Dementia

CATH MUMMERY
Dementia Research Centre
NHNN
Overview

• The problem in context

• Diagnosis

• Types of dementia

• Treatment

• The future
“The first symptom,” he wrote about his patient, “was that she was jealous of her husband. Soon, she developed a rapid loss of memory.”

“At the end,” he described, “the patient was lying in bed in fetal position completely pathetic, incontinent.”

: “Considering everything, it seems we are dealing here with a special illness.”
Transforming the Quality of Dementia Care

Consultation on a National Dementia Strategy
The PM’s challenge on dementia

• By 2015 we will deliver major improvements in dementia care and research, building on the achievements of the national dementia strategy

Driving improvements in healthcare
Dementia friendly communities
Better research

March 2012
Scale of the problem

- 800,000 people with dementia in the UK today, a number forecast to double within a generation.

- 1/3 of people over 65 will die with dementia

- 42% UK population have a close friend or family member with dementia.

- 25% of hospital beds are filled by patients with dementia

- Only 45% of cases of dementia are diagnosed in England

- £11 is spent on UK research into Alzheimer's for every person affected by the disease, compared with £289 for cancer patients.
## Dementia in the UK

<table>
<thead>
<tr>
<th>AGE (Years)</th>
<th>PREVALENCE</th>
</tr>
</thead>
<tbody>
<tr>
<td>40-65</td>
<td>0.1%</td>
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<tr>
<td>65-70</td>
<td>2.0%</td>
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<tr>
<td>70-80</td>
<td>5.0%</td>
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<tr>
<td>80 plus</td>
<td>20.0%</td>
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</tbody>
</table>
It’s a Fan!

It’s a Wall!

It’s a Spear!

It’s a Tree!

It’s a Rope!

It’s a Snake!
What is Dementia?

• Describes acquired progressive impairment of cognitive function

• **Impairment must be sufficiently severe to cause impairment in occupational or social functioning**

• **Impairment must represent a decline from a previously higher level of functioning**

DSM IV criteria for DEMENTIA (1994)
Mild Cognitive Impairment (MCI)

- Memory complaint
- Memory deficit
- Normal ADLs
- Normal general cognitive function
- Not demented
- No psychiatric symptoms

**Amnestic MCI**

- Increased risk of developing dementia: 15% progress to dementia per year (1-2% normal population)

Petersen et al 1999
Diagnosis

Important EARLY:
- For patients and families
- To guide treatment and research

Crucial for disease modifying treatments: likely to be
- Pathology specific and risky
- May work best (or only) early on

And yet clinical diagnosis is inexact, particularly in the early stages – dementia has long been recognised to have multiple causes…
### Physical Causes

- Menstrual disorders: 15
- Critical period: 35
- Consequences of confinement: 8
- Falls upon the head: 3
- Progress of age: 49
- Ataxic fever: 3
- Suppression of haemorrhoids: 2
- Mania: 18
- Monomania: 15
- Paralysis: 5
- Apoplexy: 2
- Syphilis, and abuse of mercury: 3
- Errors of regimen: 6
- Abuse of wine: 11

### Moral Causes

- Disappointed affection: 5
- Frights: 7
- Political shocks: 8
- Disappointed ambition: 3
- Want: 5
- Domestic trials: 12
- Unknown causes: 14

**Total**: 235

"A Treatise on Insanity"
Esquirol 1845
Causes of Dementia

> 65

- AD
- Vascular
- DLB
- Other

< 65

- AD
- Vascular
- FTD
- DLB
- OTHER

OTHER EG.
- "Parkinson’s Plus" – PSP, CBD
- Prion Diseases
- Hereditary e.g. Huntington’s disease treatable
What is different about Young Onset Dementia?

- Much wider range of causes
- Atypical presentations of degenerative dementias
- Genetic forms of dementia
- Infective/inflammatory conditions
- NB TREATABLE CAUSES
“Reversible dementias”

- Depression
- Space Occupying Lesions
- Deficiency states
  - B12, B1, B6
- Endocrine/metabolic
  - hypothyroidism, uraemia
  - Hashimoto’s encephalopathy
- Infections
  - HIV, TB, syphilis
- Inflammatory
  - SLE, Behcet’s, neurosarcoid
- Toxicity
  - Alcohol
  - drugs, CO poisoning, lead
- Wilson’s disease
- Limbic encephalitis
  - (paraneoplastic/VGKC abs)
Time to diagnosis?

- time taken to diagnose early onset Alzheimer’s - average 39 months

- time taken to diagnose early onset frontotemporal degeneration (FTD) – 49 to 59 months

Rosness et al, 2008
DIAGNOSIS – MADE ON HISTORY

• Essential to obtain an independent account

• Self assessment
  – very subjective; poor correlation with formal assessment
  – attending alone or with concerned friend/relative?

