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
Age Structure of Australia
1971 - 2050

1971
Total (mil.): 13.1

Aged 65
Born 1905-1906
Males: 44187
Females: 47704
Sex Ratio: 92.6
(males per 100 females)

Highlight surplus of males or females

Animate
play
pause
speed

Present: 1980
End: 2050

Translating dementia research into practice
Translating dementia research into practice
Age Structure of Australia
1971 - 2050

2010
Total (mil.): 21.3

*Projected Data

Aged 65
Born 1944-1945
Males: 103626
Females: 103321
Sex Ratio: 100.3 (males per 100 females)

Highlight surplus of males or females

Animate
play
pause
speed

Present: 1980
End: 2050
Age Structure of Australia
1971 - 2050

2020
Total (mil.): 23.2
* Projected Data

Aged 65
Born 1954-1955
Males: 130627
Females: 137011
Sex Ratio: 95.3 (males per 100 females)

Highlight surplus of males or females

Animate
play
pause
speed

Translating dementia research into practice
Age Structure of Australia 1971 - 2050

2030
Total (mil.): 24.8
* Projected Data

Aged 65
Born 1964-1965
Males: 144827
Females: 149668
Sex Ratio: 96.8 (males per 100 females)

Animate
play
pause
speed

Highlight surplus of males or females

©UNSW as represented by the DCRC-ABC 2012
Translating dementia research into practice
Australia’s ageing population ¹

• By 2050 the population aged ...
  – 65 yo+ will double: 3m $\rightarrow$ 7.5m (13% $\rightarrow$ 25%)
  – 85yo + will quadruple: 415,000 $\rightarrow$ 1.6m
• By 2025: more 65+ yo’s 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
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 $\approx 10\%$ of GDP or about $130b$ and rising above inflation.
• Drivers – costs, demand, greater expensive investigations, medicines and procedures.
• Dementia costs $0.8\%$ GDP or $\approx 6b$ 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
Dementia Doubles in Frequency Every 5 Years After Age 60

% Affected

Age

Projections of dementia worldwide

Global Cost of Dementia

- 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

World Alzheimer Report, ADI, 2010
Dementia in Australia

• 330,000 people with dementia in 2013
• 74% aged 75+ but ≈8% < 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
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

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
Bill’s story

• Diagnosis = relief!
• Wife grateful
• Changes work duties
• Starts anti-Alzheimer Rx
• Arranges enduring Power of Attorney, e-Guardianship, Will & Advance Directive
• Monitors driving
Bill's story

- Diet, exercise, mental stimulation
- Life priority decisions
  - more family time
  - plans holiday abroad
<table>
<thead>
<tr>
<th>Remember this shopping list</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Milk</td>
</tr>
<tr>
<td>• Sausages</td>
</tr>
<tr>
<td>• Peas</td>
</tr>
<tr>
<td>• Flour</td>
</tr>
<tr>
<td>• Oranges</td>
</tr>
<tr>
<td>• Steak</td>
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<tr>
<td>• Cheese</td>
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<td>• Apple</td>
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<td>• Yoghurt</td>
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<td>• Sugar</td>
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</tbody>
</table>
Dementia definition

- Loss of at least one cognitive function
  - memory
  - 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
MRI: 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
Natural history of Alzheimer's disease

- Early diagnosis
- Mild - Moderate
- Severe

Symptoms
Diagnosis
Loss of functional independence
Behavioural problems
Nursing home placement
Death

Years
MMSE
Symptom Progression in AD

- MCI
- Mild subjective
- Objective memory loss
- Normal ADL function
- MCI
- Forgetfulness
- Short-term memory loss
- Hobbies, interests lost
- Impaired instrumental functions
- Mild AD
- Repetitive questions
- Progression of cognitive deficits
- Impaired BADL
- Transitions in care
- Moderate AD
- Aphasia
- Dysexecutive syndrome
- Severe AD
- Agitation
- Altered sleep patterns
- Total dependence: eg dressing, feeding, bathing, toilet

BADL = basic activities of daily living.

