated with metastatic but also remote effects on brain that can resemble a dementia.

Questions?

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