Research developments in dementia and learning disabilities

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MSNAP Special Interest Day Learning disabilities and dementia
Overview

• Background: prevalence & neuropathology
• Focus on Down syndrome as a genetic form of dementia - closer to Familial Alzheimer’s disease
• Role of brain amyloidosis in dementia
• Pre-clinical (asymptomatic) or prodromal state (some impairment) and dementia state
• Primary prevention
• Biomarkers: PET amyloid-ligand, MRI, mitochondrial, retinal, neurophysiological (EEG) dysfunction
Epidemiology

• Improved longevity in ID (1930s, c.18.5 years; 1990s, 66 years)
• By 2020 the number >65 years with ID will double
• Ageing and associated conditions more relevant
• ID population at increased risk of developing dementia, esp. Down syndrome
Higher prevalence

• In >65 years 8.5% (x3 more than non-ID population)
• Alzheimer’s disease commonest (c. 60%)
• Others: Vascular dementia, Lewy body dementia, Fronto-temporal dementia
• Down’s syndrome-AD commoner; vascular rare
Comparison of dementia age-specific prevalence rates
Alzheimer's disease

• 50% have AD pathology but others are “mixed dementia”
• Histopathological process starts well before symptoms appear
• Genetic causes rare (c.1%) & earlier onset-Amyloid Precursor Protein: APP, Presenilins: PS1; PS2 (part of γ-secretase)
• Trisomy 21
Alzheimer’s disease-risk factors

• Age
• Family history increases risk
• Apolipoprotein E; there are three isoforms e2 (10 to 20%), e3 (60%), e4 (20-30%)
• E4e(3 or 2) (x3); e4e4 (x8 to x12): 40 to 65% of AD population
• If e4 earlier onset; e2 “protective”
• Other risk genes lesser impact e.g. TREM-2
Alzheimer’s disease-risk factors

• Cardiovascular risk factors- hypertension, hyperlipidaemia, diabetes, obesity, smoking
• Fewer year in education-?cognitive reserve building or socio-economic factors
• Social & cognitive engagement
• Moderate (x2 risk; loss of consciousness or PTA >30min) to severe (x4 risk; >24 hours) traumatic brain injury
• Repeated (even mild TBI) increases risk
Mild cognitive impairment

• Notable decline in cognition in absence of decline in activities of daily living
• Amnestic version more predictive of future AD (50% in 3 to 4 years will develop AD)
• MCI does not always lead to dementia & may revert to normal
Alzheimer’s disease in Down syndrome (trisomy 21)

- Survival improved: under 10 years in 1900s; now 1 in 5 are 55 yrs or over
- 40% in the 50-59 age group, versus ~5% in over 65 yrs in non-Down
- By 40-yrs., pathological hallmarks of Alzheimer’s disease almost universally
- Not all over the age of 40 years have a clinical diagnosis of dementia

Photo from Down’s Syndrome Association
Down syndrome-the *APP* gene

**Link with Alzheimer’s disease:**
An extra copy of the gene, Amyloid Precursor Protein (*APP*)

**Gene dosage effect**

*APP* breaks down to produce Amyloid-beta-central to dementia
Summary

• Alzheimer’s disease (AD) neuropathology occurs almost universally in adults with Down syndrome (40 s)

• Clinical symptoms manifest many years after pathology established, by which time treatment options less likely to modify disease process

• Aim is to discover biological and other measurable features to help identify the “pre-symptomatic” and “prodromal” condition of AD and ultimately those individuals likely to benefit from disease modifying interventions

• Treatments based on: amyloid cascade hypothesis: triplication of the APP gene on chromosome 21 leads to overproduction of amyloid-beta (Aβ) that initiates and drives the disease
Cummings NEJM 2004

Amyloid cascade hypothesis
Alzheimer’s disease neuropathology in DS

CORONAL SECTIONS:

(A) Ant. pole of temporal lobe (B) Amygdala & entorhinal cortex (C) Body of hippocampus (D) Calcarina in the occipital pole

D. A. Devenny et al., 2005
Alzheimer’s disease pathology in DS-Cored amyloid plaque components

Other components:
- B: Microglia (CD45)
- C: Astrocytes (GFAP)
- D: Phosphorylated tau (Tau-1)

