What Is It?

- Dementia (from Latin)
  - de- "apart, away"
  - mens (genitive mentis) "mind"

Source: Dr. Wikipedia

First Assessment Considerations

- Delirium vs dementia vs pseudodementia
- Delirium signals medical emergency
  - Acute confusional state with transient cognitive impairment
  - Develops over short period of time
  - Caused by direct physiologic consequence of a GMC
  - Can be reversible if patient does not die
  - Don’t assume staff is aware of this
Delirium

- Main defect = **variable attention**
  - Easily distractible, less aware of surroundings
  - Trouble with commands, concentrations
- **Fluctuating** cognitive abilities
- Disturbed sleep-wake cycle
- ↓ LOC/ arousal
- Disorientation, hallucinations
- Rapid changes in mood (+/-), self-awareness, global cognitive impairment
- ↑ or ↓ psychomotor activity

Delirium Differential

- Often don't know history
- Unclear etiology
- Dementia not only in context of delirium
- 50% may die with delirium (5-30% mortality)
- 25% with continued cognitive impairments

Contexts for Delirium

- Surgery:
  - 10-15% general; 30% open heart surgery; 50% hip fractures
- Elderly:
  - 10-38% at hospital admission; higher in nursing homes
  - up to 80% hospitalized for acute physical illness
- Primary intracranial pathology
- Systemic disease secondarily affecting the brain
- Exogenous toxic agents (antihypertensives, antiarrhythmics, benzos, NSAIDs, anti-Parkinsonian meds).
- Withdrawal from substances of abuse (ETOH, sedative/hypnotics)

Easy way to remember causes of delirium?

- **I** Infection
- **W** Withdrawal
- **A** Acute metabolic
- **T** Trauma
- **C** CNS pathology
- **H** Hypoxia
- **D** Deficiencies
- **E** Endocrine
- **A** Acute vascular/MI
- **T** Toxins-drugs
- **H** Heavy metals
Easy way to remember differential diagnoses/ possible delirium?

V—Vascular: cerebral arteriosclerosis, thrombi, emboli, and hemorrhages (MIXED Dementia?).
I—Inflammatory: neurosyphilis, chronic encephalitis (inclusion body encephalitis, and Jacob–Creutzfeldt disease), and cerebral abscess.
N—Neoplasms: primary and metastatic neoplasms of the brain and meninges.
D—Degenerative and deficiency diseases suggest senile and presenile dementia, Pick disease, Wernicke encephalopathy, and pellagra. Pernicious anemia may be associated with dementia.
I—Intoxication: alcoholism, bromism, lead poisoning, and a host of other toxic or drug-induced encephalopathies. Idiopathic and suggest normal-pressure hydrocephalus.
C—Congenital disorders include the encephalopathies, Tay–Sachs disease, cerebral palsy, Down syndrome, Wilson disease, and Huntington chorea. Congenital hydrocephalus and many other causes must be considered. Porphyria is often forgotten in the differential.
A—Autoimmune disease suggests lupus erythematosus and multiple sclerosis, although severe dementia is uncommon in the latter.
T—Trauma: should prompt the recall of concussion and epidural, subdural, and intracerebral hematomas. Heat stroke may cause temporary memory loss. The dissociative reaction of psychoneurosis may be precipitated by trauma.
E—Endocrine disorders with memory loss are myxedema, insulinoma with chronic hypoglycemia, and hypoparathyroidism. If a pituitary invades the hypothalamus there may be memory loss. Addison disease.

Pseudodementia vs dementia

- **Pseudodementia:** cognitive deficits secondary to depression
  - Can mimic dementia (memory, onset) but treatable
  - Profile includes apathy, psychomotor slowing, learning/memory deficits, attention
  - During assessment, can have improved performance if engaged.
    - Trails B vs. A
    - Digits Backward vs. Forward

Dementia: diagnosis by exclusion and symptom clusters

- Memory impairment PLUS
  - Aphasia, apraxia, agnosia, exec functioning (at least 1)
- MUST cause impaired social/occupational activities ***
  - Interview with patient/partner
- MUST represent decline from previous levels
- NOT due to delirium or other medical condition

