An introduction to dementia

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21st Century is century of neurodegenerative disease

- 19th C – infectious disease
- 20th C – heart disease, cancer
- 21st C - neurodegenerative diseases
  - Alzheimer’s and other dementias
  - Cerebrovascular disease/ stroke
  - Parkinson’s disease
  - Macular degeneration
  - Balance and gait disorders, falls

Our brains ...
- ≈1.3 Kg of 12% fat, 8% protein, 78% water
- Consume 20% of body’s O₂ & almost 20% of blood flow
- Contain about 100 billion neurons, each with 1000 to 10,000 synapses and each neuron is supported by 10-50 support (glial) cells
- Most mysterious of body’s organs but now...
  - more accessible through revolutions in neuroimaging, IT, genomics, other -omics
Australia’s ageing population

- By 2050 the population aged ...
  - 65 yo+ will double: 3m → 7.5m (13% → 25%)
  - 85yo + will quadruple: 415,000 → 1.6m
- By 2025: more 65+ yo than > children 0-14 yo
- 30th June 2011, 4252 people 100 years or older

1 Dementia in Australia, AIHW, 2012

Australia: Population projections

Population (approx):
- 2014: 23.5 million
- 2030: 29.0 million
- 2050: 35.3 million

In 2030, Australia's population will be approx **28.48 million**

Approx 1 in 5 will be 65 years or older


Population (%):
- 2014: 10.5%
- 2030: 16.9%
- 2050: 23.5%

In 2030, Australia's population will be approx **28.48 million**
There will be almost 3 times as many centenarians as there are today

2013: 6,364 centenarians 2030: 18,923 centenarians

Costs

- Cost of health in Australia is ≈10% of GDP or about $130b and rising above inflation
- Drivers – costs, demand, > expensive investigations, medicines and procedures
- Dementia costs 0.8% GDP or ≈$6b pa.
- By 2050, dementia costs >1.8% GDP

Prevalence of dementia

- > 6% of population ≥ 65 years old
- 20% of persons ≥ 80 years
- 30% of ≥ 90 years old
- Prevalence doubles every five years after 60
Projections of dementia worldwide

- Total estimated cost worldwide US$604 billion in 2010
- If dementia were...
  - a country, it would have the world’s 18th largest economy
  - a company, it would be the world’s largest by annual revenue
We started to notice that his memory was failing, we were helpless. Over the ensuing years my mother cared for him. We took my father to many doctors, none of them could tell us what was wrong.

Dementia in Australia *

- 330,000 people with dementia in 2013
- 74% aged 75+ but almost 10% < 65 yrs
- 70% live in community
- Projections: 400,000 by 2020; 900,000 by 2050
- 3rd leading cause of death
- 4th leading cause of disease burden
- 3rd leading cause of disability burden; (1st in 65+)

* Dementia in Australia, AIHW, 2012
Christine Bryden, Australia

I felt as if time had stood still - surely this wasn’t happening to me … You’re joking, I’m too young to get Alzheimer’s!
from her 1998 book, “Who will I be when I die?”

People with dementia and their CGs

• PWD all over the world have
  – Cognitive decline
  – Functional decline
  – Behavioural disturbances
• CGs all over the world face
  – Stress, depression, burden
  – Financial and social hardship
  – Stigma, ignorance
Dementia in Australia

- Aboriginal and Torres Strait Islanders have higher rate
- 200,000 family carers
  - >80% provide >40 hrs pw
- Direct health and aged care costs = $4.9bn
- If add unpaid costs of carers > $6bn pa
- 0.8% GDP → 1% GDP by 2030 → 1.8% by 2050

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Bill’s story

- 70 y.o. architect
- Married, 3 children + GC
- Mistakes at work
- Admits to anxiety 2 yrs
- Referred for assessment
- Alzheimer’s diagnosed

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Bill’s story

- Diagnosis = relief!
- Wife grateful
- Changes work duties
- Starts anti-Alzheimer Rx
- Monitors driving

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Bill's story

- Diet, exercise, mental stimulation
- Life priority decisions
  - more family time
  - plans holiday abroad

Remember this shopping list

- Milk
- Sausages
- Peas
- Flour
- Oranges
- Steak
- Cheese
- Apple
- Yoghurt
- Sugar

