

Dementia Past, Present and Future

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CNSF 2015

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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

Ramirez-Bermudez. Arch Med Research, 2012

Kraeplin'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

Ramirez-Bermudez. Arch Med Research, 2012

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

Stewart. Br J. Psychiatry, 2002

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
Freedman et al. *Behavioural Neurology*, 2014

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)

Reisberg et al. Drug Dev Res, 1988

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:
Rascovsky 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

- overflow (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

Video

Logopenic Progressive Aphasia

Impaired Repetition

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 FTLT

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

Aarsland et al. Cur Neurol Neurosci Rep 2012

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)

Vascular Cognitive Impairment (1993)

- Umbrella term ranging from very mild to
severe cognitive impairment

Hachinski et al. Lancet 1974, Roman et al. Neurology, 1993

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