DSM V: Major NCD

- Evidence of significant cognitive decline from a previous level of performance in one or more cognitive domains (complex attention, executive function, learning and memory, language, perceptual-motor, or social cognition) based on:
  - Concern of the individual, a knowledgeable informant, or the clinician that there has been a significant decline in cognitive function; and
  - A substantial impairment in cognitive performance, preferably documented by standardized neuropsychological testing or, in its absence, another quantified clinical assessment.
- The cognitive deficits interfere with independence in everyday activities (i.e., at a minimum, requiring assistance with complex instrumental activities of daily living such as paying bills or managing medications).
- Not due to delirium or other mental disorder.
DSM V: Minor NCD

- Evidence of modest cognitive decline from a previous level of performance in one or more cognitive domains (complex attention, executive function, learning and memory, language, perceptual-motor, or social cognition) based on:
  - Concern of the individual, a knowledgeable informant, or the clinician that there has been a modest decline in cognitive function; and
  - A modest impairment in cognitive performance, preferably documented by standaredized neuropsychological testing or, in its absence, another quantified clinical assessment.
- The cognitive deficits **DO NOT** interfere with capacity for independence in everyday activities (i.e., complex instrumental activities of daily living such as paying bills or managing medications are preserved, but greater effort, compensatory strategies, or accommodation may be required).
- Not due to delirium or other mental disorder.

DSM-V Specifiers

- Specify whether due to:
  - Alzheimer’s disease
  - Frontotemporal lobar degeneration
  - Lewy body disease
  - Vascular disease
  - Traumatic brain injury
  - Substance/medication use
  - HIV infection
  - Prion disease
  - Parkinson’s disease
  - Huntington’s disease
  - Another medical condition
  - Multiple etiologies
  - Unspecified

- Specify whether with or w/out behavioral disturbance

- Specify whether mild, moderate, or severe (for major NCD only)

DSM V: Major NCD

- **Probable** Alzheimer’s disease is diagnosed if either of the following is present; otherwise, **possible** Alzheimer’s disease should be diagnosed.
  - Evidence of a causative Alzheimer’s disease genetic mutation from family history or genetic testing.
  - All three of the following are present:
    1. Clear evidence of decline in memory and learning and at least one other cognitive domain (based on detailed history or serial neuropsychological testing).
    2. Steadily progressive, gradual decline in cognition, without extended plateaus.
    3. No evidence of mixed etiology (i.e., absence of other neurodegenerative or cerebrovascular disease, or another neurological, mental, or systemic disease or condition likely contributing to cognitive decline).

DSM V: Minor NCD

- **Probable** Alzheimer’s disease is diagnosed if there is evidence of a causative Alzheimer’s disease genetic mutation from either genetic testing or family history.

- **Possible** Alzheimer’s disease is diagnosed if there is no evidence of a causative Alzheimer’s disease genetic mutation from either genetic testing or family history, and all three of the following are present:
  2. Steadily progressive, gradual decline in cognition, without extended plateaus.
  3. No evidence of mixed etiology (i.e., absence of other neurodegenerative or cerebrovascular disease, or another neurological or systemic disease or condition likely contributing to cognitive decline).
### Onset & Prevalence
- Generally late life
- Depends on etiology
- Can occur in children – uncommon
- Rates of dementia:
  - 5-10% over age 65
  - 25-45% over age 85
- 10-15% mildly impaired

### Causes
- Alzheimer’s disease
- Lewy-Body disease
- Normal Pressure Hydrocephalus
- Alcohol
- Frontotemporal
- Multiple Sclerosis
- HIV/AIDS

### More Causes
- Vitamin Def. (B12, B3)
- CVA
- TBI
- Parkinson’s
- Huntington’s
- Epilepsy
- Endocrine Dysfunction

### Yet More Causes
- Anoxia/Hypoxia
- Poisoning
- Med Reactions
- Infection - meningitis, encephalitis, syphilis
- Substance Abuse
- Wilson’s Disease
- Nutritional Defic.
Cortical vs. Subcortical

- Cortical Prototype
  - AD
- Subcortical Prototype
  - HD, PD
  - ? MS, HIV, HCV

Cognitive Factors

- “Memory”
  - Immediate vs. Delayed
  - Retrieval vs. Recognition
  - Retention/Rapid Forgetting
- Attention
- Fluency

Subcortical Profile

- Memory:
  - Impaired retrieval
  - Relatively better recognition
- Impaired Attention
- Slowed processing
- Semantic better than letter fluency

Cortical Profile

- Memory:
  - Impaired retrieval
  - Impaired recognition
- Relatively good attention
- Letter better than category fluency
- Poor naming, visuospatial abilities
Tests

- Recall vs. Recognition - CVLT
- Word Retrieval/ Naming - BNT
- Fluency - Letter and Category
- Digit Span

Progressive?

