“Memory loss and the diagnosis of common dementias”

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Disclosures

• Bocacare employee
Jewish Sheltering Home merged with the Home for Aged and Infirm Israelites and opened its new 202-bed home September 14, 1952 at 5301 Old York Road.

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Objectives

• Understand different types of memory
• Understand terms used to describe cognitive impairment
• Know the four major chronic neurocognitive disorders and how they present
• Know how to initially approach your patients with cognitive disorders
<table>
<thead>
<tr>
<th>Causes of Cognitive Impairment</th>
<th>Subacute/Rapidly progressive</th>
<th>Chronic</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Acute onset</strong></td>
<td></td>
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<tr>
<td>Days to weeks</td>
<td>Weeks to months</td>
<td>Months to years</td>
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<tr>
<td><strong>Vascular</strong></td>
<td>Multi-infarct/Thalamic/Callosal ICH/SDH</td>
<td>CNS Vasculitis Intravascular lymphoma</td>
</tr>
<tr>
<td><strong>Infectious</strong></td>
<td>Encephalitis Meningitis Systemic infections/Pneumonia/UTI</td>
<td>HIV Dementia/Encephalitis Lyme’s Disease Whipple’s disease PML</td>
</tr>
<tr>
<td><strong>Toxic/Metabolic</strong></td>
<td>Illicit drugs/or solvents Electrolyte abnl Hypoxia Wernicke’s</td>
<td>Heavy metals/Wilson’s/Vitamin deficiency (B-12, niacin)/ Endocrine dysfunction (Thyroid/parathyroid) Uremic/Hepatic encephalopathy</td>
</tr>
<tr>
<td><strong>Autoimmune</strong></td>
<td>Anti-NMDA paraneoplastic ADEM CNS Vasculitis/cerebritis (e.g. SLE)</td>
<td>Hashimoto’s encephalopathy Paraneoplastic Cerebritis Sprue/Sarcoid/Behcets</td>
</tr>
<tr>
<td><strong>Metastatic</strong></td>
<td>neoplasm</td>
<td>Tumors/lymphoma</td>
</tr>
<tr>
<td><strong>Iatrogenic</strong></td>
<td>Medications</td>
<td>Medications</td>
</tr>
<tr>
<td><strong>Neurodegenerative</strong></td>
<td>CJD</td>
<td>CJD/NPH</td>
</tr>
<tr>
<td><strong>Systemic</strong></td>
<td>Hypertensive encephalopathy/Delirium</td>
<td></td>
</tr>
<tr>
<td><strong>Other</strong></td>
<td>Seizure/Trauma</td>
<td>Depression (At the mild NCD stage or the mildest level of major NCD, depression and/or apathy are often seen.)</td>
</tr>
</tbody>
</table>
Memory

• Ability to encode, store, retain and subsequently recall information and past experiences. It is how we use past experience to affect or influence current behaviour.

• Short-term memory
  – Ability to remember and process information at the same time.
  – Retains a small amount of information (typically about 7 items) in mind in an active, readily-available state for seconds to minutes.
  – Depends on regions of the frontal and parietal lobe.
  – Example:
    • In order to understand this sentence, the beginning of the sentence needs to be held in mind while the rest is read.

• Short-term memories become long-term memory through the process of consolidation, involving rehearsal and meaningful association.

http://www.human-memory.net/types_episodic.html
Long Term Memory

- Depends on de novo protein synthesis and changes in the molecular components of neuronal networks in specific cortical areas depending on the different memory types
- Divided into two main types:
  - Procedural memory ("knowing how")
    - Memory of skills and how to do things, particularly the use of objects or movements of the body
    - Acquired through repetition and practice
    - Allow us to carry out ordinary motor actions automatically.
    - Also referred to as implicit memory, because previous experiences aid in the performance of a task without explicit and conscious awareness of these previous experiences,
  - Declarative memory ("knowing what")
    - Memory of facts and events that can be consciously recalled (or "declared").
    - Also called explicit memory, since it consists of information that is explicitly stored and retrieved.

http://www.human-memory.net/types_episodic.html
Declarative Memory

- Declarative memory is sub-divided into episodic memory and semantic memory.
  - Episodic memory
    - A person’s memory of his/her personal experiences and specific events in time in a serial form.
    - We use this memory to reconstruct the actual events that took place at any given point in our lives.
  - Semantic memory
    - Record of facts, meanings, concepts and knowledge about the external world that we have acquired.
    - It refers to general factual knowledge, shared with others and independent of personal experience.

http://www.human-memory.net/types_episodic.html
Different types of long-term memory are stored and processed in different regions of the brain

• Declarative memories
  – *Encoded* by the hippocampus, entorhinal cortex and perirhinal cortex (all within the medial temporal lobe of the brain), but are *consolidated and stored* in the temporal cortex and elsewhere.

