Clinical Approach to Dementia

NEURO 410

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Objectives

• To define dementia, list its causes, and illustrate them with a case-based approach
• To cover MCI as a prelude to dementia
• To review how depression can mimic dementia and figures in its differential diagnosis
• To describe briefly the treatment of these conditions including pharmacotherapeutics
Old People

The "elite" elderly

The "usual" aging

The "frail" elderly

The institutionalized
Reasons for Diagnosis Difficulty in Seniors

- Age-related changes
- Multiple Different medical conditions
- Unusual disease Appearances
- Effects of Drugs
- Mental, visual & hearing deficits
Geriatric Assessment
Consultative Geriatric Team

- Physician
- Nurse
- Physiotherapist
- Recreational Therapist
- Psychogeriatrician
- Social Worker
- Occupational Therapist
- Secretary
Comprehensive Geriatric Assessment

• Concerned with the care of *frail* elderly people, especially when they become ill.
• Assessment and management of multiple interacting issues
  – medical, social, functional
  – changes with age
  – unusual looking diseases
  – Caregiver breakdown
Dynamic Model of Frailty

- Ability to maintain independence hangs in the balance due to a combination of individual assets and deficits
  - Health vs. Illness
  - Attitudes and Health Practices
  - Disability
  - Other Resources
Confusion / Memory Loss

- Selective memory loss (only) Mild Cognitive Impairment
- Delirium (New medical illness esp. serious)
- Drugs
- Depression
- Dementia, including Alzheimer’s Disease
Dementia & Alzheimer Disease: A Public Health Problem

- AD: the most common form of dementia
- Estimated that approx. 20 million people are affected with dementia worldwide (now 418,000 in Canada)
- Prevalence of Dementia in those over 65 years of age is approximately 8% and reaches over 35% in those over 85
- AD is associated with annual costs of more than $100 billion in the US alone

Mayeux and Sano, 1999; Evans et al, 1989
Confusion / Memory Loss

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DEMENTIA

• A NEGATIVE PROGRESSIVE CHANGE THAT LEADS TO WORSENING THINKING, MEMORY, FUNCTION & BEHAVIOUR
DSM IV Criteria for Dementia

- Memory Impairment
- One of (the four A’s)
  - Aphasia
  - Apraxia
  - Agnosia
  - Erosion of Executive Function
- Which impairs independent daily function
Prevalance and Differential

• Prevalence
  – 8% at age 65 years
  – 16% at age 75 years
  – 35% at age 85 years

• Differential must rule out
  – Delirium
  – Depression
  – Drugs
Prevalence of 4 major types of dementia

- Pure DLB: 3%
- DLB with AD: 12%
- Mixed VaD and AD: 10%
- Pure VaD: 5%
- FLD: 15%
- Other: 15%
- AD: 60%
Types of dementia

- Alzheimer’s Disease
- Vascular: Multiple (sometimes tiny) strokes
- A mix of the two above
- Fronto-Temporal (Pick’s); Lewy Body Dementia; & several others
First:
What Is Memory?

• The ability to store and retrieve information

• Memory systems:
  – Working memory
  – Long-term
As people age, they experience memory loss: Is it normal?

- Is it age-related memory loss?
- Is it Mild Cognitive Impairment (MCI)?
- Is it Dementia?
Memory Loss: When It’s a Problem

Memory impairment

• Incapacity to learn new info or to recall recently learned info

• Possible causes include:
  – Drug intoxication
  – Depression
  – Head injury
  – Stroke
  – Dementia, such as Alzheimer’s Disease
AD : 10 Warning Signs

• Memory loss affecting day-to-day function
• difficulty performing familiar tasks
• language/speech problems
• disorientation to time & space
• poor or decreased judgment
• problems with abstract thought
• misplacing objects
AD: 10 Warning Signs

- Mood & behaviour
- Personality alterations
- Loss of initiative
Amyloid Cascade Hypothesis

Mis-metabolism of APP

Neuropilic Tangles
- Conversion to fibrillar amyloid
- Cytokines il-1 & il-6
- Complement reactive O$_2$ species

Non-fibrillar Amyloid deposits
- Glial cell activation
- Pro-inflammatory mediators & Neurotoxic substances
Pathogenesis of the Alzheimer syndrome: a convergence syndrome

- Aging
- Apoptosis

Genetic

Pathological cascade

- Free radicals
- Neurotoxins

Amyloid plaques

Neurotransmitter failures

Current symptomatic therapy

*FAD gene mutations
Presenilins
Chromosomes 1, 14
APP
Chromosome 21

*Apolipoprotein E genotype
Chromosome 19

*Down’s syndrome
Chromosome 21
Symptomatic domains of typical AD over time

Adapted from Gauthier et al. Clinical Diagnosis and Management of Alzheimer’s Disease. Martin Dunitz, 1999
What causes dementia?