Dementia definition

- Loss of memory
- Loss of at least one other cognitive function
  - Language
  - Executive abilities - planning, organisation, abstract thinking, conceptual shift
  - Visuo-spatial abilities
- Represents a decline
- Impairs daily function - occupational or social
Dementia - concepts

- Dementia is an umbrella term to describe a syndrome
- Alzheimer's disease is most common
- Some causes reversible - but rare
- Mild Cognitive Impairment
  - intermediate between normal and dementia

AETIOLOGY OF DEMENTIA

- Over 100 causes
- Alzheimer’s disease (AD) up to 50%
  - includes other degenerative dementias
- Vascular (VaD) or multi-infarct dementia (MID) about 15-20%
- Mixed AD and VD about 15%
- Lewy body disease (up to 20%)
- Fronto-temporal dementias
- Alcohol
- Head injury

Potentially reversible or able to be halted causes of dementia

- B12 or folate deficiency
- Thyroid deficiency
- Calcium excess
- Tumours
- Normal pressure hydrocephalus
- Infection eg HIV, syphilis
Diagnosis and assessment

• Normal ageing
• Depression or another psychiatric syndrome
• Delirium – an acute brain syndrome
• Dementia type
• Deficits of patient
• Assets of patient
• Effects on carer

MRt: profound atrophy

MRI scan of brain showing ischaemic changes


### PiB-PET Scans: AD vs MCI vs control

From the online newspaper of Prof Yasser Metwally

### Early Dementia -Vs- Ageing

Suspect early dementia if:
- Progressively worse
- Difficulty learning even with effort
- Events, not just details, forgotten
- Interferes with normal function
  - e.g. hobbies, social life, shopping
- Other cognitive difficulties
  - hard to understand a story/follow movie
  - difficulty finding words
  - can’t do calculations
  - more disorganised

### Alzheimer’s disease

- Memory loss
- Language disturbances
- Visuospatial deficits
- “Dysexecutive”: Impaired judgment, motivation
- Neuropsychiatric symptoms:
  - depression, anxiety, sleep disturbance
  - psychosis

Alzheimer’s original patient: Auguste Deter
Pathology of AD

- **Macroscopic**: atrophy, mostly temporo-parietal and frontal
- **Microscopic**
  - loss of neurones and synapses
  - neurofibrillary tangles (NFTs)
  - amyloid plaques
  - degeneration
- **Chemistry**
  - loss of neurotransmitters, especially acetylcholine (ACh)

AD: a progressive CNS disorder with a characteristic pathology

Katzman, 1986; Cummings and Khachaturian, 1986
Proteolytic Processing of APP Gives Rise to Aβ

Amyloid plaque

PLAQUE OF AMYLOID BETA-PROTEIN in the brain of an Alzheimer patient is visible as a black globular mass in this stained image. The plaque is surrounded by a halo of abnormal neurites (axons and dendrites) and degenerating neural cell bodies that appear darker than the normal neurites.

Courtesy of Ron Petersen

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Translating dementia research into practice
Tangles – tau protein

The need for a flexible cytoskeleton - I

Vesicle travelling down neurofibrillary “tramline”
Causes of AD unknown, possible factors

Genetic
• Early onset - Familial AD (FAD), auto dominant
  - age of onset 40s & 50s, rare
  - mutations on C14, C21, C1
• Late onset sporadic AD
  – associated with ApoE4 (gene on C19)

Environmental

Risk factors for AD: 1

Risk factors for AD:
Down’s syndrome
Strong risk factors for AD

- Age
- Down’s syndrome
- Family history
- Certain genes associated with increased risk but do not cause AD eg ApoE4

Less strong risk factors for AD

- High blood pressure in mid-life
- High cholesterol in midlife
- Diabetes (Type II)
- Obesity
- Family history of Down’s
- Head injury
- ? Depression
- Low education, little cognitive stimulation
- Others – (prob. not Aluminium exposure)

Can Alzheimer’s disease be prevented?
What was that shopping list?