- Is it required?
- Onset
  - Sudden vs. Insidious
- Course
  - Gradual vs. Step-wise

Reversibility

- Around 10%?
- NPH, Shunt, Metabolic
- Dehydration
- UTI

Interview Questions

- Orientation
  - x3, x4
- Initiative
- Family History
- Repeats self, ask same questions repeats self, asks same questions, repeats self
- Talks about same thing over and over again
Interview – ADL’s and IADL’s

• Basic Activities of Daily Living (ADL’s)
  – Bathing, grooming, dressing, personal hygiene, toileting
• Instrumental Activities of Daily Living (ADL’s)
  – Driving – getting lost, directions, accidents, tickets
  – Cooking – forgetting to turn off stove, trouble with recipes
  – Finances – forgetting bills, balancing checkbook
  – Housekeeping
  – Shopping
  – Reading, Writing, Rithmetic

Dangers

• Falls
• Safety Awareness – Attention
  – Leaving stove on
• Driving

Diagnosis

• Neurologic Exam
• Neuroimaging
• Labs (infection, metabolic, etc.)
• Collateral Information
• Neuropsych profile

Normal Aging

• Forgetfulness/ retrieval (good with cues)
• Slowed processing
• Naming
Premorbid

- Demographic Predictors
  - Parents
  - Occupation
  - Siblings
  - SES

Premorbid Measures

- TOPF
- Barona
- OPIE
- ANART
- WTAR
- WRAT Reading
- PIAT

NP Profile

- Depends on etiology

Alzheimer’s Disease

- Most common
- Base rate: 55 – 75% (mixed dementia possible)
- A syndrome, diagnosed by exclusion
- Definitive DX only with neuropath
- 3-5 years post DX: institutional care
- Death occurs 8-12 years post DX
- (excluding Down’s, genetic dominant forms)
AD Risk factors

- Age
- Family History O.R. 3.5
- Genetic predisposition (ApoE 4)
- Brain injury/illness OR 1.3-2.5
- Education/Occupation
- Late onset depression
- MCI (10 – 40% convert over 4 yrs)
- Maternal age > 40 OR 1.7

Functioning

- Remarkably preserved social skills
- “Empty” or repetitive speech/behavior
- Carphologia, motor restlessness
- Depression, apathy
- Family reports of changes in habits
- Paranoia, delusions
- Environmental triggers of “sudden” onset

Behavioral Changes

- Disinhibition
- Aggression, hitting
- Bowel & Bladder
  - Elderly caring for elderly
- Taking clothes off
- Agitation

Psychiatric

- Psychosis
- Depression
- Anxiety
- Paranoia
- Caregiving
- Predictors to SNF:
  - Sleep
  - Aggressiveness
**Intervention**

- Family Interventions
- Home Health Assistance
- Day Care Program
- Physical Exercise
- Cognitive Stimulation?
- Pharmacotherapy

**Neurotransmitters**

- Acetylcholine
  - Nucleus Basalis of Meynert
  - Frontal Lobes

**Pharmacotherapy**

- Acetylcholinesterase Inhibitors
  - Tacrine (cognex)
  - Donepezil (Aricept)
  - Galantamine (Reminyl)
  - Rivastigmine (Excelon)

- N-methyl-D-Asparate (NMDA Blocker)
  - Memantine (Namenda) - mod to severe

- Generally for mild to moderate stage
- Benefits cognition, behavior, ADL, global cognition
- Anti-oxidants

**Apolipoprotein E4**

- Involved in cholesterol transport
- Weak genetic link for late onset AD
- Allele combinations from E 2,3,4
- E4 confers elevated risk
- E4/4 highest, O.R. 13.3 (E3/4 OR 4.2)
- E4 Prevalence in population varies
Pathology

- Plaques
- Tangles

Plaques

- Abnormal cluster of protein fragments
- Protein recently discovered in the brain could play a key role in regulating the creation of amyloid beta, the major component of plaques implicated in the development of Alzheimer’s disease
- Plaques – deposits of the protein beta-amyloid that accumulate in the spaces between nerve cells
- In spaces between nerve cells
- Beta-amyloid is chemically “sticky” and gradually builds up into plaques.

