Young Onset Dementia – A New Horizon

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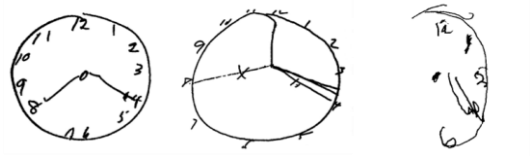
Young onset dementia - definition

- 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



diagnosis | 13 months | 29 months

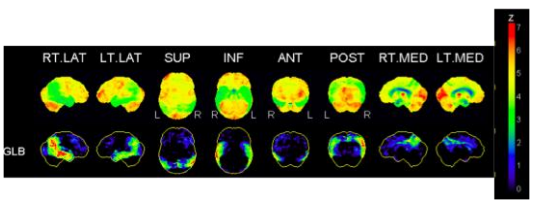
"Typical" presentation of AD

Normal → Pre-clinical ~30 yrs → Prodromal ("MCI") ~5 yrs → dementia ~9-10 yrs

Typical progression of cognitive impairment:
episodic memory → semantic memory → attention executive (frontal) & visuospatial

Reflects pathological spread (esp. NFTs):
medial temporal → temporal neocortex → other multimodal association cortex

^{18}FDG-PET - Quantitative analysis using *NeuroStat 3D SSP* in AD



Courtesy Dr Chris Rowe, Austin PET Centre 2011

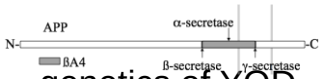
"Atypical" presentation of AD

More likely in younger onset AD than typical amnestic presentation

- 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)

*Initial main features are focal but not episodic memory, atypical in symptoms not age onset, course AD here may be accompanied by incidental pathologies – CAA, vascular, Lewy bodies, etc

Galton et al Brain 2000;123:484-498



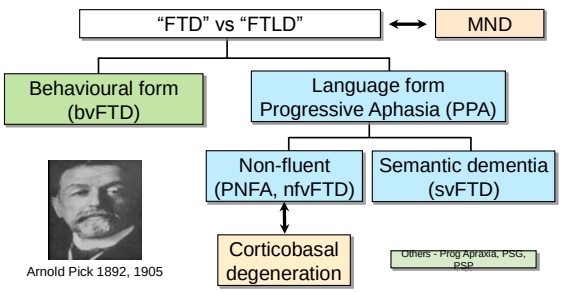
Familial AD – genetics of YOD

- 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



Arnold Pick 1892, 1905

Behavioural variant FTD: Revised Criteria

Rascovsky et al Brain 2011; 134:2456-77 for the International bvFTD Consortium

- **Clinical features** (persistent, recurrent, not single events)
  - Disinhibition* (socially inappropriate, loss of manners, rash, careless)
  - Apathy/inertia
  - Loss of sympathy/empathy
  - Perseverative, stereotypyic or ritualistic behaviour*
  - Hyperorality and dietary changes*
  - Neuropsychological - executive/generative deficits

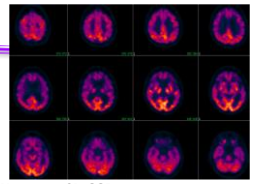
No other explanation: major psychiatric illness, TBI, strokes, infections, etc

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

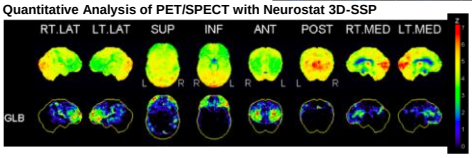
Symptom checklists are helpful clinically - Cambridge Behavioural Inventory:

bvFTD - FDG-PET

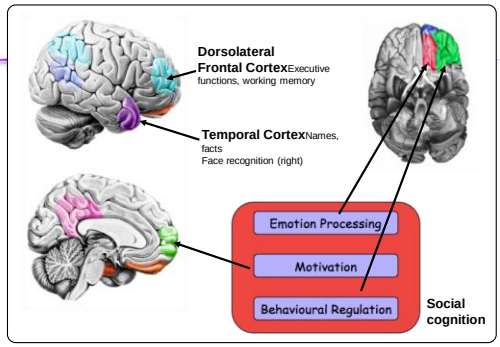
53 year old female with 18 months of worsening personality change, repetitive behaviours, marked reduction in speech.Neuropsychology identified language and executive dysfunction worse than memory impairment.



Quantitative Analysis of PET/SPECT with Neurostat 3D-SSP



FTD - Clinicoanatomical Correlations



Primary Progressive Aphasia

Semantic variant (SD)	Logopaenic aphasia (LPA)	Non-fluent variant (PNFA)
•Word comprehension defects •Anomia •Fluent speech •Repetition normal •Cannot define words	•Word finding pauses++ •Anomia •Know meaning •Sentence repetition poor	•Effortful speech, groping •Loss of prosody •Agrammatism •Anomia •Phonemic paraphasias •Apraxia of speech
		
TDP-43+ inclusions	AD	Tau+

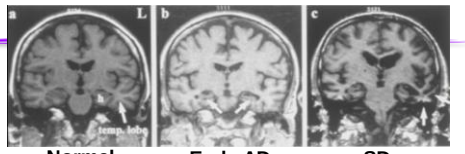
Gorno-Tempini et al., Neurology 2011; 76:1006-1

Picture naming in SD over time

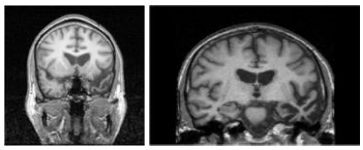
	1998	2001	2003
dog	√	√	√
horse	√	√	creature
zebra	√	horse	creature
kangaroo	koala	australian	creature
eagle	pidgeon	bird	DK

- ***Word definitions:***
- Violin: "What's a violin?"
- Caterpillar: "Is that a kind of cat?"

svFTD - Coronal MRI views

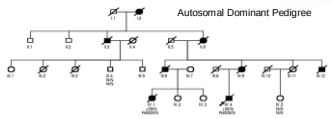


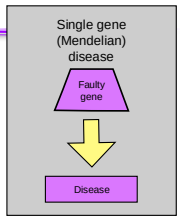
Normal Early AD SD



SV-FTD - 100% abnormal; L temporal lobe

Classifying FTD - Genetics/Familial FTD





- 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

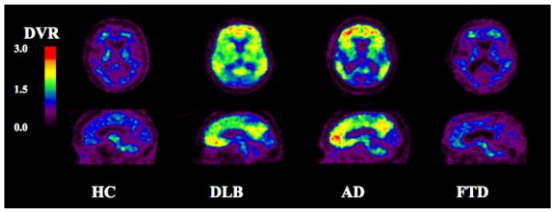
- Gene mutations present in ~80% if have autosomal dom pattern, so much more common than in Alzheimer's disease
- 3 commonest genes have different mechanisms
  - C9ORF72 gene on ch 9 – commonest, esp if MND/psychosis
  - Ch 17 – closely located MAPT (tau) and Progranulin genes
- Negative family history does NOT exclude FAD (ascertainment...)
- bvFTD much more commonly genetic than language variants (especially semantic variant)

Management

- Information - www.ecdc.org.au, www.ftdrg.org
- 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

Antecedent-Behaviour-Consequence Model: Merrilees et al Amyotroph Lateral Scler 2010; 11: 298–302

^{11}C-PiB PET in different dementias



PiB detects Aß in fibrillar plaques - not Aß oligomers

Rowe CR et al Neurology 2007;

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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