Making the Diagnosis

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Objectives
• Diagnosis: WHAT and WHY
• Dementia evaluation
• Disease diagnostic criteria

What is a Diagnosis?
• Identification of:
  • Clinical syndrome
    • When and where in the nervous system
  • Pathological syndrome
    • What and where in the nervous system

Why Make a Diagnosis?
(since there are no effective treatments for neurodegenerative diseases...)
• Satisfaction of curiosity
• Education
  • Life planning, quality of life of patient and family
  • Health maintenance
• Focuses appropriate therapeutic interventions
• Medical progress
• Research advances

“Gentleman,
This is a Football.”

Vince Lombardi
Dementia - Definition
An acquired deterioration of cognitive abilities that impair the successful performance of activities of daily living.

Mild Cognitive Impairment – MCI Diagnostic Criteria
- modest cognitive decline
- Does not interfere with independence in activities of daily living (ADLs), but more effort, compensation, accommodation needed
- Based upon:
  - Patient, informant, clinician
  - Cognitive screening or Neuropsychological testing

Dementia Diagnostic Criteria
- Significant cognitive decline
- Interference with
  - independence in activities of daily living (ADLs)
  - assistance needed at least with complex instrumental activities of daily living (ADLs)
- Based upon:
  - Patient, informant, clinician
  - Cognitive screening or Neuropsychological testing

Dementia Abilities Affected
Cognitive
- Learning and Memory
  - > 70 yr: 10%
  - > 85 yr: 20 – 40%
- Language
- Complex attention
- Executive
  - Suppression
  - Problem-solving
- Visuospatial – perceptual motor
- Calculation
- NT: acetylcholine, neurotrophins

Neuropsychiatric / Social
- Social cognition
- Depression
- Withdrawal
- Disorientation
- Agitation
- Hallucinations
- Delirium
- Insomnia
- NT: serotonin, norepinephrine, dopamine

Dementia Evaluation
Cognitive Screening Instruments
- Montreal Cognitive Assessment (MoCA)
- SLUMS (Saint Louis University Mental Status Examination)
- Mini Mental Status Evaluation (MMSE; Folstein, Folstein,McHugh)
  - Now under copy write protection
- Frontal Assessment Battery (FAB)

Dementia – Screening Evaluation
Mental Status Exam
- Memory and Learning
- Language
- Visual Perceptual
- Higher Order Parietal Function
- Executive Function
- Social - Behavioral
Dementia – Screening Evaluation

**History**
- Swallowing
- Falls / balance
- Sleep
  - sleep apnea, snoring
  - restless leg disorder
  - daytime sleepiness, naps
- Diurnal variations
- Continence
- Psychiatric – Hallucinations, delusions
- Cognitive Reserve
  - educational level, learning disability
  - social circumstances, financial resources
  - pre-morbid personality
  - vocational history
- Family history - genetic factors

**Basic Activities of Daily Living**
- Bathing
- Personal hygiene / grooming
- Dressing
- Handling clothes
- Toileting
- Continence
- Functional mobility – transferring
- Feeding

**Instrumental Activities of Daily Living**
- Telephone – communication
- Use of technology (i.e. remote controls, etc)
- Shopping
- Food preparation
- Housekeeping
- Laundry
- Transportation
- Medications
- Finances

**Clinical Dementia Rating Scale - CDR**

- **Domains:**
  - memory (primary domain)
  - orientation
  - judgment + problem solving
  - community affairs
  - home + hobbies
  - personal care
- **Rating:** For each of 6 categories
  - 0: normal
  - 0.5: MCI (minimal interference with function / activities)
  - 1: mild dementia (need for some assistance with I-ADL’s)
  - 2: moderate dementia (needs assistance with most I-ADL’s and some B-ADL’s)
  - 3: severe dementia (continuous supervision; major care needs)
- **Scoring:**
  - CDR Overall: 0 – 3 (algorithm; CDR = memory unless…)
  - Sum of boxes (CDR-SB): 0 – 18

“In a tertiary memory disorder clinical practice setting, there is much greater diagnostic yield from obtaining a detailed and comprehensive history than from ordering a battery of esoteric tests.”