Tangles

- Tangles – deposits of the protein tau that accumulate inside of nerve cells
- Inside nerve cells
- Twisted strands of another protein

Progression
Core Clinical Criteria for Dementia

- Cognitive or behavioral impairment in at least 2 domains
- Functional impairment in daily activities
- Represents a decline from previous functioning
- Not due to delirium or other major psychiatric disorder

Probable AD Dementia

- Meets clinical criteria for dementia
- Insidious onset
- Clear progression over time
- Cognitive deficits
  - Amnestic presentation
  - Non-amnestic (language, visuospatial, executive) presentation
- No cerebrovascular disease, stroke, or evidence of other etiologies (DLB, FTD, etc.)
Possible AD

- Atypical course
- Insufficient historical information
- Etiologically mixed presentation

Pathophysiological/Biomarker Evidence

- AD is first and foremost a clinical diagnosis
  - Biomarkers can be used only to support the diagnosis
    - Positive
    - Clearly negative
    - Indeterminate

Neuroimaging & Biomarkers

- MRI: volume loss w/ predilection for hippocampi
- PET: hypometabolism in AD and preclinical phase in temporal, frontal regions
- fMRI: increased level of blood oxygenation (compensatory hypothesis) in preclinical, early AD
- Amyloid PET: amyloid deposition
- CSF proteins: elevated tau and/or beta-amyloid
**NINCDS**

- **Definite Alzheimer’s disease**: The patient meets the criteria for probable Alzheimer’s disease and has histopathologic evidence of AD via autopsy or biopsy.

- **Probable Alzheimer’s disease**: Dementia has been established by clinical and neuropsychological examination. Cognitive impairments also have to be progressive and be present in two or more areas of cognition. The onset of the deficits has been between the ages of 40 and 90 years and finally there must be an absence of other diseases capable of producing a dementia syndrome.

- **Possible Alzheimer’s disease**: There is a dementia syndrome with an atypical onset, presentation or progression; and without a known etiology; but no co-morbid diseases capable of producing dementia are believed to be in the origin of it.

- **Unlikely Alzheimer’s disease**: The patient presents a dementia syndrome with a sudden onset, focal neurologic signs, or seizures or gait disturbance early in the course of the illness.

**Variants?**

- Asymmetric
- Posterior Variant (pAD)
- Behavioral Variant? (bAD)
- Dysexecutive Variant? (deAD)

**Special**

- Down Syndrome – 100% have AD pathology
AD Continuum

The continuum of Alzheimer’s disease

Mild Cognitive Impairment (MCI)

- Prevalence: 14-18% over age 70 (increasing with age)
- Prognosis:
  - Epidemiological Studies: 6-10% progress to AD
  - Memory Disorder Clinics: 10-15% progress to AD

MCI Subtypes

COGNITIVE COMPLAINT:
Not normal for age, not demented, cognitive decline, essentially normal functional activities

MCI

Amnestic MCI

- Single Domain (Associated with AD, vascular dementia, and depression)
- Multiple Domain (Associated with frontotemporal dementia)

Non-Amnestic MCI

- Single Domain
- Multiple Domain (Associated with dementia with Lewy bodies and vascular dementia)

New Recommendations: MCI

The diagnosis of mild cognitive impairment due to Alzheimer’s disease: Recommendations from the National Institute on Aging and Alzheimer’s Association workgroup

Marilyn S. Albert, Steven T. DeKosky, Dennis Dickson, Bruno Dubois, Howard H. Feldman, Nick C. Fox, Anthony Gunning, David M. Holzman, William J. Jagust, Ronald C. Petersen, Peter J. S. Snyder, Maria C. Carrillo, Bill Thies, Creighton H. Phelps
## MCI Evaluation

Table 1: Summary of clinical and cognitive evaluation for MCI due to AD

<table>
<thead>
<tr>
<th>Establish clinical and cognitive criteria</th>
<th>Establish illness criteria reflected by patient or informant or clinician (i.e., historical or observed evidence of decline over time)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Objective evidence of impairment in one or more cognitive domains, typically including memory, (i.e., FRAAT or baseline testing to establish level of cognitive function in multiple domains)</td>
<td>Preservation of independence in functional abilities</td>
</tr>
<tr>
<td>Not demented</td>
<td>Examine ability of MCI consistent with AD pathophysiological process</td>
</tr>
<tr>
<td>Rule out vascular, traumatic, medical causes of cognitive decline, where possible</td>
<td>Provide evidence of longitudinal decline in cognition, when feasible</td>
</tr>
</tbody>
</table>

Abbreviations: AD, Alzheimer’s disease; MCI, mild cognitive impairment.