• Procedural memories
  – Do not involve the hippocampus
  – They are encoded and stored by the cerebellum, putamen, caudate nucleus and the motor cortex

• This means that with damage to the medial temporal lobe (the structure that includes the hippocampus), a person may lose his memory of facts and events but still recall how to do things.

http://www.human-memory.net/types_episodic.html
Terminology

- Normal aging
- Subjective memory loss
- Mild cognitive impairment
- Dementia
- Neurocognitive disorders
Cognitive change with normal aging

• In normal aging there are declines in:
  – Episodic memory - captures the “what,” “where,” and “when” of our daily lives
  – Information processing and learning something new
  – Doing more than one task at a time and shifting focus between tasks

• Semantic and procedural memory remain stable.
  – Semantic memory - the ability to recall concepts and general facts that are not related to specific experiences.
  – Procedural memory - your memory of how to do things, such as how to tell time by reading the numbers on a clock, typically stays the same.

Subjective cognitive impairment

• Defined as the feeling that there something wrong with your memory without any objective parameters to supporting this.

• May be a major risk factor for the subsequent development of dementia

• May precede mild cognitive impairment in a continuum of Alzheimer’s disease manifestations

• May be accompanied by subtle brain changes.
Mild cognitive impairment

• Transitional state between cognition of normal aging and mild dementia.
• A deficit in 1 or more cognitive domains with relative preservation of functional independence
• Heterogeneous group.
  – Some progress to Alzheimer's disease
  – Others may progress to another dementia
  – Some will never progress.
• Three types
  – Amnestic MCI
    • Main deficit is in memory
    • Most likely to progress to Alzheimer's disease.
      – Patients with amnestic MCI progress to Alzheimer's disease at a rate of 10-15% per year compared with healthy control subjects with a rate of 1-2% per year.
  – MCI in multiple domains
    • Mild impairments in multiple cognitive domains without requiring memory deficits.
  – MCI presenting as impairment in a single cognitive domain other than memory.
    • E.g. - a pronounced language disturbance
• These terms are still frequently used but superseded now by the term “Mild Neurocognitive Impairment”

Peterson et al., *Current concepts in mild cognitive impairment* Arch Neurol. 2001;58:1985-92
Dementia 1984

• “Dementia is the decline of memory and other cognitive functions in comparison with the patient’s previous level of function as determined by a history of decline in performance and by abnormalities noted from clinical examination and neuropsychological tests.”

Disorders previously classified as Dementia, delirium, amnestic, and other cognitive disorders are now referred to as “Mild or Major Neurocognitive Disorders”.

Major or mild NCD are differentiated based upon the individual’s level of independence in everyday functioning.

- Mild NCD – patients have preserved independence, although there may be subtle interference with function or a report that tasks require more effort or take more time than previously.
- Major NCD - impairment is severe enough to interfere with independence, such that others will have to take over tasks that the individuals were previously able to complete on their own.

Each Neurocognitive disorder is subtyped according to the known or presumed etiological/pathological entity (or entities) underlying the cognitive decline.

- Subtypes are distinguished on the basis of a combination of time course, characteristic cognitive domains affected, and associated symptoms

Six cognitive domains are defined
Cognitive Domains

• Complex attention
  – Normal tasks take longer than previously.
  – Begins to find errors in routine tasks;
  – Finds work needs more double-checking than previously.
  – **Has difficulty holding new information in mind, such as recalling phone numbers or addresses just given, or reporting what was just said. Is unable to perform mental calculations.**

• Executive function
  – Difficulty getting things done (executing activities)
  – Has increased difficulty multitasking or difficulty resuming a task interrupted by a visitor or phone call.
  – **Abandons complex projects. Needs to focus on one task at a time. Needs to rely on others to plan instrumental activities of daily living or make decisions.**

• Learning and memory
  – Has difficulty recalling recent events, and relies increasingly on list making or calendar.
  – Occasionally may repeat self over a few weeks to the same person.
  – **Repeats self in conversation, misplacing personal belongings, forgetting events or appointments, getting lost on a familiar route**

• Language
  – Has noticeable word-finding difficulty.
  – May substitute general for specific terms.
  – May avoid use of specific names of acquaintances.
  – Grammatical errors involve subtle omission or incorrect use of articles, prepositions, auxiliary verbs, etc

• Perceptual-motor
  – May need to rely more on maps or others for directions; Uses notes and follows others to get to a new place.
  – May find self lost or turned around when not concentrating on task.
  – **Has significant difficulties with previously familiar activities (using tools, driving motor vehicle), navigating in familiar environments; inability to operate simple implements, or orient clothing to the body**

• Social cognition
  – Has subtle changes in behavior or attitude, often described as a change in personality, increased extraversion or introversion, decreased inhibition, or subtle or episodic apathy or restlessness
  – **Behavior clearly out of acceptable social range;**
Distribution of the Major Age-Related Neurocognitive Disorders

Major or Mild Neurocognitive Disorder
Due to Alzheimer’s Disease

- Typically presents in an elderly person initially with a slowly progressive decline in memory and executive dysfunction followed by a gradual decline in other domains of cognition.