D. A. Devenny et al., 2005
Leading hypothesis

amyloid (Aβ) produced from APP is the culprit
Amyloid Precursor Protein metabolism & potential drug targets

L.M. Shaw et al., 2007
AD neuropathology & dementia diagnosis in Down syndrome versus age

(adapted from Mann et al., 1989)
Definitions of biomarkers

World Health Organization:
“any substance, structure, or process that can be measured in the body or its products and influence or predict the incidence of outcome or disease”

National Institutes of Health:
“a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention.”
The Defeat Dementia in Down’s syndrome projects (DiDS)

**Mechanistic studies**

**Brain imaging project**
- 50 cross-sectional MRI and PET scans
- 15 follow up MRI and PET scans

**Mitochondria functioning project**
- 26 MRS scans
- 18 muscle biopsies

**EEG project**
- 40 EEG assessments
- 10 follow up cognitive assessments (30 expected)

**Retinal markers project**
- 52 OCT cross-sectional scans
- 4 follow up eye and cognitive assessments (30 expected)
- 20 DARC assessments expected

**Biomarker studies**

- **Pittsburgh Compound-B** (analogue of Thioflavin T) with positron emission tomography (PET) and magnetic resonance imaging, it allows us to quantitate Aβ plaques

- Create maps of binding potentials: location and quantity of fibrillar amyloid

*Klunk et al., 2004*
Model of dynamic biomarkers of the Alzheimer’s disease pathological cascade in non-DS AD
Comparison of clinical, cognitive, structural, metabolic & biochemical changes as a function of estimated years from expected symptom onset in autosomal dominant AD

Bateman et al., 2012
Proposed staging framework for preclinical Alzheimer’s disease (non-DS)

Stage 1
Asymptomatic amyloidosis
- High PET amyloid tracer retention
- Low CSF Aβ_{1-42}

Stage 2
Amyloidosis + Neurodegeneration
- Neuronal dysfunction on FDG-PET/fMRI
- High CSF tau/p-tau
- Cortical thinning/Hippocampal atrophy on sMRI

Stage 3
Amyloidosis + Neurodegeneration + Subtle Cognitive Decline
- Evidence of subtle change from baseline level of cognition
- Poor performance on more challenging cognitive tests
- Does not yet meet criteria for MCI

MCI ➔ AD dementia

RA Sperling et al., 2011
Imaging study in Down syndrome

**MRI**
- MPRAGE (T1)
- SPACE (T2)
- DTI
- fMRI (resting state)

**PiB-PET**
PiB-PET in Down syndrome with or without dementia
Total cortical binding (using PiB) versus age in Down syndrome

Non-displaceable binding potential versus age in the 14 healthy non-DS volunteers
Changes in PIB binding in given regions over two time points in an individual

Wilson, Annus, Hong, Fryer, Cole, Smith, Menon, Aigbirhio, Zaman, Nestor, Holland, 2015, unpublished
Mean cortical thickness across groups - effects of amyloid
Model of dynamic biomarkers of the Alzheimer’s disease pathological cascade
Looking at the retina

Retinal Nerve Fibre Layer (RNFL) thickness and macular thickness will decrease with age and begin to decline at an earlier age.

Moreno-Ramos (2013) found a significant decrease in retinal thickness in AD patients.
Methods

Heidelberg Optical Coherence Tomography Spectral Domain (SD-OCT)
Summary

- People with DS have thicker RNFL measures throughout adult life
- DS retina does not decrease in thickness or volume with age as seen in control participants

Possible associations with AD

- Muller glial cell swelling
- Amyloid deposition in the retina and clustering around the vessel walls
- Accumulation of apoptotic cells in the retinal layers that are not cleared affectively
- Mitochondrial abnormalities

Amyloid deposits in DS retina
Figure from Rafii et al.
Mitochondrion

Oxidative phosphorylation

ATP

Kelvinsong, Wikimedia
Mitochondria are very involved in AD pathology

Mitochondrial dysfunction may exist before amyloidosis

Amyloid and mitochondria interact

Mitochondrial dysfunction and mtDNA mutations are key hallmarks of biological aging
Phosphocreatine recovery kinetics (PCr)

• Rate of replenishment of PCr, quantified as the PCr recovery half time (t1/2), relies entirely on oxidative phosphorylation
• PCr donates a phosphate group to ADP during exercise effort:

  \[ \text{PCr} + \text{ADP} \leftrightarrow \text{creatine} + \text{ATP} \]
Participants required to lift an object with their leg in 1-min bouts

Phosphocreatine (PCr) levels drop during exercise...