Daniel Kaufer
Memory and Learning

- Forgetfulness for conversations, shopping items, paying bills
- Word List:
  - Number of trials to learn
  - Free recall
  - Cued recall
  - Recognition
- Sentence / paragraph memory
- Visual memory: geometric designs
- Intentional memory versus incidental memory (orientation)
- Habit learning (hand posture sequences)
- Semantic memory (infrequent object recognition)
- Working memory (Digits in reverse order)
- Auditory verbal short term memory (Repetition of words, digits, sentences)

Language

- Rate of production
- Single word level processing
  - Word finding pauses
  - Word/name finding
  - Lexical substitutions
  - Speech sound errors
  - Fluency
  - Confrontation naming
- Multi sensory cues are necessary to distinguish visual agnosia from semantic memory impairment

Language

Comprehension – Single Word Processing

- Lexical comprehension
  - define the word
  - multiple choice meaning
  - Specific attributes of semantic representation
    - Does a camel live in the ocean?
    - Is asparagus red?
    - Are two words of the same category?
    - fruit, clothing, furniture

Language

Sentence Level Processing

- Repetition
  - Monosyllabic word
  - Multisyllabic words
  - Multisyllabic phrase
  - Sentences of increasing length
- Fluency, effort, rate, prosody
- Apraxia of speech: motor speech apparatus
  - irregular timing
  - Speech sound errors
  - Dysarthria due to muscle weakness

Language

Comprehension – Sentence Level Processing

- Complex sentences
  - Point to objects in order other than the verbal sequence
    - Is it the boy that the girl chased? Who did the chasing?
- Reading
  - Letter sound correspondence rules
  - Pseudo words - "TIG"
- Sight vocabulary - orthographically irregular
  - Dough     Choir
  - Pint
- Follow written command ("close your eyes")
- Writing to dictation
  - Regular and irregular words
- Apractic agraphia: difficulty with automatic mechanical formation of letters

Visual Perceptual

- Location of objects in space: reach for an object
- Copying a geometric figure
  - Accuracy
  - Organizational approach
- Spatial neglect
- Orientation of lines, whether parallel
- Part–whole discrimination: Simultagnosia
- Neural figure: big letter made up of smaller different letters
- Facial recognition
  - Features of the examiner’s face
  - Famous faces
- Color processing
  - Name color
  - Match colors
Higher Order Parietal Function

- Calculations
  - Which number is larger
  - Day to day to calculations such as making change
- Cortical sensation
  - Gaphhesthesia
  - Double simultaneous stimulation
  - Stereognosis: recognizing unseen object in hand
  - Line drawing on arms/legs
- Left/right discrimination
  - Patient's body parts
  - Examiner's body parts
- Somatosensory map (limb positions)
- Intracranial pressure
- Kinetesthesia: difficulty in demonstrating learned gestures
- Tactile feedback using implements; Pariesthesia
- Oral - Buccal: blow-out a match
- Pantomime: distinguishes true apraxia from disorder of verbal comprehension

Executive Functioning

- Category naming fluency
  - Letters: harder (12 +/- 2)
  - Semantic category: easier (18 +/- 6)
- Perseveration, difficulty shifting sets
- Design fluency: unique designs with 9 dot array
- Alternating patterns
- Alternating number and letters (Trails B)
- Inhibitory control
- Stroop test (say color of a color word rather than read the word)
- Working memory: ability to hold and manipulate data
  - List Numbers in reverse order
  - Reordering sequence of numbers
- Visual working memory: reorder sequence of geometric figures

Social Functioning - Behavior

- Survey Instruments:
  - Neuropsychiatric inventory
  - Frontal behavioral inventory
- Observation:
  - Behavioral disinhibition
  - Insight
  - Self-monitoring
  - Repetitive motor activity
  - Poor social discourse
  - Depression
  - Anxiety
  - Apathy/initiation
  - Hallucinations
  - Delusions

Neurocognitive Disorders

- Alzheimer's disease
- Lewy Body disease
- Vascular cognitive impairment
- Frontotemporal lobar degeneration
- Traumatic brain injury
- Chronic traumatic encephalopathy
- Parkinson's disease
- Huntington's disease
- Cortical/basal degeneration
- Progressive supranuclear palsy
- Depression
- HIV infection
- Prion disease
- Another medical condition
- Multiple etiologies

Dementia Classification by principle anatomic localization

Cortical

- Alzheimer's
- FTD-behavioral variant
- FTD – Primary progressive aphasia – nonfluent (PNFA or agrammatic – NF-AG)
- FTD – PPA – semantic type (semantic dementia)

The Clinical – Pathological Principle

The clinical presentation

is consistent with

the gross anatomical localization,

not

the microscopic pathology
Dementia Classification by principle anatomic localization

Subcortical
• Huntington’s disease
• Parkinson’s disease
• Progressive supranuclear palsy
• Wilson’s disease (hepato-lenticular degeneration)
• Depression

White Matter Dementias
• Subcortical arteriosclerotic encephalopathy (Binswanger’s)
• Metachromatic leukodystrophy
• Traumatic brain injury
• Normal pressure hydrocephalus
• Systemic lupus erythematosus
• Gliona
• HIV
• Cobalamin (B12)

