Dementia
Past, Present and Future

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Objectives

By the end of this presentation, participants will be able to discuss:

• Major advances in dementia over past 50 yrs
• Exciting current developments
• Potential future developments
Disclosure Statement

☑️ I have nothing to disclose
Dementia in 1965

Little interest among neurologists

Behavioural neurology was just developing

Focus in behavioural neurology was on disorders such as aphasia

Not Dementia
Fifty Years Ago

No focus on following “common” disorders:

- Alzheimer’s disease
- Dementia with Lewy bodies
- Frontotemporal dementia/Pick’s disease
- Mild cognitive impairment
- Vascular cognitive impairment

Above all described in some form before 1965
Alzheimer’s Disease

Case reported by Alzheimer (1906)
- Auguste D, age 51
- Severe memory deficits, aphasia and apraxia
- Paranoid delusions and hallucinations
- Neuronal loss, plaques, neurofibrillary tangles
- Possible atherosclerosis (debate about this)

Emil Kraepelin (Clinical Psychiatry, 8th ed. 1910)
- Coined term “AD” as a “new” disease
- Alzheimer considered it early senile dementia

GE Berrios. Intl J Geriatric Psychiatry, 1990
Kraepelin’s Omissions

When he coined term AD, did not mention:
• Delusions and hallucinations (were present)
• Arteriosclerotic changes (possibly present)
Above were dropped from AD

AD was thus considered to be:
• Pre-senile (based on age 51 of Auguste D)
• Not associated with cerebrovascular disease
• Different from senile dementia (meant dementia in old age)

GE Berrios. Intl J Geriatric Psychiatry, 1990
Pre-senile vs Senile Dementia (1960’s)

Pre-senile dementia (< age 65)
• Commonly due to Alzheimer’s disease

Senile dementia
• Commonly, and incorrectly, attributed to atherosclerosis/cerebrovascular insufficiency

Fisher. CMAJ, 1951
De Boni and McLachlan, Life Sciences, 1980
1970s

Shifts in concept

- Dementia over age 65 usually due to AD instead of cerebrovascular disease
- Pre-senile and senile dementia with AD pathology are the same disease

Importance of CVD in AD not recognized
AD in 1980s -1990s

• Severe cholinergic depletion in AD
• Role of tau vs amyloid debated
• Discovery of genes (P Hyslop & colleagues)
  - autosomal dominant: APP, Presenilin 1 & 2
  - Susceptibility gene: ApoE e4
• NINCDS-ADRDA criteria for AD (1984)

Review: Reichman and Rose, Menopause 2012
Approval of Drugs for AD in Canada

1997: donepezil
2000: rivastigmine
2001: galantamine
2004: memantine
AD in 2015

- Don’t know cause
- No highly effective treatment
- CVD common in AD
- New criteria: NIA-AA, McKhann et al 2011
- Biomarkers: Imaging, CSF, genetics
- Cognitive reserve (eg bilingualism)
- Brain fitness movement
  - physical exercise, cognitive training, diet
Bilingualism

Delays onset of AD by up to 5 years

Bialystok, Craik, Freedman. Neuropsychologia, 2007
Craik, Bialystok, Freedman, Neurology, 2010
Future Developments

Pre-symptomatic diagnosis
• Biomarkers will likely play big role in pre-symptomatic diagnosis (eg amyloid, tau, functional and structural neuroimaging)

Effective symptomatic treatment
Pre-symptomatic Treatment
Prevention
Mild Cognitive Impairment

Core syndrome

- Concern regarding a change in cognition
- Impairment in one or more cognitive domains
- Independence in functional abilities
- Not demented

Amnestic MCI often pre-AD

Albert et al. Alzheimer’s & Dementia, 2011
Mild Cognitive Impairment

Term MCI

• 1988: First used to describe subjects with GDS stage 3 (Reisberg et al)
• 1995: Used as an independent diagnostic category (Petersen et al)

Petersen et al. JAMA, 1995
Golomb et al. Dialogues Clin Neurosci, 2004
Frontotemporal Dementia (FTD)

• Same as Pick’s disease
• In 1965, common teaching was that Picks could not be clinically distinguished from AD
• First two criterion papers enabled distinction from AD (1994, 1998)
• Now clear that classical clinical features of Pick’s disease differ from AD
• Most recent criterion paper: Rascovksy et al. Brain, 2011
Early Behavioural Disinhibition

Case (video 1)