- Atypical presentations occur in 6-14% of patients
  - In these patients language, visual/perceptual-motor, or executive problems start before and are more pronounced than memory deficits.
  - Often appear in younger patients
  - Frequently not recognized by primary care physicians

Senile plaques and neurofibrillary tangles. Bielschowsky silver stain

Neurofibrillary tangles. Bielschowsky silver stain

Diagnostic and Statistical Manual of Mental Disorders (DSM-V®)
by American Psychiatric Association
Vascular Neurocognitive Disorder

• Population prevalence estimates for vascular dementia in the United States range from 0.2% in the 65–70 years age group to 16% in individuals 80 years and older
• Vascular pathology may range from large vessel stroke to microvascular disease
• Presentation is heterogeneous, relating to the types of vascular lesions, their location and extent.
  • Present with a single or multiple infarctions
  • May have an acute, stepwise or fluctuating decline in cognition, and intervening periods of stability and even some improvement
  • May have gradual onset with slow progression
• Vascular disease may coexist with other NCD
  • “Mixed Neurocognitive disorder - Treatable

Diagnostic and Statistical Manual of Mental Disorders (DSM-V®)
by American Psychiatric Association
Neurocognitive disorder with Lewy bodies or due to Parkinson’s disease (Lewy body dementias)

- Lewy body dementia - an umbrella term that includes Dementia with Lewy bodies and Parkinson’s disease Dementia.

- Dementia with Lewy bodies presents in elderly patients initially with changes in complex attention and executive function rather than learning and memory.

- Parkinson’s Disease Dementia occurs in patients with established Parkinson’s disease in a similar manner.

The hallmarks of Lewy body dementias are α-synuclein neuronal inclusions (Lewy bodies, and Lewy neurites), accompanied by neuronal loss.
Neurocognitive disorder with Lewy bodies (Lewy body dementia)

• Patients with LBD have at least 2 of the following core features:
  – Fluctuating levels of cognition / alertness
  – Recurrent visual hallucinations
  – Spontaneous features of parkinsonism.
    – Tremor, bradykinesia, rigidity
    – Must begin after the onset of cognitive decline; by convention, major cognitive deficits are observed at least 1 year before the motor symptoms

• Early or suggestive features also include:
  – Sleep disorders
    • REM sleep behavior disorder is a condition in which a person acts out their dreams.
    – May precede onset of dementia by several years
  – Severe neuroleptic sensitivity
  – Supportive features include
    • Repeated falls and syncope
    • Transient unexplained loss of conscious
    • Severe autonomic dysfunction e.g. orthostatic hypotension
    • Urinary incontinence
    • Hallucinations in other modalities
    • Systematized delusions
    • Depression

Diagnostic and Statistical Manual of Mental Disorders (DSM-V®) by American Psychiatric Association

Walker et al. Lancet. 2015 October 24; 386(10004): 1683–1697
Frontotemporal Neurocognitive Disorder (Frontotemporal dementia)

- Third most common cause of dementia overall and a common cause of NCD in individuals younger than 65 years.
  - 75% - 80% of cases of frontotemporal NCD occur in individuals younger than 65 years.
  - 40% of individuals with frontotemporal NCD have a family history of early-onset NCD.
  - 10% show an autosomal dominant inheritance pattern.

- Pathology
  - Characterized by atrophy of the frontal and temporal lobes (lobar atrophy).
  - All show abnormal protein inclusions in neurons and glial cells.

- Initial Presentations
  - **Behavioral variant**: characterized by the progressive development of behavioral and personality change.
    - **For diagnosis** patients should show three or more of the following behavioral symptoms:
      - Behavioral disinhibition. Apathy or inertia.
      - Loss of sympathy or empathy.
      - Perseverative, stereotyped or compulsive/ritualistic behavior.
      - Hyperorality and dietary changes.
      - And, prominent decline in social cognition and/or executive abilities.
  - **Language variant**: characterized by a prominent decline in language ability, in the form of speech production, word finding, object naming, grammar, or word comprehension.

- Both presentations have a relative sparing of learning and memory and perceptual-motor function.

