Dementia – Inspiring Hope, Retaining Realism

Henry Brodaty
Today’s topics

• Cause of AD
• It’s important
• Diagnosis
• Prevention
• The silver bullet
• Quality of life
• Conclusions
Let’s get our terms straight

• Dementia/s – cognitive & functional decline
  - Alzheimer’s disease (AD)
  - The other (non-Alzheimer’s) dementias
    • Vascular dementia
    • Lewy body dementia
    • Fronto-temporal dementia
    • 100 others

• Mild Cognitive Impairment – phase before dementia
Cause: Brain in AD

- Brain atrophy, loss of nerve synapses and branches
- Breakdown of APP releasing $A\beta$ protein $\rightarrow$ clumps $\rightarrow$ toxic to brain $\rightarrow$ plaques
- Phosphorylated tau $\rightarrow$ paired helical filaments $\rightarrow$ NFTs
- Chemicals in brain $\downarrow$ esp ACh
The cause of AD??

• Make excess $A\beta$ protein
  – Familial AD, mutations in APP, PSEN1 or 2
  – Onset in 40s, 50s.

• Decreased clearance of $\beta$- amyloid
  – Late onset AD, ApoE4

• Role of tau

• Many other pathways involved, eg…
Many other factors ...

- Support cells (astrocytes, glial cells) in brain
- Inflammation
- Insulin resistance in brain
- Progranulin
Cause: realism

• For young onset autosomal dominant AD cause seems clear
• For late onset sporadic AD, we know risk factors and pathological paths but not cause
Why is dementia important...globally?

- 47 million people → 131 m by 2050
  - 2/3 in developing countries
- ≈10m new cases per year, every 3.2 seconds
- Cost US$818 billion, 1.09% of global GDP
Why is dementia important in Australia?

- 413,000 in 2017 → 1.1 million by 2056
- 244 new cases of dementia each day in 2017
- Cost to community $14 billion in 2017
  - 61% direct costs, 38% opportunity costs
  - → $28b by 2056

¹ The Economic Cost of Dementia in Australia 2016-2056, NATSEM 2017
Why is dementia important in Australia?

• If 5% fewer people aged 65+ were prevented from developing dementia, Australia would save $5.7b from 2016-25 & $120.4b by 2056 \(^1\)

• 28,000 develop dementia when less than 65 years of age \(^2\)

\(^1\) The Economic Cost of Dementia in Australia 2016-2056, NATSEM 2017; \(^2\) Dementia in Australia, AIHW, 2012
Why is dementia important?

- Because we fear it
Getting old isn’t too bad … except for a little forgetfulness
Why is dementia important?

- Because we fear it
- Because we are getting older as a population
- Because we are living longer as individuals
- Because age is the major risk factor for dementia
- Because we have it OR we know someone who has it
- Because we see what dementia does
The hope

- CURE? PREVENTION?
- Are numbers decreasing?
- Studies from Sweden, Denmark, Spain, Netherlands, USA show that the number of new cases per each age group has declined in the last 20 years
- Better education, health care, diet, lifestyle may be responsible
The realism

- Prevalence, number of existing cases, is ↑
  - Ageing of population outweighs decline in new cases
  - People with dementia are living longer
- Obesity & diabetes epidemics may increase numbers of new cases
- Developing countries are ageing rapidly
Diagnosing Dementia
Diagnosing Dementia: the gap

- 2-3 year gap from symptoms to diagnosis
- 50% of (mild) dementia undiagnosed by GPs
- *Timely Diagnosis* project¹
  - Aim to reach 5000 GPs
  - Face-face or online

¹ DTA, AA, LaTrobe and DCRC
Diagnosis: the revolution

Tradition: History + Exam + Tests → Diagnosis

The revolution:

- **Neuroimaging**
  - MRI scans
  - PET imaging, now of amyloid & tau protein
- **Cerebro-Spinal Fluid (Lumbar puncture)**
- **Genetics** - advances but not yet for most
- **Blood test** - advances but not yet
PET amyloid imaging: normal vs AD

- 35% persons 60+ amyloid+
- Amyloid+ → ↑ risk clinical progression
- Will all amyloid+ develop AD?
- When??

Hotter colours = more amyloid
Lumbar puncture = Spinal tap

Change in proteins in CSF

- Decrease in amyloid beta protein and increase in tau and phospho-tau proteins
- If all measures are normal in pt with mild memory disturbances almost excludes AD
Diagnosis of AD - realism

- Biggest challenge is in primary care
- No test 100% accurate yet
- No blood test sufficiently accurate to use yet
- The older the patient, the more likely the brain will have multiple pathologies AD, vascular changes, α-synuclein, TDP43
- Predictive testing not accurate enough and not recommended
- And if there was a test......???
Would you be tested today to see if you would develop AD in…?