Time taken for PCr to recover is dependent on mitochondria

Mitochondrial function and cognition

Correlation with global measures of cognition
What prospects for treatments?

By the time a clinical diagnosis is made—it’s probably too late!

The clinical phenotype ‘lags behind’ the neuropathology by 10 to 15 years—the histopathology is necessary but not sufficient

This creates a problem when considering early interventions
Primary prevention-when safe to intervene?

Ballard et al., The Lancet Neurology 2016 15, 622-636 DOI: (10.1016/S1474-4422(16)00063-6)
“Biomarkers could only serve as true replacements for clinical relevant endpoints if we completely understood the normal physiology of a biological process, the pathophysiology of that process in the disease state, and effects of an intervention – pharmacological, device, or otherwise – on these processes.”

K. Strimbu and J. A. Tavel, 2011
How is it that there needs to be considerable tissue pathology before clinical manifestation?
Defining the prodromal phase or re-defining disease?

Neuropathological abnormalities alone do not constitute a ‘diagnosis’ in the absence of clinical signs and symptoms

\[ \frac{1}{\text{functional capacity}} \times \text{threshold} \times \text{decompensation} = \text{Clinical manifestation} \]
Non disease-modifying or preventative dementia drugs

• Cholinesterase inhibitors and memantine
• Others: vitamin E in DS
• May slow cognitive decline; evidence of improved quality of life for patients and carers
• May help behavioural/psychological problems: irritability, aggression, mood, hallucinations
Disease-modifying or preventative dementia drugs

• Monoclonal antibodies directed against various domains of Aβ (e.g. solanezumab – targets soluble Aβ, crenezumab - targets soluble and fibrillar Aβ, gantenerumab - targets fibrillar Aβ)
• Active antibodies: directed against Aβ
• Reduce production by BACE inhibitor (e.g. MERC MK-8931 or verubecestat)
Amyloid—what does it do?

- Trigger—once initiated then cannot modify outcome by reducing amyloid

- Threshold—below which no disease

- Driver—lowering amyloid would slow disease at any stage
Any clinical drug trials in Down syndrome?

• Immunotherapy (passive or active) to remove Aβ – a feasibility trial in USA
• No BACE inhibitor trials yet
• No gamma-secretase modulator trials yet
• No tau targets tried yet
Summary & conclusions 1

• Striatal binding of PiB (Aβ) an early feature of DS, occurs pre-clinically
• ‘Sharp’ rise in prevalence of PiB binding around 35 to 45 with saturation post-50s
• Retinal nerve fibre layer is thicker in DS c.f. age-matched controls unlike that in AD and MCI
• Skeletal muscle mitochondrial dysfunction present in DS pre-symptomatically
• Skeletal muscle mitochondrial dysfunction pre-dates amyloid PiB-binding, correlates with striatal binding
Alzheimer's disease is a complex disease.

By the time clinical diagnosis is possible, it’s likely too late for disease modification.

Need to define or characterise the “prodromal” or “pre-symptomatic state” which will require discovery of biomarkers.

Classical neuropathology is only one facet of the disease and eliminating it may not be enough to treat.

People with Down syndrome are most likely to benefit most from treatments aimed at preventing the deposition of amyloid-beta in the brain and its consequences.

We need clinical trials urgently.
Neurodegeneration In Aging Down Syndrome
• **Pittsburgh, Wisconsin, Arizona & Cambridge ($12.5 M)**

• To identify potential AD-related biomarkers in a group of **180** adults with Down syndrome

• Baseline, 16, 32 and 48 months.

• Aβ- and tau-PET, structural and functional MRI; fluorodeoxyglucose-PET

• Cerebrospinal fluid Aβ and tau.

• Measure cognition and function

• Blood for genetics, lipidomics and proteomics at baseline.
Wolfson Brain Imaging Centre, University of Cambridge

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THANKS FOR YOUR LISTENING!
Alzheimer’s disease in people with Down’s syndrome: the prospects for and the challenges of developing preventative treatments

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