Frontotemporal Dementias
• Frontal: behavioral variant (“FTD”)
• Primary progressive aphasia
  • Semantic type (semantic dementia)
  • Nonfluent / agrammatic type
• Corticobasalar degeneration (CBD)
• Progressive supranuclear palsy (PSP)
• ALS - FTD

Behavioral Variant FTD (bvFTD)
• Character change and disordered social conduct
• Insidious onset and gradual progression
• Early emotional blunting and loss of insight
• Perception, spatial skills, praxis and memory are relatively spared

bvFTD
• Personality, behavioral control, comportment
• Hyperoral, hypersexual, eating (Kluver Bucy)
• Social awareness, socially inappropriate, disinhibition
• Excessively ebullient
• Inappropriately aggressive, lack of empathy (impaired theory of mind)
• Grossly impaired judgment
• Early diagnosis errors: mania, psychosis

bvFTD
• Earlier onset cp. AD
• Right frontal involvement
• May progress to:
  • CBD
  • PSP
• May be associated with motor neuron disease (C9orf72 mutation; ubiquitin)
International Consensus Research Criteria for bvFTD (Rascovsky, et al. 2011)

- Neurodegenerative Disease
- Progressive deterioration of behavior and / or cognition
- Possible bvFTD
- Behavioral disinhibition
- Apathy or inertia
- Loss of sympathy or empathy
- Perseverative, stereotyped, or compulsive / ritualistic behavior
- Hyperorality and dietary changes
- Neuropsychological profile: executive / generation deficits with relative sparing of memory and visuospatial functions

Probable bvFTD
- Significant functional decline by CDR or ADL scale
- MRI: frontal – anterior temporal atrophy
- Hypometabolism in frontal – anterior temporal by SPECT or PET

Definite bvFTD
- Brain biopsy or autopsy c/w bvFTD or known pathogenic mutation
- Exclusions
  - Other explanatory medical or psychiatric conditions
  - Alternative explanatory biomarkers (AD or others)

Semantic type
Primary Progressive Aphasia (svPPA)

- Preserved:
  - Autobiographical memory
  - Ability to read aloud
  - Ability to write to dictation orthographically regular words
  - Perceptual matching and drawing reproduction

- Progresses to multi-modality agnosia (faces, emotions of others, words, objects)
- Behavioral changes, but not executive

International Consensus Research Criteria for Semantic Variant Primary Progressive Aphasia - svPAA (Gorno-Tempini et al. 2011)

- Primary progressive aphasia: difficulty with language
  - Language deficits cause impaired ADLs
- Clinical diagnosis of svPAA
  - Core Features
    - Impaired confrontation naming
    - Impaired single word comprehension
    - Impaired object knowledge, particularly of low frequency or low familiarity items
    - Surface dyslexia or dysgraphia
    - Spared repetition
    - Spared speech production (grammatic and motor speech)
- Predominant anterior temporal in svPPA with definite pathology
  - Brain biopsy or autopsy or svPAA or known pathogenic mutation

Nonfluent / agrammatic type Primary Progressive Aphasia (nfvPPA)

- Progressive disorder of language
  - Nonfluent spontaneous speech with at least one of: agrammatism, phonetic paraphasias, anomia
- Insidious onset and gradual progression
- Other aspects of cognition relatively well preserved

Semantic type
Primary Progressive Aphasia (svPPA)

- Onset: 50’s, 60’s
- Insidious onset and gradual progression
- May not be demented early on
- % frequency behavioral variant
- Left (frontal), anterior temporal, more posterior than nonfluent type, may be bilateral
- Usually non-tau (TDP-43)
International Consensus Research Criteria for Nonfluent / Agrammatic Variant Primary Progressive Aphasia - nfvPAA
(Gorno-Tempini et al. 2011)

- Primary progressive aphasia: difficulty with language
  - Language deficits cause impaired ANS
  - Clinical diagnosis of nfvPAA
    - Agrammatism in language production
    - Effortful, halting speech with inconsistent speech sound errors and distortions (speech apraxia)
    - Agrammatism of syntactically complex sentences
    - Impaired single word comprehension
    - Impaired object knowledge
  - Imaging supported nfvPAA: Predominant left frontal, inferior frontal gyrus, anterior insula
  - nfvPAA with definite pathology: Brain biopsy or autopsy histopathology of specific neurodegenerative pathology (FTLD-tau, FTLD-TDP, AD, other) or known pathogenic mutation

Corticobasal Degeneration (CBD)

- Progressive asymmetrical extrapyramidal rigidity with corticospinal signs
  - +/- mild postural action tremor
  - Unresponisve to L-dopa
  - % with rigidity: 1/5 with tremor (Wenning)
  - Develop akinetic – rigid syndrome, gait, dysarthria
  - Cannot direct voluntary actions
  - Alien hand, cataleptic postures

Corticobasal Degeneration (CBD) Diagnostic Criteria
(Boeve et al. 2003)