2 years?
5 years?
or 20 years?
Can we prevent dementia?

• Disease **elimination**
  – eg smallpox vaccination
  – best prospect is AD vaccine for those at risk

• Disease **postponement**¹: delay AD onset by…
  – 2 years, ↓ prevalence by 20%
  – 5 years, ↓ prevalence by 50%

¹Brookmeyer et al. (1998)
Is early life the important target?

- 60-70% of world dementia in developing countries
  - Low foetal birth weight
  - Poor or no education
  - Poor socio-economic environment
- 12.4% West Australia’s Kimberley Aboriginal people have dementia = 5.2x non-indigenous

1Smith K et al, Neurology, 2008;71: 1470-1473
• Look after your heart
• Be physically active
• Mentally challenge your brain
• Follow a healthy diet
• Enjoy social activity

yourbrainmatters.org.au
Dosage effect

As cardiovascular risk factors accumulate, AD dementia risk increases

- Hypertension
- Smoking
- Hypercholesterolemia
- Obesity
- Diabetes
- Physical inactivity

Luchsinger et al 2005

Number of risk factors

Slide adapted from Michael Valenzuela
STATINS HALT ALZHEIMER'S

40p a day pill used by millions tackles cruel brain disease

By Jo Wiley, Health Correspondent

STATINS used by millions of people in Britain to prevent heart disease could be the key to beating Alzheimer's, say researchers.

A daily dose of the pill, costing as little as 40p, may ward off the cruel brain disease.

Scientists found that statins - the main drug most frequently prescribed in the UK and commonly given to elderly patients - increased blood flow to the brain while boosting learning and memory.

The breakthrough could have real consequences for the long-term health of the nation. At least 850,000 people here have dementia, with more than half suffering from Alzheimer's. The figure is expected to soar by 1.7m within the next 40 years as the population ages.

The study brings hope of halting the disease through early intervention. More than six million people in this country take

DAYS AFTER RECORD HIGH TEMPERATURES

SNOW CHAOS SWEEPS BRITAIN (WE DID WARN YOU)

See page three
Statins to prevent AD

Two reviews in 2016 conflict:

• Good evidence that statins neither prevent nor increase risk of cognitive impairment or dementia¹

• Statins linked to reduced AD risk – differences by sex, race & statin²

¹McGuiness B et al, 2016; CD003160 (1) Cochrane Database of Systematic Reviews

²Zissimopoulos JM et al, 2016, JAMA Neurology
Physical activity
Can exercise protect against dementia?

• Preserve cognition and slow cognitive decline
• Decreased incident dementia
• 8/11 RCTs in healthy older persons: cognitive & fitness improved
  – especially cognitive speed and attention
• Biomarkers ↑ e.g. brain volume
• Animal studies – growth factors↑, BDNF↑, neurogenesis↑, inflammation↓, AD path. ↓

Graff-Radford NR, Alzheimer’s Research and Therapy 2011, 3:6
Physical activity benefits older adults to prevent dementia: Never too late to start

- Moderate intensity (brisk walking) 30 min 5d/week is minimum
  - more is better, puffed and sweaty
- Evidence for specific exercise:
  - more than one type exercise may be better
  - resistance training may be better (SMART)

The power of physical activity

Erickson et al., 2011
The hope: physical activity...

- Improves fitness
- Improves physical health - ↓ heart disease, Hi BP, diabetes, some types of cancer, osteoporosis, sarcopenia
- Reduces morbidity & mortality
- Improves mental health
- Improves confidence, quality of life

http://www.mednwh.unimelb.edu.au/research/health_promotion.htm
Mental Activity
Mental Activity & Dementia

• Meta-analysis of 22 studies, 29,000 individuals

• ↑ complex mental activity in late life = ↓ risk of dementia by half; OR = 0.54 (0.49-0.59) \(^1\)

• Dose - response relationship evident\(^1\)

• Results suggest complex patterns of mental activity in the early, mid- and late-life stages are associated with ↓ dementia incidence\(^1\)

• Results held when covariates in source studies were controlled for\(^2\)

Cognitive training

• Systematic review of RCTs with longitudinal follow-up (>3mths) in healthy elderly¹
  – 7 RCTs met inclusion criteria, low quality
  – Strong effect size for cognitive exercise intervention vs wait-and-see controls
  – Longer FU duration (>2yrs) → ES no lower

