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Step 1: Comprehensive Initial Assessment

Patient presents with cognitive concerns. Begin with a full clinical assessment:

- **History**:
    - **Onset and Progression of Symptoms**: Determine whether the cognitive decline is sudden, fluctuating, gradual, rapid (<1-2 years) or stepwise.
    - **Functional Impact**: Assess the patient's ability to perform activities of daily living (ADLs) and instrumental activities of daily living (IADLs). Early impairment in IADLs may indicate the onset of dementia.
    - **Comorbidities**: Identify vascular risk factors (e.g., hypertension, diabetes), psychiatric conditions (e.g., depression, anxiety), and other neurological disorders that may contribute to cognitive impairment.
    - **Medications**: Review current and recent medications for agents that may affect cognition, such as anticholinergics, benzodiazepines, or opioids.
    - **Family History**: Inquire about a history of dementia or neurodegenerative diseases in family members, which may suggest a genetic predisposition.
    - **Behavioral and Psychiatric Symptoms**: Note any changes in behavior, mood, or personality, such as apathy, disinhibition, or hallucinations, which can aid in differentiating between dementia subtypes.
- **Neurologic Examination**: Motor signs, apraxia, parkinsonism , language/speech changes, upper
    - **Motor Signs**:
        - **Parkinsonism**: Bradykinesia, rigidity, and resting tremor are characteristic of Parkinson's disease dementia and dementia with Lewy bodies (DLB).
        - **Axial Rigidity and Postural Instability**: Early falls and axial rigidity are hallmark features of progressive supranuclear palsy (PSP).
        - **Limb Apraxia and Cortical Sensory Loss**: Suggestive of corticobasal syndrome (CBS).
        - **Vertical Supranuclear Gaze Palsy**: A classic sign of PSP.
        - **Saccadic Intrusions**: May be observed in DLB and PSP.
    - **Language and Speech**:

        - **Nonfluent/Agrammatic Speech**: Characteristic of nonfluent/agrammatic variant primary progressive aphasia (nfvPPA).
        - **Semantic Deficits**: Impaired object naming and comprehension suggest semantic variant PPA (svPPA).
        - **Word-Finding Difficulties**: Prominent in logopenic variant PPA (lvPPA).
    - **Behavioral Changes**:
        - **Disinhibition, Apathy, and Compulsive Behaviors**: Common in behavioral variant frontotemporal dementia (bvFTD).
    - **Upper Motor Neuron (UMN) Signs**:
        - **Spasticity and Hyperreflexia**: May be present in CBS and PSP.
    - **Visual-Spatial Deficits**:
        - **Difficulty with Depth Perception and Object Recognition**: Indicative of posterior cortical atrophy (PCA).
- **Cognitive Screening**:
    - **MMSE**:
        - 26–30: Normal to Questionable cognitive impairment
        - 21–25: Mild cognitive impairment
        - 11–20: Moderate cognitive impairment
        - 0–10: Severe cognitive impairment
    - **MoCA**:
        - 26–30: Normal to Questionable cognitive impairment
        - 18–25: Mild cognitive impairment
        - 10–17: Moderate cognitive impairment
        - <10: Severe cognitive impairment

***Source**: Perneczky R, Wagenpfeil S, Komossa K, Grimmer T, Diehl J, Kurz A. "Mini-mental state examination and clinical dementia rating scale: predictive validity for Alzheimer disease in clinical practice." Am J Geriatr Psychiatry. 2006 Feb;14(2):139-46. Nasreddine ZS, Phillips NA, Bédirian V, et al.*

"The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment." J Am Geriatr Soc. 2005 Apr;53(4):695-9.

⚠ *Disclaimer: MMSE and MoCA are screening tools. Scores within the "normal" or "questionable" ranges do not definitively exclude cognitive impairment. Clinical judgment should guide further evaluation.*

Step 2: Core Diagnostic Workup

Recommended for all patients with cognitive concerns:

- **Laboratory Tests**:
    - TSH, Vitamin B12, Methylmalonic Acid (MMA), Homocysteine, Folate (B9), Thiamine (B1), CBC, CMP, Glucose, Albumin, Treponemal antibody
- **MRI Brain (without contrast)**:
    - SWI/SWAN (assess microbleeds)
    - Thin-slice hippocampal imaging
    - Axial FLAIR
    - 3D volumetric T1-weighted imaging

📚 *References:*

UCSF Memory and Aging Center MRI Protocol: UCSF Protocol PDF

Alzheimer's Disease Neuroimaging Initiative (ADNI) MRI Protocol: ADNI MRI Protocol

Serum Biomarkers:

- pTau181
- pTau217
- pTau217/Aβ42 ratio
- Neurofilament light chain (NfL)

⚠ *Note: While pTau181, pTau217, and the pTau217/Aβ42 ratio are promising biomarkers, their clinical utility is still being established. Interpret results in the context of the clinical presentation.*

