“Recent advances in dementia research – implications for practice”

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The dementia research landscape: a time of change

- Public awareness
- Priority for governments
- Importance of diagnosis: ... of diseases and dementia
- Translating advances to practice is a major challenge
- Great opportunities for UCLP
Research into Cause, Cure and Care

Advances in many dementias: FTD, DLB & AD…

1. The new genetics: GWAS
2. The new culprits? Amyloid cascade & oligomers
3. New diagnostic markers: CSF & amyloid imaging
4. New diagnostic criteria
5. Treatment promises, failures and concerns
Alzheimer’s disease genetics
AD and the “new genetics”

- 1920/30s – inherited forms of AD recognised
- 1991 – First pathogenic mutation in APP (the London mutation - 717)
- 1993 – ApoE4 (Chr19) risk factor reported
- 1995 – Presenilin1 (Chr14) and PS2 (Chr1)
- 2009 – Genome wide association studies (GWAS)
Genetic risk factors and sporadic AD

- ApoE4 – strongest genetic risk factor
  - ~3x with one allele; ~9x with two
- Genome Wide Association Studies (2009)
  - CLU (Clusterin)
  - PICALM
  - CR1
  - BIN1
- Involved in cholesterol metabolism, complement cascade ... offers new targets
The new culprits in the amyloid cascade?
APP processing, Aβ aggregation, and amyloid pathology

Haass, Schlossmacher et al, Nature
The new era of biomarkers in Alzheimer’s disease: MRI, CSF (and PET)
NICE clinical guideline 42
Dementia

Key priorities for implementation

Structural imaging for diagnosis

- Structural imaging should be used in the assessment of people with suspected dementia to exclude other cerebral pathologies and to help establish the subtype diagnosis. Magnetic resonance imaging (MRI) is the preferred modality to assist with early diagnosis and detect subcortical vascular changes, although computed tomography (CT) scanning could be used.
At diagnosis of AD the hippocampus is 10-20% smaller than in controls.

Rates of h/c atrophy ~3-4%/y; controls <1%/y.
Serial coronal MRI of initially mild FAD
CSF in AD – proving very useful

- Aβ1-42 reduced (x ~0.5 vs Controls)
- Tau increased     (x ~2 vs Controls)
  Tau/Aβ ratio increased >1 suggests AD

Good sensitivity and specificity vs controls
(tau also up in CJD, FTD)

NB - use polypropylene tubes and get the samples to the lab!
CSF Aβ reduction and tau elevation
~85% sensitive, 85% specific for AD (even at MCI stage)

Hansson et al.
Lancet Neurology 2006
Amyloid Imaging in AD
Klunk 2004 – PIB (C11); now multiple ligands (F18)
Amyloid binding increases some years before AD

“Converted” to AD

No change in 4 yrs

Brooks, Archer, Fox et al.,
New criteria for AD
Earlier diagnosis? Earlier Treatment?
Improving diagnosis

- National priority – “Dementia Strategy”
- Alzheimer’s Society “…it is crucial to highlight the value of early diagnosis and intervention…”
- New criteria
  - Dubois et al 2007
  - NIA-AA 2011
Research criteria for the diagnosis of Alzheimer’s disease: revising the NINCDS–ADRDA criteria

Core diagnostic criteria
A. Presence of an early and significant episodic memory impairment that includes the following features:
   1. Gradual and progressive change in memory function reported by patients or informants over more than 6 months
   2. Objective evidence of significantly impaired episodic memory on testing: this generally consists of recall deficit that does not improve significantly or does not normalise with cueing or recognition testing and after effective encoding of information has been previously controlled
   3. The episodic memory impairment can be isolated or associated with other cognitive changes at the onset of AD or as AD advances

Supportive features
B. Presence of medial temporal lobe atrophy
   - Volume loss of hippocampi, entorhinal cortex, amygdala evidenced on MRI with qualitative ratings using visual scoring (referenced to well characterised population with age norms) or quantitative volumetry of regions of interest (referenced to well characterised population with age norms)
C. Abnormal cerebrospinal fluid biomarker
   - Low amyloid β1-42 concentrations, increased total tau concentrations, or increased phospho-tau concentrations, or combinations of the three
   - Other well validated markers to be discovered in the future
D. Specific pattern on functional neuroimaging with PET
   - Reduced glucose metabolism in bilateral temporal parietal regions
   - Other well validated ligands, including those that foreseeably will emerge such as Pittsburgh compound B or FDDNP
E. Proven AD autosomal dominant mutation within the immediate family
Disease modification in AD: beyond cholinesterase inhibitors
Some failures, some concern, some promise

- Symptomatic treatments (now with wider NICE guidance) have modest benefit
- Increasing concern about neuroleptic use
- Search for disease modification – need to recruit into trials
  - Anti-tau therapies
  - Gamma-secretase inhibitors
  - Amyloid Immunotherapy
  - And others
Amyloid Plaques in transgenic mice prevented by immunisation

Hippocampus
Placebo (PBS) treated

Hippocampus
$\text{Aβ}_{42}$ treated
Immunotherapy - vaccination in humans

- Active study – AN1792
- ~300:72 subjects
- 15 months – series of vaccinations
- Clinical, safety, cognitive & MRI measures
Autopsy evidence of extensive patchy removal of plaques


Holmes et al Long terms effects… Lancet 2008
Several ongoing immunotherapy trials in AD

Bapi phase 2 completed – phase 3 by 2012-3

Rinne J
Lancet
Neurology
2010

Salloway S
et al
Neurology
2009
Summary

- Some progress in understanding the cause(s) of AD
- New markers and criteria will influence practice
- Need to find disease modification therapies – may need to trial earlier in the disease

Thank you