## Biomarkers

Table 2: Biomarkers used in evaluation for AD

<table>
<thead>
<tr>
<th>Biomarkers of AD degeneration</th>
<th>CSF: Ab, t-tau, p-tau</th>
<th>PET: amyloid imaging</th>
<th>MRI: hippocampus volume, regional neuronal density, atrophy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rate of decline</td>
<td>FDG-PET imaging</td>
<td>SPECT perfusion imaging</td>
<td>Losses in ventricular volume, cortical and subcortical gray matter, white matter, regional changes in glucose metabolism, voxel-based and multivariate analysis</td>
</tr>
</tbody>
</table>

Table 3: MCI criteria incorporating biomarkers

<table>
<thead>
<tr>
<th>Diagnostic criteria</th>
<th>Biomarker probability of AD</th>
<th>Aβ (PET or CSF)</th>
<th>Neuronal injury (mTFC, s-FDG, s-AIR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MCI over clinical criteria</td>
<td>Uninformative</td>
<td>Uninformative</td>
<td>Uninformative</td>
</tr>
<tr>
<td>NCI due to AD — mild likelihood</td>
<td>Intermediate</td>
<td>Intermediate</td>
<td>Intermediate</td>
</tr>
<tr>
<td>NCI due to AD — high likelihood</td>
<td>Highest</td>
<td>Highest</td>
<td>Highest</td>
</tr>
<tr>
<td>NCI — unlikely due to AD</td>
<td>Lowest</td>
<td>Lowest</td>
<td>Lowest</td>
</tr>
</tbody>
</table>

Abbreviations: AD, Alzheimer’s disease; Aβ, amyloid beta peptide; PET, positron emission tomography; CSF, cerebrospinal fluid; FDG, fluorodeoxyglucose; s-AIR, structural magnetic resonance imaging.

## MCI with Biomarkers

Table 4: Preclinical AD

**Alzheimer’s & Dementia**

Toward defining the preclinical stages of Alzheimer’s disease: Recommendations from the National Institute on Aging and the Alzheimer’s Association workgroup

Reisa A. Spelbring, Paul H. Assen, Laurel A. Bender, David A. Bennett, Suzeanna Craft, Anne M. Fagan, Takeshi Hatanaka, Clifford R. Jack, Jeffery Kaye, Thomas J. Montine, Denise J. Park, Eric M. Reiman, Christopher C. Rowe, Eric Sieminski, Yuxiong Stern, Kristine Yaffe, Maria C. Carrillo, Bill Thies, Marcelle Morrison-Bogda, Molly V. Wagster, Creighton H. Phelps.
Conversion from MCI to AD

- Predictors of Conversion Biomarkers
  - Genetic factors: APOE4 mutation
  - Structural changes
    - Atrophy: medial temporal lobes, hippocampi, paralimbic, and temporoparietal cortex
    - Enlarged ventricles
  - Biochemical changes
    - Elevation in total tau and amyloid β-protein-42 in CSF
  - Behavioral Markers
    - Clinical status
    - Neuropsychological fx. (verbal memory recall & executive fx.)
Diagnostic decision-making

- Normal?
  - Yes
  - No → Functional Impairment?
    - Yes → Dementia
    - No → MCI

Vascular Dementia
- 10% of all dementia cases (#2 or #3)
- Sudden-onset: following stroke
- Stepwise progression: multi-Infarct
  - Multiple vascular events (maybe subclinical)
- Gradual: small vessel disease?
- Binswanger’s Disease
  - Subcortical leukencephalopathy

Lewy Body Dementia
- Second/third most prevalent dementia
- Can co-occur with AD
  - Includes pathology similar to AD (plaques, tangles)
  - Also includes presence of lewy bodies in subcortical regions and diffuse cortical regions
- Earlier onset (50-85)
- Deficits similar to AD except increased:
  - visual hallucinations
  - fluctuation of attention
  - visuomotor defects
  - visuospatial & executive functions
### LBD

- **Hallmark features:**
  - Visual Hallucinations
  - Fluctuating Course
  - REM sleep disturbance
  - PD-like motor symptoms (Parkinsonism)
    - Tremor
    - Rigidity
    - Cog-wheeling
    - Lewy Bodies – found in cortex rather than Basal Ganglia