- Core features
  - Insidious onset; progressive course
  - No identifiable cause (e.g. tumor, infarct)
  - Cortical dysfunction with at least one of:
    - Focal or asymmetrical ideomotor apraxia
    - Alien limb phenomenon
    - Cortical sensory loss
    - Visual or sensory hemineglect
    - Constructional apraxia
    - Focal or asymmetric myoclonus
    - Apraxia of speech / nonfluent aphasia
  - Extrapyramidal dysfunction with at least one:
    - Focal or asymmetrical appendicular rigidity, without L-dopa response
    - Focal or asymmetrical appendicular dystonia

Corticobasal Degeneration (CBD)

- Supportive investigations
  - Variable degrees of focal or lateralized cognitive dysfunction, with relative preservation of learning and memory on neuropsychological testing
  - Focal or asymmetric atrophy on CT or MRI, typically maximal in parietofrontal cortex
  - Focal or asymmetric hypoperfusion on SPECT or PET, typically maximal in parietofrontal cortex, basal ganglia and / or thalamus

Progressive Supranuclear Palsy
(Richardson, Steele, Olszewski, 1963)

- Supranuclear vertical gaze paresis
- Symmetric rigidity
- Late apathetic, executive dementia, slowness in thinking
- Emotional: irritable, euphoric
- May begin as non-fluent aphasia
- Onset: 50 – 60 years (45-75)
Progressive Supranuclear Palsy (PSP)

Suspection:
- Falls with preserved consciousness
- Ocular palsies
- Extrapyramidal symptoms
  - Neck dystonia
  - Pseudobulbar palsy

Progressive Supranuclear Palsy (PSP)

Oculomotor
- Voluntary eye movements:
  - Vertical: down (more often) or upward
  - All directions involved later
- Initial hypometric pursuit saccades to OKN, especially downward; later, refixation saccades involved as well
- Preserved eye movements with visual fixation and head movements ("supranuclear"; not paralytic)

Progressive Supranuclear Palsy (PSP)

Axial Dystonia
- Gradual stiffening and extension of neck
- +/- hand / foot dystonic postures, stiff limbs
- +/- Babinski responses
- Facial features
  - "worried" expression / furrowed brow: tonic contraction of procerus
  - "perpetual surprise": retracted upper lids
  - Mouth open (pseudobulbar palsy)
  - Unmoving, forward looking eyes

Progressive Supranuclear Palsy (PSP)

Diagnostic Criteria
(Litvan et al. 1996)

Inclusion criteria:
- Gradually progressive
- Onset at age 40 or later
- Possible: Either vertical (upward or downward gaze) supranuclear palsy OR Both slowing of vertical saccades and prominent postural instability with falls in the first year of disease onset
- Probable: Vertical (upward or downward gaze) supranuclear palsy and prominent postural instability with falls in the first year of disease onset
- Definite: possible or probable criteria plus histopathological evidence of PSP

Supportive criteria:
- Symmetric akinesia or rigidity, more proximal than distal
- Abnormal neck posture; retrocollis
- Poor response to L-dopa
- Early dysphagia and dysarthria
- Early onset of cognitive impairment (> 2: apathy, abstract thought, verbal fluency, utilization / imitation behavior, frontal release signs)

Exclusion criteria:
- Recent encephalitis
- Alien limb syndrome
- Cortical sensory deficits
- Focal frontal or temporoparietal atrophy
- Hallucinations or delusions without dopaminergic therapy
- AD cortical dementia
- Prominent cerebellar symptoms
- Prominent autonomic symptoms
- Severe, asymmetric Parkinsonian signs
- Relevant structural abnormality
- Whipple's disease

Progressive Supranuclear Palsy (PSP)

Diagnostic Criteria
(Litvan et al. 1996)
ALS - FTD

- **ALS:**
  - Upper motor neurons (progressive lateral sclerosis):
    - Slow, strangled speech
    - Appendicular spasticity
    - Hyperactive gag and jaw jerks
    - Brisk DTR’s, Hoffman, Babinski
  - Lower motor neurons (motor neuron disease):
    - Weak, dysarthric voice
    - Diminished gag
    - Atrophy: face, tongue, arm, leg
    - Fasciculations
    - Weakness
    - Hyporeflexia

- **bvFTD** is most common FTD association
  - May be more subtle
  - Prominent anxiety and weight loss
  - Shortened life span
  - Strongly familial (most often C9ORF72 gene)

Outline of Clinical Evaluation:

- History
  - Onset with first symptoms: abrupt, subacute, insidious
  - Course: static, progressive, fluctuating, improving
- Mental status examination
- Physical and neurological examination
- Select laboratory studies
- Select imaging studies
- Response to treatment (eventually)