DEMENTIA AND MILD COGNITIVE IMPAIRMENT
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Week 7

Educational Objectives:

1. Define dementia and mild cognitive impairment
2. Understand the appropriate work-up for patients with complaints of memory loss
3. Develop a differential diagnosis and initial evaluation and treatment plan for patients with dementia

CASE ONE:

Mr. F, a 79-year-old gentleman, comes to see you for a follow-up visit. You last saw him a year ago as he missed his last appointment six months ago. For the first time, he is accompanied to the visit by his wife. Mr. F has no complaints and states that everything is fine. He has a history of HTN and DM; both of which are well controlled at the time of the visit. He is taking lisinopril 10 mg daily, metformin 500 mg twice a day, atorvastatin 10 mg daily and a baby aspirin. He is a retired accountant. His exam today is normal. You make no changes to his medical regimen and you ask to see him back in six months. On the way out of the office, his wife asks if you can schedule the follow-up in the morning as he is no longer driving and she needs to bring him to his visit.

Questions:

1. **Discuss your initial approach to this patient given the report that he is no longer driving.**
   The fact that this patient is no longer driving should bring up a concern for loss of function. Driving and use of transportation are considered instrumental activities of daily living (IADLs). Other IADLs include managing money and medications, shopping, and cooking. Loss of IADLS may be a sign of dementia. More basic activities of daily living (ADLs) including dressing, eating, toileting, and grooming are generally impacted later in the course of dementia.

   The American Geriatrics Society defines a dementia syndrome as a chronic acquired decline in memory with at least one other area of higher cognitive functioning (such as language, visuospatial, executive functioning, or judgment) that is sufficient to affect daily life. The lifetime risk of developing dementia in those over the age of 65 is 17 to 20%. In patients aged 71 to 79 the prevalence of

dementia is 5%. Age is the largest risk factor for dementia. Other risk factors include family history of dementia, cardiovascular comorbidities, apolipoprotein E4 genotype, and lower education level (Simmons, 2011).

The initial approach to the patient should include an assessment of this patient's functioning with a focus on IADLs. Determining the level of impairment or chronicity of functional loss, if present, is important. The Functional Activities Questionnaire, an informant based measure of activities of daily living, measures ten domains, each being scored on a scale with 0 for normal to 3 for dependent. Domains included in this questionnaire are: financial matters such as check writing and bill paying; handling business affairs such as tax records; general shopping skills such as purchasing groceries; participation in hobbies or games; performance of typical kitchen related activities such as making a cup of coffee; preparing a balanced meal; attention to current events; recent memory such as remembering appointments; complex attention including comprehension of TV programs, books or daily events; and travel outside of one's neighborhood. A cut off point of 9 is indicative of mild dementia on this 30 point scale. Sensitivity of the Functional Activity Questionnaire in distinguishing dementia from normal controls is 85% (Pfeffer, 1982).

Given that the patient is no longer driving, addressing the concern for safety of driving in an elderly patient would be appropriate. Specific questions that can be used to evaluate for driving safety in the elderly include:
1. How many times has the patient been stopped or ticketed for a traffic violation in the last three years?
2. How many accidents has the patient been in, or caused, within the last three years?
3. In how many accidents was the patient at fault in the last three years?

Prior accidents and violations are associated with unsafe driving. The American Academy of Neurology also recommends using caregiver assessment of driving ability as marginal or unsafe as caregiver assessment correlates modestly with on-road driving test (ORDT) performance (Iverson, 2010). Patients self-report is not as useful, in one study of patients with mild Alzheimer's disease, 94% of patients rated themselves as safe, but only 41% passed an ORDT (Brown, 2005). Patients with early dementia who are still driving should undergo a driving evaluation through a local Motor Vehicle Administration. These evaluations should be repeated every six months (Rabins, 2014).

Driving laws and reporting of unsafe driving by clinicians vary from state to state. A useful resource for mature driving laws is http://www.ghsa.org/html/stateinfo/laws/olderdriver_laws.html.

CASE ONE CONTINUED:

> Mr. F's wife tells you he is no longer driving because he has had a few episodes of getting lost while driving. He has been more forgetful over the past two years but this has worsened over the last few months. He stopped managing the family finances about six months ago. He is still able to manage his activities of daily living (ADL's). You decide to reschedule his follow-up visit for two weeks to further evaluate his cognitive decline.