### Normal Pressure Hydrocephalus

- **Urinary Incontinence**
  - (Wet)
- **Gait Instability**
  - (Wobbly)/ magnetic
- **Confusion/Cognition**
  - (Wacky)
  - Apathy, forgetfulness, inertia,
  - Inattention, slowed processing

### More NPH

- Memory: discrepancy between (often severely) impaired recall and intact or much less impaired recognition.
- Dementia is thought to result from traction on frontal and limbic fibers that also run in the periventricular region
- Treatment: surgical ventriculoperitoneal (VP) shunt to drain excess CSF into the lining of the abdomen (where the CSF will eventually be absorbed)

### Frontotemporal Dementia

- Described in 1890s by Pick and Serieux
- Onset – Late 50s, earlier than AD
- Genetic/Family Component
- ~10% of all dementia cases
- 20-50% of cases < age 65
- Only known risk factor is genetics
  - 20-40% have known family history of FTD
Differences Between FTD and AD

- **Age at diagnosis**
  - FTD in 50’s & 60’s (only 10% age 70+)
  - AD prevalence increases with age
- **Memory Loss**
  - More prominent in early stages of AD
  - More prominent in later stages of FTD
- **Behavior Changes**
  - Often the 1st sign in FTD; occur later in AD
- **Problems w/ spatial orientation more common in AD**
- **Speech**
  - Word-finding problems common in AD; less difficulty with speech comprehension/ expression/ reading
- **Hallucinations & delusions relatively common in AD**

FTD Subtypes

- **Behavioral Variant (bvFTD)**
- **Primary Progressive Aphasia**
  - Logopenic Variant
  - Nonfluent / Agramatic Variant
  - Semantic Dementia
- **Motor Variant**
  - Corticobasal (Ganglionic) Degeneration (CBD or CBGD)
  - Progressive Supranuclear Palsy (PSP)

Pathology

- **Focal frontal / temporal atrophy (can be asymmetric)**
- **Absence of amyloid plaques and neurofibrillary tangles**
- **Tangled tau proteins**
- **Pick bodies - Argyophilic globular inclusions**
  - Amygdala, dentate gyrus, pyramidal cells in CA1 and subiculum, hypothalamic lateral tuberal nucleus, dorsomedial putamen, globus pallidus, locus ceruleus, areas of cerebellum, and frontal and temporal cortex

bvFTD

- Rascovksy et al. (2011)
- Most common variant
- Typical age of onset is 40-65
- Median survival 3 to >8 years
- Most are tau+/ubiquitin/TDP42+ FTLD or AD
bvFTD/ Pick’s

- Considered cortical
- Symptoms similar to AD
  - Less memory, math and v/S, but more personality changes
  - Kluver-Bucy like – hyper-orality
  - Social comportment - more frontal

Frontal Behavior

- Disinhibition
- Apathy
- Inappropriate social behavior
- Lack of social tact
- Lack of Empathy
- Distractability
- Loss of insight into self and others
- Utilization Behavior

Frontal Behaviors

- Blunted Emotions
- Neglect of personal hygiene
- Repetitive / compulsive behaviors

bvFTD Criteria

A. Egocentric behavioral disturbance (one of the following symptoms (A.1-A.3) must be present)
   A.1. Sexually inappropriate behavior
   A.2. Loss of memory or awareness
   A.3. Inappropriate, rash or bizarre actions
   B. Early anxiety or irritability (one of the following symptoms (B.1-B.2) must be present)
   B.1. Anxiety
   B.2. Irritability
   C. Early loss of sympathy or empathy (one of the following symptoms (C.1-C.2) must be present)
   C.1. Diminished response to other people’s needs and feelings
   C.2. Diminished social interest, interest/disinterest or personal warmth
   D. Early pronenesses, stereotypes or compulsions/ritualistic behavior (one of the following symptoms (D.1-D.2) must be present)
   D.1. Single repetitive movements
   D.2. Complex, compulsive or ritualistic behaviors
   E. Hypersomnia or dietary changes (one of the following symptoms (E.1-E.2) must be present)
   E.1. Abnormal food preferences
   E.2. Binge eating, increased consumption of alcohol or cigarettes
   F. Overconcentration or consumption of inanimate objects
   G. Neuropsychological profile: executive functioning deficits with relative sparing of memory and neuropsychological functions (all of the following symptoms (G.1-G.5) must be present)
   G.1. Deficits in executive tasks
   G.2. Retrieval of episodic memory
   G.3. Retrieval of visuospatial skills
PPA