• Type of memory problem?
  – “short term” - day to day memory, repeated questioning, messages, conversations
  – Cannot recognise faces
  – “I can’t remember words” (semantic)

• Ask about:
  – News items, “soaps”, sporting events
  – Local area driving, walking
  – Using lists, losing things
  – Route taken to appointment
  – Name of doctor they are seeing (after 5 min interval)
Cognitive assessment/neuropsychology

- Traditional method of assessing patients:
  - Mini-mental state examination
  - Detailed cognitive assessment by clinician e.g. ACE
  - Formal neuropsychometry

- Extensively studied as a marker of progression

- Standard outcome measure in trials e.g. ADAS-COG
MR imaging – measuring progression
PIB imaging
Cerebrospinal fluid markers

- CSF tau is raised and Aβ42 is decreased in AD compared to controls
  - Specificity and sensitivity 85%

- Predicts conversion from MCI to AD
Alzheimer's disease Natural History (Other Outcomes)

Early diagnosis Mild-to-moderate Severe

MMSE/ADAS-Cog
MRI Vol
ADL
TAU

Time (years)

Dementia is not a diagnosis but a syndrome.
Dear Dr,

I would be grateful if you could assess this pleasant 71-year-old lady who has been complaining of memory problems over the past 2 years. She has no past medical history apart from osteoarthritis of her left knee and hysterectomy 20 years ago.
• From patient:
  – Losing objects at home (jewellery, glasses)
  – More forgetful
  – Relies on lists for shopping
• From daughter

– Stressful time 2 years ago (husband died, had to move house)
– Repeats same question
– Forgets messages
– Does not remember some details of a recent trip with daughter to the Lake District
– Difficulty remembering names of people recently introduced to her
– Once forgot tap water on in bath
– Got lost while driving to visit her daughter on the other side of London
– Difficulty with managing till at charity shop
– Less talkative in social gatherings
• General and neurological examinations unremarkable

• Looks bemused, head turning

• MMSE 22/30 (disoriented in time + place)

• Word finding difficulties naming objects and animals

• Poor verbal recall
• Difficulties with calculations
• Difficulty recognising fragmented objects
• Difficulties copying hand gestures
Alzheimer’s Disease

- Commonest cause of dementia
- Insidious Onset with memory impairment
- Global Cognitive Deficits
- Neurological Examination Normal

Episodic memory
New learning +
delayed recall

Semantics +
Verbal fluency
Visual +
Perceptual
difficulties

Language
calculation

Ideomotor apraxia

Fairly predictable pattern of progression

GLOBAL
AD – atypical presentations

- Visual Dysfunction
- Biparietal Syndrome
- Aphasia logopaenic
- Frontal Syndrome
56 year old man with anxiety and behavioural change

To: GP and High Street opticians

A&E following injury

To neurologist

To cognitive neurologist

Dementia Research Centre
Queen Square, London
Posterior Cortical Atrophy

Often been to optician

Difficulty with

- object recognition eg in a catalogue
- face recognition eg tv characters
- spatial location of objects – picking something up
- judging distances
- seeing objects moving
- reading words/texts
- seeing colours
Dear Dr

I would be grateful if you could assess this 66-year-old gentleman. His wife noted that his memory has been getting worse over the past 18 months. More recently, he has been seeing people in the living room that are not there. He is on bendrofluazide for mild hypertension.
• From patient
  – Owns a DIY shop
  – Memory not as good as before
  – Sees people in living room
From wife

Good days and bad days

On bad days:

- Forgetful of day-to-day events
- Cannot run the shop
- Sometimes thinks that there are other people upstairs
- Sometimes does not recognise his own house
- Sometimes thinks that his wife is a duplicate impostor
- Walking slowed, recent falls
o/e

- Bradykinesia, postural instability
  - features of parkinsonism

- MMSE = 22/30
  - disorientation in place
  - poor recall
  - difficulty copying intersecting pentagons

- Difficulties recognising fragmented letters and objects.
Species there were quite a few of them little chaps. Just like one spider upside down on the back of another. No sign of eyes or mouth. Rather jolly chaps!
Dementia with Lewy Bodies (DLB)

Marked fluctuations

Visual hallucinations

Visual misperceptions e.g. lamp as person

Delusional ideation
  Visual misidentification – spouse/home = imposter
  False beliefs – strangers in home, dead family visiting
  Capgras syndrome

Executive dysfunction
Parietal lobe deficits/memory problems

Parkinsonism
REM sleep behaviour disorder
Autonomic dysfunction
Depression
Sensitivity to neuroleptics
• From patient

• 4 years
  – obsession with clawing sensation in body
  – Increasingly restless
• From relatives:
  – Given up on all interests except romantic fiction
  – Withdrawn from social life
  – Poor self care
  – Less affectionate
  – Increasingly egocentric
  – Gluttony