• Review of cog. training or rehab in dementia²
  – 11 RCTs, no benefit

Valenzuela & Sachdev (2009) Am J Geriatr Psychiatry 17(3)
Realism mental training

- Reverse causality
- Which mental activity
  - Crosswords?? Sudoku??
  - Musical instrument? New language?
  - Computer cognitive training, are benefits:
    - Sustained?
    - Generalise beyond computer?
      - ACTIVE Study 10 years later → benefits
DIEB TO BEAT ALZHEIMER'S

Med food good for the brain as well as the heart

By Giles Shefrick

A MEDITERRANEAN diet boosts brain power and slashes the risk of Alzheimer's, research shows.

Experts say eating like the Greeks with lashings of olive oil can protect against the onset of devastating mental decline.

The sure-fire regime has long been considered a good way to stave off heart disease. Now scientists have said it is good for the brain too, whatever your age.

Peach analysis suggests those who regularly eat plenty of fish, fruit, vegetables and nuts but consume little dairy or red meat have a much lower rate of memory loss.

The finding is all the more significant as declining quality of the sunshine way of life comes after researchers found links between diet and mental function.

Study author Roy Hardmon, from Swinburne University of Technology in Melbourne, Australia, said: “There is encouraging evidence a
Mediterranean Diet Pyramid*

Daily

- Bread, pasta, rice, couscous, polenta, bulgur, other grains, and potatoes

- Fruits

- Beans, legumes, nuts

- Cheese and yogurt

- Fish

- Eggs, poultry

- Sweets

Red meat - a few times per month in very small amounts

A few times per week

*Adapted from Consumer Reports, Nov/94
Nutrition / Supplements

- Fish/Seafood/ω3?
- Folic acid & B Vits?
- Vitamin D?
- Caffeine?
- Vitamin E?
- Vitamin C x

*Food sources better than supplements*
Smoking and AD

• Current smoking
  – increase risk for AD

• Previous smoking
  – Risk not significantly increased

Anstey K. Am J Epidem 2008
Alcohol

- Some evidence benefit with moderate alcohol
  - i.e. abstinent → higher risk, j-shaped curve
- Not all studies confirm
- Interaction with ApoE4 – contradictory results?
- Heavy alcohol is risk factor
- Which alcohol – (red) wine?
  - Evidence not strong
- What is moderate?
Natural therapies

- Ginkgo biloba
- Turmeric, curcumin
- DHA, omega 3
- Fo-ti root
- Soy isoflavone
- Vitamin E, Selenium
- Folate, B6, B12
- Saffron
- Brahmi
- Huperzine A
Many unproven claims

Can Coconut Oil Prevent Alzheimer's?
Diet: realism

- Mediterranean diet has best evidence
- Diet, exercise, vascular health, diabetes, obesity – all linked
- Obesity in mid-life is a risk factor; late life not
- Most claims are based on observational studies eg Okinawa diet
- RCTs for long periods impossible
Other factors

- HRT – neither harmful nor beneficial close to menopause
- Hearing loss ↑risk RR 1.55-2.32
- Less ‘socialisation’
  – increases risk of cognitive decline/ dementia
  – moderates effect of Alzheimer pathology on cognitive function
- Air pollution?
Environmental factors

• 30% of population attributable risk of AD cases from 7 environmental factors
• If 25% lower prevalence of these risk factors → 3 million fewer AD cases worldwide
• Highest estimated Pop\(^u\) Attributable Risk for AD
  – Global: low education (19·1%, 95% CI 12·3–25·6)
  – USA: physical inactivity (21·0%, 95% CI 5·8–36·6)
  – Europe and UK similar (20·3%, 95% 5·6–35·6)

Barnes & Yaffe, 2011; Norton et al, 2014
Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER)

- Diet
- Cognitive training
- Exercise – PMR and aerobic
- Manage metabolic and vascular risk factors
- Social activities

Outcomes at 2 years:
  - improved test battery, executive function, processing speed, but not memory
Internet based prevention trials

- Healthy Aging Through Internet Counselling in the Elderly (HATICE) [http://www.hatice.eu/](http://www.hatice.eu/)

- **Maintain Your Brain**
  - NHMRC funded, 5 years, largest trial in world
  - 18,000 Australians 55-75 years old
  - Exercise, cognitive training, diet, depression
  - Blood pressure, cholesterol, glucose
  - Tailored to individual risk factors

[www.cheba.unsw.edu.au](http://www.cheba.unsw.edu.au)
ALZHEIMER’S REVOLUTION

125,000 ops face axe in doctors’ five day strikes

By Sophie Bolland

A REVOLUTIONARY drug to stop dementia will be trialled in Britain.
Scientists say the breakthrough treatment against memory-sapping Alzheimer’s
works by adding a rape protein that clings to and destroys cells. In preliminary
trials the protein has been proven to improve patients’ ability to
remember things.