- The different causes of dementia are:
  - Alzheimer’s disease (AD)
  - vascular dementia (VaD)
  - mixed dementia
  - Lewy body dementia
  - Parkinson’s disease
  - severe alcohol abuse
  - Creutzfeldt-Jacob disease
  - Huntington’s disease
  - frontal lobe or fronto-temporal lobe dementia (including Pick’s disease)
  - AIDS
  - metabolic disorders
  - other conditions
Requirements for Dementia Diagnosis

• Memory Impairment PLUS
• One of (the three A’s and the E)
  – Word-finding difficulties
  – Problems with familiar tasks
  – Trouble recognizing people, places, things
  – Disturbance in organizing & planning
• Which impairs independent daily function
• No associated other cause or condition
2. Exploring Cognition

Collateral History
- STM, LTM
- Language
- Praxis (dressing...)
- Executive Functioning
- Insight & Judgement
- Visuospatial
- Behaviour

Interview of the Patient
- family, current events
- anomia, fluency...
- initiate or copy action
- abstraction (proverbs, sim&diff), scenarios
- initiate or copy figure
The Course

• When did you first notice a change and what was it?

• Did this come on gradually or abruptly?
  – If abrupt, what else was going on?

• How have things progressed?
  – “Step down”? Acceleration?
Alzheimer’s Disease: Key Management Issues

- Diagnostic Disclosure
- Driving
- Capacity
- Community Resources
- Treatment
Unfortunately, most of us will at some time in our lives be touched directly or indirectly by the tragic effects of dementia.
7 Axioms of Exploring Cognition

Step I: Seek out a reliable caregiver

Step II: Map out the course of the confusional state

Step III: Hose down ALL aspects of cognition

Step IV: Perform an objective screening evaluation or scale, such as the Folstein Mini Mental Status Examination and other objective cognitive tests
7 Axioms of Exploring Cognition

Step V: Compare the cognitive loss to functional loss

Step VI: Examine the patient as thoroughly as possible (esp CNS)

Step VII: Communicate the diagnosis to patient & family with the key counseling
(Amnestic) Mild Cognitive Impairment

- Subjective complaints of memory loss
- Corroborated by an informant
- Objective memory impairment when adjusted for age & education
- Generally preserved intellectual abilities
- NO, or only slight, functional impairment
- Failure to meet dementia criteria
- No other explanation for memory loss
Treatment of MCI: Outcomes

• In two 3 year trials compared to placebo NEITHER donepezil (Aricept®) nor galantamine (Reminyl®) were successful in delaying the conversion to AD
Clinical Features of the classic “Vascular” Diagnosis

- By history, abrupt onset, stepwise deterioration, prolonged plateaus
- Early onset of urinary incontinence
- Early onset of gait abnormalities
- Early onset of seizures
- History of hypertension, stroke / t.i.a’s.
- On P.E.: patchy cognitive exam, CNS lateralization, prominent aphasia
Vascular Cognitive Impairment
New Classification (!)

- Vascular cognitive impairment, not demented
- Multi-infarct dementia
- Subcortical Ischemic Vascular Disease
- Strategic Infarcts
- Global Cortical Hypoperfusion
- Hemorrhagic Disorders
- CADASIL
Subcortical Ischemic Vascular

- Includes Binswanger’s & “etat lacunaire”
- Insidious onset (>50%), NO stepwise progression
- Focal CNS findings often VERY subtle
- Atypical “frontal” gait, prominent deficits in attention & executive function
- Primary vascular lesion: SMALL vessel diseases
Strategic Infarcts

- An increasingly recognized category of VCI, Vad
- Previous studies (in traditional MID) revealed that cumulative volumetric capacity meant > 100cc of brain. In strategic infarct dementia, may be < 1/10 of that.
- Left anterior & posterior cerebral artery territories
- Thalamic, hippocampal & dominant angular gyrus areas
The Female Brain

FOOTNOTE: Note how closely connected the small sex cell is to the listening gland.
The Male Brain

FOOTNOTE: the "Listening to children cry in the middle of the night" gland is not shown due to it's small and underdeveloped nature. Best viewed under a microscope.
Functional Impact

- How have these changes affected ability?
  - IADLs - meds, finances, driving, meal prep…
  - BADLs - dressing, personal hygiene, eating…
  - Hobbies & Special Skills
  - Socialization

- Can functional decline be explained in any other way?
  - physical disability
  - other psychiatric disorder
What is Delirium?

• A confusional state characterized by:

  1. Acute Onset and Fluctuating Course
  2. Inattention
  3. “Disorganized Thinking” or Altered LOC
  4. Psychotic features (hallucinations)
  5. Hypo- or hyper-active
Why should we care?