Pathology of AD

• Macroscopic: atrophy, mostly temporoparietal and frontal

• Microscopic
  - loss of neurones and synapses
  - neurofibrillary tangles (NFTs)
  - amyloid plaques
  - degeneration
Pathology of AD

- **Chemistry**
  - Build up of abnormal proteins aggregates
    - $\text{A}\beta$
    - Tau ($\tau$) protein - phosphorylated
  - Loss of neurotransmitters
    - especially acetylcholine (ACh)
AD: a progressive CNS disorder with a characteristic pathology

Katzman, 1986; Cummings and Khachaturian, 1996
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
Strong risk factors for AD

• Age
• Down’s syndrome
• Family history
• Certain genes associated with increased risk but do not cause AD eg ApoE4
Risk factors for A D: 1
Age

Prevalence rate %

- Baseline rates
- Campbell et al (1983)
Risk factors for AD: Down’s syndrome
Less strong risk factors for AD

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

- earlier onset than AD and M>F
- sudden onset, stepwise deterioration
- history of hypertension
- history of strokes
- evidence associated atherosclerosis
- focal neurological symptoms
- focal neurological signs
- focal pathology on brain imaging
Lewy Body Dementia

- Dementia
- Lewy bodies diffuse in cortex
- REM Sleep disorder
- Fluctuating cog. impairment ++
- Visual &/or auditory hallucinations
- Paranoid delusions
- Falls
- Extrapyramidal features
- Neuroleptic sensitivity
- Visuo-spatial deficits

Cortical Lewy bodies in diffuse Lewy body dementia
Frontotemporal Dementia

FTD

MND

Behavioural form

Language form (Primary progressive aphasia)

Progressive Nonfluent aphasia (PNFA)

semantic dementia

Slide from John Hodges
Fronto-temporal Dementias
(Pick Syndrome)

Clinical

• Onset usually 40-60y.o. (20-80 y. range)
• Up to half cases of pts <65yo
• Usually sporadic but 20% of cases familial with autosomal dominant inheritance
• Death occurs sooner than AD
  – esp if with Motor Neuron Disease
Fronto-temporal dementias

On examination

• preservation of memory until late
• early, prominent personality changes
• apathy
• irritability
• jocularity and euphoria
• loss of tact and concern
• impaired judgement and insight
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 $\rightarrow$ ↓ prevalence by 20%
    - 5 yrs $\rightarrow$ ↓ 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/ curcumin?
- Fish? Vegetables?
Mind your Body

• Regular physical exercise
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\(\sqrt{\text{?}}\); 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\(^2\)

Cognitive training

• Systematic review of RCTs with longitudinal follow-up (>3mths) in healthy elderly\(^1\)
  – 7 RCTs met inclusion criteria, low quality
  – Strong effect size for cognitive exercise intervention vs wait-and-see controls
  – Longer FU duration (>2yrs) \(\rightarrow\) ES no lower

• Review of cog. training or rehab in dementia\(^2\)
  – 11 RCTs, no benefit

Valenzuela & Sachdev (2009) Am J Geriatr Psychiatry 17(3)
The “second patient”

Effects on carers

- High levels of stress
- Physical health suffers
- Social isolation
- Financial hardship
Alzheimer’s Australia

• Support -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
• Dementia Alliance International
  www.dementiaallianceinternational.org/
Drugs for AD

Four drugs approved - all symptomatic, non curative:

**Cholinesterase inhibitors**
- Aricept (donepezil)
- Exelon (rivastigmine)
- Reminyl (galantamine)

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

Souvenaid – Nutriceutical/ Medical food
The cutting edge

- Drugs to prevent AD
- Drugs to cure AD
  - >200 trials recruiting
  - Vaccines, block build up of $\beta$ amyloid protein
  - $\gamma$ and $\beta$ Secretase prevent $\beta$ 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

- 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.fightdementia.org.au
www.yourbrainmatters.org.au/

ADI : www.alz.co.uk