Step 3: Interpretation and Further Evaluation

- ➤ **If pTau217 or pTau181 elevated, or pTau217/Aβ42 ratio abnormal:**

- **Interpretation**: Suggests hippocampal/parahippocampal degeneration consistent with Alzheimer's-type pathology (T+)
- If symptoms are **mild (MMSE >21 or MoCA >17)**:
  - Consider eligibility for **anti-amyloid therapy (ATM)**
  - Counsel on therapy risks, benefits, and goals

⚠ *Disclaimer: Coverage criteria for anti-amyloid therapies may vary by payer. While newer agents such as donanemab are approved for patients with MMSE >20, clinical trials consistently show these therapies are most effective when initiated at the earliest symptomatic stages-ideally when cognitive impairment is minimal. Clinical judgment should guide both timing and appropriateness of treatment.*

- ➤ **Proceed with confirmatory testing** to establish AT(N) profile and assess treatment readiness:
  - **CSF Panel**:
    - CBC, Protein, Glucose, Albumin
    - NSE
    - Aβ42/40 Ratio (e.g. Mayo AMYR)
    - pTau181 and Total tau (t-tau) (e.g. Mayo ADEVL)
  - **Amyloid-PET**: Approved by CMS for treatment eligibility

⚠ *Disclaimer: CMS currently requires only amyloid PET to confirm eligibility for anti-amyloid therapy. However, pTau and total tau levels are highly valuable for prognostication, disease staging, and identifying likely responders to disease-modifying therapy.*

- ➤ **If NfL or NSE elevated:**
  - Indicates **neuronal injury or degeneration (N+)**, not specific to Alzheimer's disease
- ➤ **If biomarker levels are borderline but phenotype is concerning:**
  - Especially in early-onset, rapid progression, or strong family history:
  - Proceed with full **CSF panel** (as above)
  - Consider **Amyloid-PET** for confirmation if CSF is declined or inconclusive
- ➤ **If results are normal:**
  - Reassuring against Alzheimer's disease

  - Still consider:
  - Lewy body dementia
  - Frontotemporal degeneration
  - Functional or psychiatric cognitive syndromes
  - Reassess in **6–12 months**:
    - Repeat MoCA
    - Repeat MRI
    - Serial pTau217 and NfL levels

- ⚠️ **Immediate RPD Workup Trigger:**
  - Clinical history suggests **rapid decline (symptom onset to dementia within 1–2 years)** and elevated NfL or pTau
  - Proceed directly to Rapidly Progressive Dementia evaluation

Step 4: Rapidly Progressive Dementia (RPD) Workup

🗂️ **Rapidly Progressive Dementia (RPD)** refers to a category of cognitive disorders characterized by a **swift and significant decline in cognitive abilities**, typically progressing from **symptom onset to dementia within less than 24 months**-and often within **12 months**. Unlike typical neurodegenerative diseases such as Alzheimer's, which progress over years, RPD requires urgent evaluation due to its broad differential diagnosis, including:

- Autoimmune encephalitis
- Infectious etiologies (e.g., prion diseases, viral encephalitis)
- Neoplastic/paraneoplastic syndromes
- Toxic-metabolic and vascular causes
- Atypical presentations of neurodegeneration

Because many causes of RPD are **treatable or reversible**, early recognition and expedited workup are critical.

- **Laboratory Tests**:
  - ESR, CRP
  - ANA, ANCA, Anti-thyroid antibodies
  - HIV, Syphilis serology

  - Vitamins B1, B12, E
  - Paraneoplastic and autoimmune encephalitis panels
- **CSF Analysis**:
  - Cell count, Glucose, Protein
  - Aβ42/40, pTau, Total tau, NSE
  - 14-3-3 protein, RT-QuIC
  - Oligoclonal bands
  - Autoimmune encephalitis markers
- **Neuroimaging**:
  - MRI Brain with **diffusion-weighted imaging (DWI)**
  - FDG-PET if frontotemporal degeneration suspected
- **Additional Evaluations**:
  - EEG (encephalopathy, seizure activity)
  - Syn-One skin biopsy (if synucleinopathy suspected)

Reference: Geschwind MD. Rapidly Progressive Dementia. Continuum (Minneap Minn). 2016 Apr;22(2):510–537.

Step 5: Follow-Up and Monitoring

- If **diagnosis remains uncertain**:
  - Reassess every **6–12 months**
  - MoCA or MMSE
  - MRI brain
  - Serum biomarkers (pTau217, NfL)
- If **diagnosis is confirmed**:
  - Initiate appropriate management
  - Educate and support patient and caregivers

Step 6: Questions remain?

If you're ever unsure, refer to your friendly neighborhood Ochsner Neurocognitive Program. We're here to help.