- It is common
- It is deadly
- Doctors often fail to recognize it
Delirium is common

- Medical patients in hospital
  - Prevalence on admission: 10-22%
  - Incidence during hospitalization: 7-31%
- Postoperative delirium
  - Orthopedic surgery: 40-60%
  - Cardiac surgery: 33%
Delirium - “The Bad Guy” Drugs

- Pain killers Narcotics
- Anticholinergics including antihistamines
- Valium- like agents
- Psychiatric compounds

Drugs for Parkinson’s Disease
- Common Drugs but less likely
“Stay Awake, Now...”
CASE I

• This 86 y.o. lady appears at your clinic in follow-up with her daughter. You had seen her 9 weeks ago for short-term memory loss (12-18 months’ duration), withdrawal from her usual recreational activities and failure to thrive. Because she had admitted to slight sadness and very poor sleeping with 12 lb weight loss in the previous 6 months, you had diagnosed major depression & treated her with Sertraline (Zoloft). Nine weeks later, she appeared again with improved spirits, more energy, and a weight gain of 5 lb. You extended her prescription.
CASE  I

• On this visit, her daughter points out that her memory is still impaired, & worse than previously. In a recent game of bridge, she was not keeping up. The daughter was concerned about her driving ability on a trip to Westlock last week.
Recognition of Depression

- **S** sleep poor, recent worsening
- **I** interest ↓, poor energy, ↓ enjoyment
- **G** guilt with lowered self esteem
- **E** energy down; withdrawal
- **C** concentration poor, as is MEMORY
- **A** appetite diminished; weight loss
- **P** psychomotor retardation or AGITATION
- **S** suicidal ideation; thoughts of death
CASE I

- Which details on history would you pursue?
- Is lab work of help?
- Is a CT scan indicated? An MRI scan?
- What are the diagnostic possibilities?
CASE II

• This 81 y o lady presents to your office, anxious for an exam because she is convinced she has Alzheimer’s. In recent months she has noticed significant impairment in memory, as well as some difficulties with concentration. Her memory appears to affect STM and LTM. She used to be an avid reader but discontinued this when she found she was retaining very little.

• She also describes symptoms of inner nervousness which has bothered her for 5 months. With prompting from her husband, she also relates her belief that the police are watching her activities very carefully. She has noticed them parking outside her home and is worried they are going to convict her of a crime she did not commit.
CASE II

• She describes herself as a lifelong poor sleeper but that this has worsened. She has not experienced speech and language difficulties, problems in navigation, or difficulties in executive functioning. In terms of behavior she is much more anxious than previously and her husband describes her as more irritable.

• There is no FH of depression or dementia. There is no h/o head injuries but she did suffer a CVA with no sequelae.
CASE II

- Which further details would you seek?
- What is the likely diagnosis?
- Would you prescribe a drug at this point?
Major Depression – Prevalence in Seniors

- In LTC facilities 13-15%
- In the community 2%
- In acute care hospital 25%
Symptomatic domains of typical AD over time

Adapted from Gauthier et al. Clinical Diagnosis and Management of Alzheimer’s Disease. Martin Dunitz, 1999
Recognition of Depression

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Atypical Features of Depression

- Senior not always aware of sadness
- Cognitive impairment common (help!)
- New development of anxiety
- Somatization/ bodily preoccupation
- 50% psychotic features (paranoid del.)
- “the dwindles”
- High prevalence of suicide (men, alone)
CASE III

Mr. R. F., a 63 year old man, presents in your office accompanied by his wife. The main reasons for his visit pertain to a change in his behavior that has been ongoing now for two years. Over this time, he has exhibited irritability, belligerence, and frequent outbursts with loss of temper. To his wife, he appears less patient, more angry, and less flexible in his overall approach. She also mentions that he has shown a definite tendency to sleep more than previously, often retiring at 1900 hours in the evening, and sleeping for several hours at a time on weekend days. His personal hygiene is declining dramatically.
CASE III

You make several probing inquiries about his cognition. Both he and his wife do acknowledge some loss of recent memory, as well as speech and language difficulties. His insight into these described changes is nil. Work performance has fallen off, as has judgment. He had a near car crash last week & later joked about it. A Folstein Mini Mental Status Examination clocks a score of 28/30.

His complete physical examination is entirely within normal limits. No psychotic features have been identified.
CASE III

The likeliest diagnosis is:

- Agitated Major Depression
- Atypical Alzheimer’s Disease
- Lewy Body Dementia
- Fronto-temporal Degenerative Dementia
- Personality Disorder
- None of the above
CASE III

• How would you proceed from here? What tactics would you employ?