2. **In the last few minutes of this visit, are there any brief screening tests you could perform to further evaluate for dementia?**
   The most studied brief screening test for dementia is the Mini-Mental State Examination (MMSE). Pooled estimates across 14 studies revealed a sensitivity of 88.3% and a specificity of 86% when calculated at a cut-off score of 23/24 or 24/25 out of a possible score of 30 (Lin, 2013). The MMSE assesses multiple domains including orientation, attention, concentration, memory, language, and construction ability. The MMSE takes five to 12 minutes to perform and may take longer in patients with dementia. Scoring on the MMSE needs to be interpreted with the patient's educational level and age, as population studies have shown that there is variance across age groups and educational levels, with the older and less educated populations having a lower mean MMSE score (Rosa 1993). For example, a MMSE score of < 22 could be used as the cut-off for patients with a 7th grade education or less. The MMSE is also available in Spanish. Interpretation of the Spanish version of the MMSE score also needs to take into consideration potential cultural differences. A study by Jones did show variance in scoring of 12 of the 21 items on the MMSE when comparing Spanish to English versions. For example, the orientation to state and season questions were more difficult for Spanish-language examinees then those taking the exam in English (Jones, 2006).

   Given the time constraints at this end of the visit evaluation, the MMSE may be better performed at a later visit but perhaps today you have time for a shorter cognitive screening test, such as the mini-Cog and the verbal fluency test.

   The mini-Cog is a brief screening test that can be administered in two to four minutes. Although not as well-studied as the MMSE, it has a reported sensitivity of 76% and specificity of 89%. The mini-Cog is not dependent on educational level. The patient is asked to listen carefully, repeat back and remember three unrelated items. The patient is then instructed to draw the face of a clock. The patient should be instructed to put the numbers on the face of the clock and then asked to draw the hands to a clock to read a specific time with 11:10 or 8:20 being the most commonly used. The patient is then asked to recall the three items. It is scored on a five point scale, with a point for each object recalled and two points for a correct clock. Scores of 0 to 2 are suggestive of dementia (Lin, 2013).

The verbal fluency test is another brief screening test which can be administered in one minute. The reported sensitivity is 88% with a specificity of 96%. The patient is asked to name as many animals as they can in 60 seconds. A score of less than 15 (one point for each animal) is suggestive of dementia. Lower cut-off values should be considered with patients with a lower educational level (Lin, 2013).

CASE ONE CONTINUED:

> **You perform a mini-Cog, Mr. F recalls 1/3 objects, and his clock drawing was abnormal. He scores a 1 on the mini-Cog, and you are concerned about a diagnosis of dementia. You schedule him to return with his wife in two weeks for further investigation of the potential diagnosis of dementia.**

3. **Discuss your approach to the follow-up visit for Mr. F.**
   Your initial history should focus on the time course and nature of his impairments. It is important to obtain information from both the patient and a family member or caregiver as patients with dementia may lack insight into their deficits. The physical exam should focus on the neurologic exam looking for focal abnormalities to suggest vascular dementia and findings to suggest Parkinsonism. A history of ascending paresthesias, tongue soreness and limb weakness may be suggestive of vitamin B12 deficiency. A broad shuffling gait and urinary incontinence may suggest normal pressure hydrocephalus. Medication side effects should be evaluated as psychoactive medications such as benzodiazepines and medications with anticholinergic effects may be contributing to symptoms. A history of head trauma, headache, or seizures may suggest a subdural hematoma. Complaints of fatigue, cold intolerance, constipation and weight gain may suggest hypothyroidism. A history of alcoholism, nystagmus or a broad-based gait may suggest Wernicke-Korsakoff syndrome. A recent hospitalization or acute illness and a waxing and waning nature of inattention may be more suggestive of a delirium.

   Because depression can cause symptoms of cognitive impairment, an evaluation for depression should also be performed, and could include use of the Geriatric Depression Scale. A brief five item Geriatric Depression Screen is also available. Answering two of the following questions as indicated in bold would be considered a positive screen for depression and would require further evaluation for depression.

   - Are you basically satisfied with your life? **NO**
   - Do you often get bored? **YES**
   - Do you often feel helpless? **YES**

- Do you prefer to stay at home rather than going out and doing new things? **YES**
- Do you feel pretty worthless the way you are now? **YES**

Your initial brief screening test for dementia should also be followed up with a more comprehensive evaluation such as the MMSE.