- Logopenic
- Nonfluent / Agramatic
- Semantic

Gorno-Tempini et al. (2011)

PPA Basic Criteria - Mesulam

Table 1: Inclusion and exclusion criteria for the diagnosis of PPA based on criteria by Mesulam

Inclusion criteria 1-3 must be answered positively:
1. Most prominent clinical feature is difficulty with language
2. These deficits are the principal cause of impaired daily living activities
3. Aphasia should be the most prominent deficit at symptom onset and for the initial phases of the disease

Exclusion criteria 1-4 must be answered negatively for a PPA diagnosis:
1. Pattern of deficits is better accounted for by other neurodegenerative nervous system or medical disorders
2. Cognitive disturbance is better accounted for by a psychiatric diagnosis
3. Prominent initial cognitive memory, visual memory, and visuospatial impairment
4. Pronounced initial behavioral disturbance
Non-Fluent / Aggrammatic

Clinical diagnosis of nonfluent/agrammatic variant PPA.
At least one of the following core features must be present:
1. Agrammatism in language production
2. Effortful, halting speech with inconsistent speech sound errors and decreased integration of speech sounds
At least 2 of 3 of the following other features must be present:
1. Invariant comprehension of syntactically complex sentences
2. Spared single-word comprehension
3. Spared object knowledge
II. Imaging-supported nonfluent/agrammatic variant PPA diagnosis
Both of the following criteria must be present:
1. Clinical diagnosis of nonfluent/agrammatic variant PPA
2. Imaging must show one or more of the following results:
   a. Predominant left posterior frontal-Insular atrophy on MRI or PET
   b. Predominant left anterior temporal hypoperfusion or hypometabolism on SPECT or PET

Semantic Dementia

Clinical diagnosis of semantic variant PPA.
Both of the following core features must be present:
1. Impaired confrontation naming
2. Impaired single-word comprehension
At least 3 of the following other diagnostic features must be present:
1. Impaired object knowledge, particularly for low-frequency or less-familiarity items
2. Surface dyslexia or dysgraphia
3. Spared repetition
4. Spared speech production (grammar and motor speech)
II. Imaging-supported semantic variant PPA diagnosis
Both of the following criteria must be present:
1. Clinical diagnosis of semantic variant PPA
2. Imaging must show one or more of the following results:
   a. Predominant anterior temporal lobe atrophy
   b. Predominant anterior temporal hypoperfusion or hypometabolism on SPECT or PET
III. Semantic variant PPA with definite pathology
Clinical diagnosis (criterion 1 below) and either criterion 2 or 3 must be present:
1. Clinical diagnosis of semantic variant PPA
2. Histopathologic evidence of a specific neurodegenerative pathology (e.g., FTLD-tau, FTLD-TDP, AD, other)
3. Presence of a known pathogenic mutation
Semantic Dementia

- Loss of semantic processing
- Verbal and non-verbal
- Loss of word meaning
- Not primary language disorder
- Dominant greater than nondominant
- Pyramids and palms
- Ubiquitin positive, tau negative inclusions
Motor Variants

• FTD with Motor Neuron Disease / ALS
  – More common in bvFTD than PPA

• Corticobasal Ganglionic Degeneration (CBGD/ CBD)
• Progressive Supranuclear Palsy (PSP)

FTD with Motor Neuron Disease

• Motor symptoms arising from motor neuron disease in FTD/ MND/ ALS
• May be called FTD with ALS
• May be 10-15% of FTD
• Ubiquitin +
• TDP -43
• May be degeneration in brain stem and spinal cord
• Decline more rapid than FTD – 2-3 years vs. 5-10

FTD / MND Symptoms

• Muscle weakness, which can involve the arms, legs, face, tongue or neck
• Clumsiness with fine movements of the hands
• Tripping or falling (due to weak or stiff legs)
• Shortness of breath (due to weak breathing muscles)
• Muscle atrophy (shrinking)
• Fasciculations (muscle twitches)
• Muscle cramps
• Dysphagia (difficulty swallowing, possibly with coughing because of food or saliva in the windpipe)
• Dysarthria (slurred speech, nasal or breathy speech)
• Spasticity (tight and stiff muscles)
• Hyperreflexia (exaggerated reflexes), usually be noted during a physical examination.
• Outbursts of laughing or crying that may not be appropriate to the situation or which may appear when the patient is mounting an effort to speak.