• No FHx; no significant PMH
O/E

- Very restless, jumping up and down
- Inappropriate affect
- Disinhibited
- Distractible
- Perseverating in actions and language

- MMSE 28/30

- Odd variable gait; otherwise normal neuro exam
Frontotemporal Dementia

- **Presents with personality & behavioural disturbance**
  - loss of empathy
  - Disinhibition/ apathy

- **Loss of insight and self care early**

- **Progression**
  - disruptive behaviour – disorderly, stealing, money
  - tactless
  - aggression / emotional incontinence
  - change in food preference/appetite
  - Hyper-religiosity
  - stereotypic and repetitive behaviours
prior to evaluation. Following an incident when the couple’s daughter had been unfairly slandered by a teacher at school, case A’s family were shocked at his lack of concern for their distraught daughter. Later, when his wife cut off the tip of her finger with a borrowed power tool, the patient responded by ensuring that the tool was returned to their neighbours before searching for his driving licence. Also he accused his wife of screaming too much while they drove to hospital.

Perry R. et al., Neurocase 2001
Frontotemporal Lobar Degeneration

FTLD

Language variants

Behavioural FTD

Prog Non Fluent Aphasia

Semantic dementia
• 67 year old man

• From him:
  – 2 years progressive memory problem
  – Dated from 3 eye operations
  – “difficult to remember names of people and things eg gardening tools”
  – “what’s a hobby?”
  – Traffic light – didn’t understand meaning of colours
Semantic dementia

• Progressive loss of semantic memory
  – Fluent speech
  – marked anomia (objects/people)
  – reduced vocabulary
  – Impaired knowledge of the meaning of the world around them
  – Phonology, prosody and grammar relatively spared

• Preservation of other cognitive domains
  – episodic memory (NB verbal memory), perceptual + visuospatial skills

• ADLs intact
• Often still employed at time of presentation
• 78 year old woman

• 5 years duration
  – Progressive difficulty with articulation, naming things and people
  – Poor writing and spelling
  – Poor calculation

  – No change in personality
  – Lives alone, ADLS fine
  – Still goes to bingo
• O/E sitting quietly, appropriate affect
• Embarrassed by speech
• Marked nonfluent dysphasia with many phonemic errors and paraphasias
• At times incomprehensible
• Normal comprehension
• Poor working memory (digit span)
• Normal neuro exam; no executive deficits
Progressive Non-fluent Aphasia

- Slow progression; circumscribed for many years
- Non-fluent effortful spontaneous language output
- Articulatory and phonological deficits
- Preserved comprehension -> delay presentation
- Writing similarly affected
- Orofacial apraxia -> difficulty swallowing
- Retention of insight -> distressed
- Behavioural features unusual and late:
  - rigidity
  - loss of concern for others
Summary

Multiple causes for dementia
Accurate diagnosis is vital

Different areas affected -> different presentations

Different pathologies have predilection for certain areas

Important to recognise – why?
Treatment

1. Symptom control
2. Current medications
3. Future therapies
Symptom control
palliative care in dementia
Palliative care in dementia google hits

![Graph showing the increase in palliative care in dementia Google hits from 1980 to 2010. The number of hits increased significantly from 39 in 1980 to 6150 in 2010.](image-url)
Families and carers

• Difference from cancer - disease trajectory and psychosocial impact
  – Many do not see dementia as a terminal illness which impacts on palliative care intervention
  – Process of adjustment is long and can lead to ‘anticipatory grief’
  – ‘Social death’-> death can be a relief cf stress and strain prior to death

• Advanced care planning
  – can raise some of the issues and decrease futile interventions.
  – capacity

Clarify roles – huge issue especially in young onset dementia
Pain

In dementia is underdetected + undertreated

- **Ferrell et al 1990**
  
  NH residents 71% had pain some of the time, 24% had constant pain.
  
  15% had received painkillers in the previous 24 hrs.
  
  Mean MMSE 21/30

- **Ferrell et al 1995**
  
  217 NH residents with dementia MMSE 12
  
  62% co pain
  
  Excluded those where communication too difficult ie 70.

Those who can’t report pain receive less analgesia

- **Closs et al 2004**
  
  those with cognitive impairment receive less analgesia post op
“Death and dying should be a natural matter to discuss..... Palliative care for me, starts, should start, the minute that you get a diagnosis... This business of dying is quite a natural process. People tend to regard dying as something unnatural, but it isn’t.”