- Dairy
  - Milk
  - Yoghurt
  - Cheese
- Staples
  - Sugar
  - Flour
- Butcher
  - Steak
  - Sausages
- Greengrocer
  - Apple
  - Oranges
  - Peas

Prevention: Eliminate v Postpone

- Disease elimination
  - eg smallpox vaccination
  - best prospect is AD vaccine
- Disease postponement (Brookmeyer R, 1998)
  - delay AD onset by
    - 2 yrs ➔ ↓ prevalence by 20%
    - 5 yrs ➔ ↓ prevalence by 50%

Can AD be prevented? May be delayed....

- Look after your heart
- Be physically active
- Mentally challenge your brain
- Follow a healthy diet
- Enjoy social activity

yourbrainmatters.org.au
www.cheba.unsw.edu.au
www.dementiaresearch.org.au
Mind your diet
- Mediterranean diet
- Antioxidants
- Tumeric/ circumin?
- Fish? Vegetables?

Mind your Body
- Regular physical exercise
**Effect of physical activity on cognition**

- 24-wk Randomised Controlled Trial
- Follow-up: 18 months
- Physical activity vs education + usual care
- 138 Ss completed study
- Main outcome measure:
- Change in ADAS-cog over 18 months

Lautenschlager et al (2008) JAMA; 300(9):1027-1037

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**Effect on ADAS-Cog**

Lautenschlager et al (2008) JAMA; 300(9):1027-1037

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**The power of physical activity**

Erickson et al., 2011
Exercise benefits

• Heart disease, blood pressure
• Obesity, Diabetes
• Sarcopenia, Osteoporosis
• Lower levels of biomarkers - CSF and PET PIB in cognitively normal adults\(^1\)
• For PWD – behaviour\(^1\); cognition?
\(^1\)Liang et al, Annals Neurology 2010

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\(^2\)


Computerised cognitive training

What are the benefits of computer programs?

• Individual programs
• Multi-modal
• Multiple cognitive domains
• Graded difficulty
• Feedback
• Accessible
Cognitive interventions healthy older adults & people with MCI

- 20 RCTs with healthy adults
  - Memory improvements in 17/20
- 6 RCTs with MCI
  - Memory improvements in 4/6
- Unclear whether these improvements generalise to everyday activities


Cognitive training

- Systematic review of RCTs with longitudinal follow-up (>3mths) in healthy elderly
  - 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 dementia
  - 11 RCTs, no benefit

Valenzuela & Sachdev (2009) Am J Geriatr Psychiatry 17(3)
Results from research trials

✓ Healthy older adults
  • Meta analysis positive results
✓ At risk adults or with mild cognitive impairment (MCI)
  • Systematic review +ve results
✓ Adults with AD
  • Meta analysis positive results

The “second patient”

Effects on carers

• High levels of stress
• Physical health suffers
• Social isolation
• Financial hardship

Alzheimer's Australia

• Support groups
• 1 800 100 500 (helpline)
• Counselling, training programs
• Information, brochures, videos
• www.alzheimers.org.au/
• Advocacy
• Research funding
• Living with memory loss program
  980 50 100 or 1-800-100-500
Drugs for AD

Four drugs approved
- all symptomatic, non curative:
  
  **Cholinesterase inhibitors**
  - Aricept (donepezil)
  - Exelon (rivastigmine)
  - Reminyl (galantamine)

  **NMDA receptor antagonist**
  - Ebixa (memantine)

The cutting edge

- Drugs to prevent AD
- Drugs to cure AD
  - >200 trials recruiting
  - Vaccines, block build up of β amyloid protein
  - γ and β Secretase prevent β amyloid protein forming
- Better ways to help families and people with dementia
- Better long term care
- Treatment of behavioural and psychological symptoms of dementia

Conclusions 1

- Dementia is common
- One in five of people over 80
- Main cause is Alzheimer’s
- For most people cause of AD is unknown
- Major public health and economic issue
- Planning for future is a priority
Conclusions 2

- Management is complex & continuing
  - Patient
  - Family
  - Medication
  - Legal and financial advice
  - Practical advice
- Pace of research is exciting

Dementia Collaborative Research Centres
www.dementiaresearch.org.au

Centre for Healthy Brain Ageing
www.cheba.unsw.edu.au

Alz Australia: www.alzheimers.org.au
www.yourbrainmatters.org.au

ADI : www.alz.co.uk