Also FTD / MND

• Corticobasal Degeneration (CBD or CBGD)
• Progressive Supranuclear Palsy (PSP)
CBD

- Pathology – Tauopathy
- May have overlapping features of PD, PSP, AD, FTD
- May have cognitive or motor symptoms
- May present with clumsiness
- Onset between 50-70
- Average duration ~6 years
- May have asymmetric PET or SPECT

CBD

- Alien limb syndrome
  - Cortical reflex myoclonus
  - Cortical sensory impairment
- Asymmetric ideomotor and limb kinetic apraxia
- Asymmetric Parkinsonism
- Cognitive:
  - Poor spatial organization, timing, and sequencing
  - Executive dysfunction
  - Disinhibition, apathy, perseveration, inattention

Progressive Supranuclear Palsy

- Verticle Gaze Palsy
  - Loss of upward or downward gaze
- Axial rigidity - Trunk/Neck
- Postural Instability, falls
  - Lunging forward when mobilizing
- Ataxia
- Bradykinesia
- Dysphagia

PSP

- Pseudobulbar Palsy
  - Masked face
  - Increased jaw and facial jerks dysphasia
- “Wide-eye” stare
- Incontinence
- Behavioral and cognitive impairment
- aka. Steele-Richarson-Olszewski
**PSP Pathology**

- Midbrain atrophy
  - Globus pallidus
  - Subthalamic nuclei
  - Dentate nucleus of cerebellum
- Autosomal dominant
- Polymorphism in tau?

**FTDP-17**

- Autosomal Dominant
- Linked to chromosome 17
- Three features
  - Behavioral and personality change
  - Cognitive Impairment
  - Motor symptoms
- Mutation of MAPT gene
- Altered Tau or ability of tau to bind

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**Parkinson's Plus**

- Group of disorder with multiple system involvement
- Two groups
  - Synucleinopathies
  - Tauopathies

**Disorders of P+**

- Multiple Systems Atrophy (MSA)
  - OPCA
- PSP
- CBD
- Dementia with Lewy Bodies (DLB or LBD)
- Pick's disease
**P+ vs. PD**

- Lack or irregular resting tremor
- Reduced response to dopaminergic drugs (Sinemet)
- Involvement of cerebellum – including pyramidal cells
- ? SPECT

**Multiple Systems Atrophy**

- Shy Drager Syndrome
- Olivopontocerebellar atrophy
- Striato-Nigral Degeneration
  - Autonomic – affects involuntary functions like Blood Pressure and digestion
  - Movement

**MSA Symptoms**

- Fainting (orthostatic hypotension)
- Abnormal heart rate
- Erectile dysfunction
- Bladder control
- Parkinsonian
- Slow, tremor, rigid
- Clumsiness / Incoordination
- Croaky, quivering voice

**MSA Demography**

- Progressive
- Rapid course of 5 to 10 years
- Tends to occur in 50’s
MSA Types

- MSA-P is Parkinsonian type
- MSA-C is cerebellar type
  - Ataxia, swallowing, speech abnormalities or quavering voice, abnormal eye movements

MSA: Other Features

- Contractures – shortening of muscles or tendons
- Pisa syndrome – body appears too lean
- Antecollis – neck bends forward and head drops
- Involuntary, uncontrollable sighing or gasping
- REM sleep behavior disorder

MSA Pathology

- Another distinguishing feature of MSA is the types of cells involved.
- While Parkinson’s disease affects the dopamine-producing neurons of a motor-controlling portion of the brain known as the nigro-striatal area, MSA affects both neurons and glial cells

Jacob-Cruetzfeldt

- Rapid Progression
- Viral infection
- Common death within 6 months
**Wilson’s Disease**

- Abnormal copper metabolism
- Peak onset in 20’s
- PD symptoms - tremor, rigidity, akinesia, “wingbeating tremor”, ataxia
- Keyser-Fleischer rings
- Autosomal recessive (chrom 13)
- Neuropsychiatric features, Liver disease

**Hallervorden-Spatz**

- Rare inherited
- Late Childhood or early adolescence
- Spasticity and rigidity
- Dystonia or chorea
- Accumulation of iron in brain

**Others**

- Sydenham’s Chorea
- Subacute Sclerosing Panencephalitis
- Vasculitis (sometimes with SLE)
- Bacterial Infections