• Are they medications that could help him?
Fronto-temporal Dementia

• Relatively new entity fully articulated in ’86
• Used to be termed “Pick’s Disease”
• Behavioral characteristics appear “early in the game” (compared to AD) & include:
  - disinhibition & poor insight
  - loss of social awareness
  - personal neglect
  - inertia and impulsivity
Dementias with fronto-temporal Features

- Fronto-temporal Degenerative Dementia
- Vascular cognitive impairment (small vessel subset)
- Alzheimer’s Disease
- Alcohol-induced Dementia
- Post-traumatic Encephalopathy
Lewy Body Dementia

- Lewy Bodies found throughout cortex & brainstem
- Classic Constellation
  - Progressive dementia (esp. inattentive)
  - Fluctuating cognition with hallucinations
  - motor features of parkinsonism, falls
  - neuroleptic sensitivity
- Response to rivastigmine (Exelon)
Presentation of CJD

- Spongiform encephalopathy associated with rapid progression to dementia over days-weeks + array of neurological signs
- most get stimulus-sensitive myoclonic jerking especially with sudden touch or sound- startle myoclonus
- terminally, mute & akinetic
- 90% dead within 1 year
Normal Pressure Hydrocephalus

- Impaired CSF absorption with ventricular enlargement disproportionate for age.
- Triad (the temporal order counts)
- Remember the CLUSTER
  - Gait Apraxia
  - Urinary Incontinence
  - Dementia: subcortical - apathy/executive dysfunction
Neurotransmitter imbalance in AD

- In terms of treatment strategies in AD, two neurotransmitters have been studied.

  - **Acetylcholine**
    - Levels of acetylcholine are abnormally low – the basis for the use of acetylcholinesterase inhibitors.

  - **Glutamate**
    - Levels of the excitatory neurotransmitter, glutamate, are elevated.
Cholinergic Treatment in AD

- Produces measurable improvement in cognition
- Effect is modest; equivalent to 6-12 month delay
- Positive behavioral effects
- Does not alter progression of neuro degeneration
- Cholinesterase inhibitors – Donepezil (Aricept), Galantamine (Reminyl) and Rivastigmine (Exelon)
Unforeseen Effects

- Benefits on behaviour in LTC pts with moderately advanced AD
  - visual hallucinations
  - apathy
  - motor rummaging
  - Anxiety & depression
Hypothetical treatment responses to ChEIs in AD

Any one of three outcomes may be considered treatment success

- Improvement followed by slower progression of symptoms
- Stabilization followed by slower progression of symptoms
- Slower progression of symptoms
- Natural disease course in an untreated patient

YEARS

MMSE

Initiation of treatment

AchEI’s: Use Particular Caution

- In those with asthma, COPD, supra-ventricular conduction disorders, and peptic ulcer disease
- In frail elderly females of low body weight
- In those with a baseline sinus bradycardia (< 50)
Memantine – new perspectives in AD treatment

- The first and only drug in a new class – NMDA receptor antagonists – for the treatment of AD
- Blocks pathological activation of NMDA receptors while preserving physiological activation required in learning and memory formation
- Indicated as monotherapy or as adjunctive therapy with cholinesterase inhibitors for the symptomatic treatment of patients with moderate to severe dementia of the Alzheimer’s type

Ebixa® Product Monograph; Danysz et al 2000
Psychosis & Agitation in the Elderly: Key Concepts

- These are COMMON, esp. in dementia
- Physical conditions, physical discomfort & medication side effects must be ruled out
- Atypical anti-psychotics are efficacious and safe
- Appropriate pharmacotherapy can play an important role in the interdisciplinary plan
Non-pharmacologic Interventions

- Ensure co-morbid conditions treated
- Provide a SAFE environment
- Equip doors & gates with safety locks
- Home installations: grab bars
- Calendars, clocks, radios for orientation
- Remember night lights
- Avoid household clutter & glare surfaces
Non-pharmacologic Interventions

- Use a predictable daily routine
- Allow pt to dress in own clothing & keep possessions handy
- Before starting activity explain clearly
- Break complex tasks into steps
- Use distraction & re-direction to divert him from problematic situations
Non-pharmacologic Interventions

- Reduce over-exposure to environmental stimulation (I.e. crowded places)
- Consider a dementia day-care unit
- Enroll the patient in the Alzheimer Society Wandering Registry
- Remember the 3 R’s: repeat, reassure, & re-direct
Caregiver Burden

- Spend from 40-100 hours per week with pt
- 90% affected emotionally (frustrated, drained)
- 75% report feeling depressed
- 60% have significant depression
- 50% have no time for themselves
- Loss of income is significant
Summary of Management of Dementia

• Diagnosis – cognitive history, neurobehavior, function, cognitive testing, PE, labs +/- CT
• Medication – consider AchEI
• Function – look at ways need support
• Mood, behavior, psychosis, safety (driving/stove/wandering) - any issues
• Medicolegal
• Disposition
• Caregiver burden
Objectives

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• To describe the treatment of these conditions including pharmacotherapeutics