Women who refuse to let their husbands see them naked

57
Drug prevention trials

Clinically normal but at high risk:
• A4 Study - Clinically normal, Aβ positive
• DIAN – TU – Dominantly inherited AD
• Alzheimer Prevention Initiative (Colombia)
  ○ mainly antibody studies (vaccine)

Prevent MCI → AD:
• Tau therapeutics
• β-secretase inhibitor
Drug trials for AD - the hope
Scientists create the first drug to halt Alzheimer's

Brain degeneration stopped by twice-a-day pill. 'Wonderful' discovery raises glimmers of hope.
NEW HOPE FOR MILLIONS

CANCER DRUG CAN STOP YOU GETTING ALZHEIMER'S
Strategies

- Anti-amyloid
  - Enzyme inhibitors
  - Immunotherapies – active, passive
- Anti-tau
- Neurotransmitter enhancers
  - Cholinesterase inhibitors
  - Memantine
  - Serotonin receptor antagonists
- Others: intranasal insulin, RAGE, NGF
Promote neuronal function

- Mitochondrial dysfunction
  - Latrepirdine (Dimebon) - failed
- Nerve growth factors: Delivery to brain is a challenge:
  - Viral vectors
  - Nanotechnology
Other treatments

- Long acting intra nasal insulin
- Deep brain stimulation targeting limbic memory circuit in pts with mild AD
- 5-HT6 Receptor antagonist, idalopiridine
- Nutraceuticals – Axona, Souvenaid
“Cures” for AD

Dr Tobinick injecting Etanercept in spine
Realism: the graveyard of AD Cures

- Trimiprosate (Alzhemed)
- Flurbiprofen (tarenflurbil)
- Anti-inflammatory
- Rosiglitazone
- Statins
- Leuprolide
- Latrepirdine (Dimebon)
- Semagacestat (γ-secretase inhibitor)
- Bapineuzemab
- Verubecestrat (β-secretase inhibitor)
- Celecoxib
- Intravenous Immunoglobulin
Why failures despite Phase 1/2 trial success?

- Wrong time? Too late in disease process?
- Wrong target? Amyloid may not be the one
- Wrong patient? 30% of trial participants did not have AD as per amyloid PET Scans
- Wrong model? May need multiple drugs simultaneously eg TB, H. bacter, leukaemia
Realism – drug treatments

- No silver bullets
- Billions invested with no return
- Pharma still interested but some not
- Most trials for AD
- World Dementia Council aim for cure by 2025 unlikely

‘The mainstay of treatments for AD is supportive care from family ..’

1 Cummings J et al, 2016 Alz Research & Therapy
Achieving quality of life....

...for person living with dementia and carer:

- Reducing stigma
- Building dementia friendly communities
- Knowledgeable, skilled and empathic health professionals in primary, acute and residential care
- Timely diagnosis & advice and quality care
- Australian Clinical Practice Guidelines
Want information on the diagnosis, treatment and care for people with Dementia?

The Clinical Practice Guidelines and Principles of Care for People with Dementia, and the Consumer Companion Guide will be of help.

Improve quality of life by...

• Proactive guidance and care
• Optimal use of medications
• Improvements in community care
• Psychological & environmental strategies to manage behavioural & psychological symptoms
• Empowering affected persons and families
• Research on how to achieve all of these
Conclusions - HOPE

• HOPE - Research on dementias: AD and Vascular, Lewy body and fronto-temporal dementia

• Research can drive drug Rx and improvements in diagnosis and care

• Australia has leaders in areas of basic, diagnostic, carer, translational, residential care research

• World wide community collaborating
Conclusions: REALISM

• Funding for research is a major issue
  - Proportionately low vs
    o Other major diseases
    o Disease burden
    o Cost of health care

• Australian Dementia Registry would boost recruitment for prevention and treatment, improve standards of dementia diagnosis & care
Conclusions

• Dementia research → hope
• Realistic expectations
• Prevent cognitive decline, delay onset of dementia
• Work towards drugs to delay or stop degenerative processes such as AD
Thank you

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Dementia Collaborative Research Centre

www.dementiaresearch.org.au