55 yr old woman with 2 year history of bvFTD
Semantic Variant PPA

Both of:
• Impaired confrontation naming
• Impaired single word comprehension

At least 3 of:
• Impaired object knowledge
• Surface dyslexia (cnight for knight) or dysgraphia (nok for knock)
• Spared repetition
• Spared grammar and motor speech

Gorno-Tempini et al. Neurology, 2011
Late Semantic Dementia

Video
Nonfluent/Agrammatic Variant PPA (Video)

At least one of:
- Agrammatism
- Effortful halting speech with inconsistent sound errors and distortions (apraxia of speech)

At least two of:
- Impaired comprehension of syntactically complex sentences
- Spared single word comprehension
- Spared object knowledge

Gorno-Tempini et al. Neurology, 2011
Logopenic Progressive Aphasia (Video)

Both of the following

• Impaired single word retrieval in spontaneous speech and naming
• Impaired repetition

At least 3 of

• Phonological errors
• Spared single word comprehension and object knowledge
• Absence of frank agrammatism

Gorno-Tempini et al. Neurology, 2011
• overflew (phonemic paraphasia)
• little ladder (semantic paraphasia)
• word finding pause towards end
• water is on damaged floor (circumlocution for word that she can’t find)

Video
Logopenic Progressive Aphasia

Impaired Repetition

Video
Caution

Some patients with AD present with features suggestive of FTD, SD, and NFPA
Disorders Linked to FTLD

- ALS
- Corticobasal syndrome
- Progressive supranuclear palsy

Miller, B. Frontotemporal Dementia
Oxford University Press, 2014
Genetics of FTLD

Positive family history: 40% of cases

Most common autosomal dominant genes

- MAPT
- Progranulin
- C9ORF72

Miller, B. Frontotemporal Dementia, OUP, 2014
Pathology in FTLD

Inclusions

• Tau
• TDP-43
• Rarely FUS

Miller, B. Frontotemporal Dementia, OUP, 2014
Future Developments

• Pre-symptomatic diagnosis using biomarkers (eg neuroimaging, CSF, blood, genetics)
• Symptomatic treatment
• Pre-symptomatic treatment
Dementia with Lewy Bodies

• Little focus until 1996 criterion paper after development of ubiquitin staining which made it easier to detect cortical Lewy bodies.

• Now recognized as a common dementia

McKeith et al. Neurology 1996
Dementia with Lewy Bodies

Criteria for Probable DLB

Dementia plus two of the following

- Recurrent visual hallucinations
- Prominent fluctuations
- Spontaneous features of Parkinsonism

McKeith et al. Neurology 65:1863-72, 2005
Added Diagnostic Features (2005)

Suggestive features

• REM sleep behaviour disorder
• Severe neuroleptic sensitivity
• Low DA transporter uptake in basal ganglia on PET/SPECT

1 suggestive + 1 core feature = Prob DLB
Fluctuations

Refer to wide swings in
• Cognition
• Attention
• Alertness

Can occur over minutes, hours, days

Video
Treatment of DLB and PDD

Double-blind placebo controlled studies
• Best evidence is for rivastigmine
• May be a class effect

McKeith et al. Lancet 2000
Emre et al. NEJM 2004
Dementia with Lewy Bodies

Main advance
- Recognition as a common disorder

Major Clinical Points
- Neuroleptic sensitivity
- May be same disorder as Parkinson’s disease with dementia
- REM sleep behaviour disorder common (may respond to low dose clonazepam)
Cerebrovascular Disease and Dementia

Multi-infarct dementia (1974)
Dementia due to single or multiple infarcts

Vascular dementia (1993)
Dementia due to infarction or hemorrhage (single or multiple)

• Umbrella term ranging from very mild to severe cognitive impairment

Hachinski and Bowler, Neurology, 1993
Key Factor Advancing VCI

Neuroimaging
Exciting Areas

Biomarkers (Neuroimaging, Blood, CSF)
- Symptomatic and pre-symptomatic dx
- Monitoring treatment

Treatment
- Pharmacological and Non-pharmacological

Prevention/Delaying Onset
- eg bilingualism, lifestyle factors

New perspectives on old disorders
- eg Chronic traumatic encephalopathy
Summary

Discussed advances over past half-century related to:

- Alzheimer’s disease
- Frontotemporal dementia
- Dementia with Lewy bodies
- Vascular cognitive impairment
- Mild Cognitive Impairment