Peter Ashley, living with dementia
Alz Soc 2012
Timing of palliative intervention

- Addington hall – 1998  Spectrum of palliative care

- Quality person-centred dementia care
- Psychosocial and pharmacological interventions
- Terminal stages requiring specialist palliation eg pain relief more detailed knowledge and skills
Existing pharmacological therapies for dementia

- Most have been aimed at AD
- Currently the only licensed treatments are symptomatic therapies
- Disease-modifying therapies currently in clinical trials
Cholinesterase Inhibitors

- Donepezil (1996)
- Galantamine (2000)
- Rivastigmine (2001)

- Licensed for mild-moderate AD
  - (MMSE 10-26)
- Significant response in less than 50%
  - Cochrane review: some improvement in cognition at 6m
- Evidence of benefits in cognitive domains (attention)
- Behavioural benefits – eg hallucinations
- May improve mood/confidence
Memantine - Ebixa®

- NMDA-receptor antagonist that affects glutamate transmission
- Licensed for moderate to severe AD: MMSE 3-20
- ~ 50% of people taking drug may benefit
- Combination therapy with AChEIs?
Memantine - Ebixa®
Possible side-effects

- Low incidence of side effects
  - Hallucinations
  - Confusion
  - Dizziness
  - Headaches
  - Tiredness

- Care in renal impairment or seizures
Other Treatments
“Doctor should we try X?”

- Vit E
  - Possible slowing in AD (Sano 2000 IU, NEJM 97)
  - No benefit in MCI (Petersen, NEJM 2005)

- Ginkgo “120mg” (Le Bars, JAMA 97) no evidence

- Statins (Simon, Annals 2002)

- HRT (-ve in prospective trials)

- Omega-3 fish oil

- EXERCISE
Summary

• Symptomatic treatments - modest benefit

• Treat:
  – Risk factors (for AD and vascular disease)
  – Co-morbidity
  – Depression

• Holistic approach – partnerships between primary & secondary care and carers

• Symptom control and palliative care important

• New therapeutic era - real prospect of disease modifying treatments
Current studies in AD by region
Pathogenesis of dementia

AD

Genetic and other risk factors

Abnormal protein deposited in the brain

Loss of brain cells (brain atrophy)

Altered levels of neurotransmitter

Symptoms and signs of the disease

Genetics: APP, PS1, PS2, ApoE4

Other: Age

Amyloid Tau

Hippocampal atrophy initially then whole brain

Cholinergic

Episodic memory problems then global deficits
Current clinical trials

- **Immunotherapy approach**
  Using drugs that stimulate the immune system in order to remove abnormal proteins that have been deposited
  - Early studies limited by side effects in patients (meningo-encephalitis)
  - Many Current studies use monoclonal antibodies- bind to proteins and stimulate the immune system in order to dissolve.
Current Clinical trials in UK

- Monoclonal antibodies
  1. A Long-Term Safety Extension Study of Studies ABE4869g and ABE4955g in Patients With Mild To Moderate Alzheimer's Disease Treated With Crenezumab
  2. An Efficacy and Safety Trial of MK-8931 in Mild to Moderate Alzheimer's Disease (Po7738 AM3) (EPOCH)
  3. A Study of Gantenerumab in Patients With Prodromal Alzheimer's Disease
Alternative hypothesis

• TauRx studies

• Using an oral drug leuco-methylthionium bis in order to prevent and dissolve abnormal tau deposition

• Oral treatment
Too little too late?

- Current trials are late in the process
- Need to identify pre symptoms
- Genetic marker ADAD
Dominantly Inherited Alzheimer Network (DIAN)

- International observational trial (US, UK, Australia) started 200
- Patients with a family history of dominantly inherited Alzheimer’s disease
- Both at risk and affected patients (128; 33 DRC)
- Biomarker study (Blood, CSF)
- Imaging
- Clinical assessment

- Only UK/European site- Dementia Research Centre, National Hospital for Neurology and Neurosurgery, Queen Square
DIAN results

- 25 years before symptom onset, levels of amyloid in the CSF began to drop.

- 15 years before symptom onset, PET scans -increased amyloid deposition in brain and the appearance of tau protein in the CSF.

- 10 years before SO impaired episodic memory
DIAN Treatment trial

- **Aim:** To assess the safety, tolerability and biomarker efficacy of gantenerumab and solanezumab in subjects who are known to have an Alzheimer's disease causing mutation.

- **Subjects**
  - known to have a mutation causing Alzheimer's disease or
  - those "at-risk" for an ADAD mutation and who are between 15 years younger to 10 years older than the age of symptom onset in their affected parent
  - Have to be cognitively normal or have mild symptoms of dementia
Return to Overview

- The problem in context
- Diagnosis
- Types of dementia
- Treatment
- The future
Conclusion

• These are exciting times in terms of dementia clinical care and research.

• Field has moved a long way in 20 years but solving one problem usually identifies many more.

• Key areas for the future
  – Continued work on accurate early diagnosis with biomarkers
  – Alzheimer’s Disease Modifying Treatments (ADMT’s)
  – Better symptomatic treatments and holistic care
Thank you!

DRC STAFF