Diagnostic and Statistical Manual of Mental Disorders (DSM-V®) by American Psychiatric Association

https://radiopaedia.org/articles/frontotemporal-lobar-degeneration-1
<table>
<thead>
<tr>
<th>Personality changes</th>
<th>Disinhibition</th>
<th>Other features</th>
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<tbody>
<tr>
<td></td>
<td>Socially inappropriate behavior</td>
<td>Loss of sympathy and empathy toward their friends and family</td>
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<td></td>
<td>Approaching strangers without regard to physical and social boundaries</td>
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<td></td>
<td>Impulsive or careless actions</td>
<td>Stereotypic behaviors</td>
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<td></td>
<td>Reckless spending, other bad fiscal decisions</td>
<td>Repetitive movements</td>
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<td></td>
<td>Criminal behaviors</td>
<td>Compulsive ritualistic behaviors</td>
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<td></td>
<td>Theft, urination in public, sexual advances</td>
<td>E.g. Hoarding</td>
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<td>Embarrassing personal remarks</td>
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<tr>
<td>Other features</td>
<td>Hyperorality</td>
<td>Poor insight</td>
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<td>Bing eating, weight gain</td>
<td>Often delays medical consultation</td>
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<td>Increased consumption of sweets or alcohol</td>
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Bang et al Lancet 2015 October 24;386(1004)1672-1682
Summary

- Four main types of major neurocognitive disorders
  - Alzheimer’s disease – Usually presents in elderly with initial complaints of memory loss and problems with executive dysfunction
  - Vascular dementia – heterogeneous presentation; frequently occurs in patients with other types of dementia; important to treat risks factors for stroke in all patients with neurocognitive disorders
  - Lewy body dementias - presents in elderly patients initially with changes in complex attention and executive function rather than learning and memory, includes patients who present initially with Parkinson’s disease.
  - Frontotemporal dementias - frequent cause of major neurocognitive disorder in patients younger than age 65, present either with either behavioral changes or language difficulty, often runs in families

- Key management issues
  - Safety concerns
    - Driving
    - Financial management
      - Scams
      - Financial security
    - Home security
      - Supervision and assisted living
      - Wandering
  - Planning for the future
    - Advanced directives - Health surrogate, Living will, Power of attorney
      - Boca Raton Regional Hospital
      - Patient and guest relations department
      - 561.955.4358 or ext 4358
      - M-F 8:30-5:00
Basic approach to patients with cognitive disorders

• **Diagnosis**
  – Clinical history and examination
    • Time course of the development of the problem is important
    • Helps to determine what the problem is and how quickly you need to work it up
    • May need a family member or friend to help tell you what has been going on
  – Laboratory testing
    • Routine labs, Urinalysis
    • B-12 level, TFTs, HIV, FTA-ABS
  – Imaging
    • At least one structural scan (either CT or MRI) should be done in every patient with cognitive impairment to rule out intracranial causes (e.g., meningioma, subdural haematoma)
  – Neuropsychological testing
    • Pattern of cognitive deficits helps to elucidate etiology
    • Establishes baseline for later comparison
    • Helps to evaluate for “pseudodementia” associated with depression

• **Treatment**
  – FDA approved – Acetylcholinesterase inhibitors, Memantine
  – Manage blood pressure and other risk factors for stroke

• **Management**
  – Safety concerns
    • Driving
    • Financial management
      – Scams
      – Financial security
  – Home security
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Clinical course of Major neurocognitive disorders

• Alzheimer’s disease
  – Mean duration of survival after diagnosis is approximately 10 years
  – Late-stage individuals become mute and bedbound.
  – Death most commonly results from aspiration in those who survive through the full course

• Lewy body dementia
  – Average duration of survival is 5–7 years.

• Frontotemporal dementia
  – Median survival being 6–11 years after symptom onset and 3–4 years after diagnosis.
  – Survival is shorter and decline is faster in frontotemporal NCD than in typical Alzheimer’s disease.
Major or Mild Neurocognitive Disorder Due to Alzheimer’s Disease

- Atypical presentations include language, visual/perceptual-motor, or executive problems before—and more pronounced than—memory deficits.
  - 6–14% of cases
  - Frequently not recognized by primary care physicians
  - Often appear in younger patients
  - Variants
    - progressive impairment in single-word retrieval and in repetition of sentences (logopenic)
    - predominant impairment in the visual identification of objects, symbols, words, or faces or visuospatial dysfunction (posterior variant)
    - progressive apathy or behavioral disinhibition and stereotyped behaviors, or with predominant executive dysfunction at testing (frontal variant of AD)
- In early-onset disease with atypical presentation, diagnostic biomarkers can be used to guide management and decision making