CASE ONE CONTINUED:

> **Mr. F's wife reports that he has become progressively more forgetful over the past three years. He has had no hallucinations. He is no longer driving or managing the finances. He has not had any wandering. His exam is without focal abnormalities. He has no findings of sensory loss, and his gait is normal. He has no history of head trauma or urinary incontinence, he does not drink alcohol, and a symptom screen for hypothyroidism is negative. His Geriatric Depression Scale does not indicate depression. He scores 22/30 on his MMSE.**

4. **What further work-up would you perform?**
   His history and testing are consistent with dementia. The American Geriatrics Society recommends a CBC (healthcare blue book cost $23), complete metabolic panel and calcium (health care blue book cost $30), vitamin B12 (healthcare blue book cost $31), and a TSH (health care blue book cost $23). Routine testing for syphilis and HIV are recommended only in patients with suspected dementia with a high-risk sexual history. Routine neuroimaging is not recommended unless the patient is less than the age of 60, or has focal neurologic deficits or experienced an abrupt onset and rapid decline. (Health care blue book cost for non-contrast head CT and MRI $407, $779 respectively).

5. **What is the most likely diagnosis?**
   Alzheimer's disease is the most common type of dementia with a frequency of 50-60%. Other etiologies include vascular dementia (15-20%) and mixed dementias which have a component of both (10-20%). Other etiologies such as Lewy Body dementia, Parkinson's, alcohol, Prion disease, traumatic, normal pressure hydrocephalus, infections, and metabolic derangements (hypothyroidism and vitamin B12 deficiency) are less common. The diagnosis of Alzheimer's disease can only be confirmed at autopsy by the presence of amyloid plaques and neurofibrillary tangles, and thus remains a clinical diagnosis. Probable Alzheimer's disease is defined by dementia documented by clinical examination and cognitive testing, deficits in two areas of cognition (one of which is memory), progressive decline, intact consciousness, onset between the ages of 40 and 90 and absence of other disorders to account for these findings (Rabins, 2014).

Given the lack of hallucinations, no evidence for Parkinsonism and vascular disease the most likely diagnosis in this case is probable Alzheimer's disease.

6. **Discuss the staging and symptom progression of Alzheimer's disease.**
This patient likely has early Alzheimer's disease with evidence of mild impairment and a time frame of 1 to 3 years from onset of symptoms. Generally during this stage of the illness, there is disorientation to date, naming difficulties, problems with managing finances, challenges recalling recent items, social withdrawal, irritability, and mood changes. The middle stage is one of moderate impairment, MMSE 11-20, generally 2 to 8 years from onset of symptoms and is characterized by disorientation to date and place, comprehension difficulties, impairment in language and calculation, impaired new learning, getting lost in familiar places, and problems with ADLs such as dressing and grooming. Patients may also experience feelings of restlessness, anxiety and depression as well as the development of delusions, agitation and aggression. Severe impairment generally occurs six to 12 years from symptom onset, MMSE scores are in the 0-10 range at this point. During this stage remote memory is gone, verbal output can be unintelligible, and people may experience problems with incontinence, motor or verbal agitation. Patients with advanced dementia may develop pressure ulcers, constipation, and weight loss and may be bed bound.

More useful resources for clinicians, patients and families is available at http://dementia.americangeriatrics.org/.

7. **Discuss your treatment plan for Mr. F.**
Treatment for dementia can involve both pharmacologic and non-pharmacologic approaches. Non-pharmacologic approaches include assuring the patient is safe in his environment and maximizing the ability of the patient to function. The patient's ability to perform IADLs such as correctly using money, medications, transportation and home environment should be assessed. Information, support, and services should be provided to patients and their families to assist in patients living safely with dementia. Caregivers should routinely be offered counseling and support, given that as many as 50% of caregivers will develop symptoms of depression. Resources for caregivers and patients are available through the Alzheimer's Association at www.alz.org.

Pharmacologic interventions include medications targeted at slowing the cognitive decline in patients and medications used to control behavior associated with the disease process. Cholinesterase inhibitors (donepezil, rivastigmine, and galantamine) and the N-methyl-D-aspartate receptor antagonist, memantine, have been approved by the Food and Drug Administration for treatment of Alzheimer's disease. Randomized, placebo controlled trials of the cholinesterase inhibitors have mostly included patients with mild to moderate Alzheimer's dementia. Most of these trials have been of short duration, six months or less. As outlined in the Annals article by Lin and colleagues, many of these trials have shown significant improvements in global cognitive functioning when measured on scales such as

the Alzheimer's disease Assessment Scale-Cognitive Subscale (ADAS-cog). It is not clear if these significant changes in scores on scales such as the ADAS-cog correlate with true clinical benefit. Most studies using cholinesterase inhibitors also have an attrition rate of about 15%, due to a proportion of patients not being able to tolerate pharmacologic therapy (Lin, 2013).   The dosing, and common side effects of cholinesterase inhibitors are listed in Table 3 of the Rabins article. Common side effects for cholinesterase inhibitors include nausea, vomiting, diarrhea, and weight loss.

Decisions to start therapy for mild to moderate dementia should involve the patient, caregivers and a family-centered discussion about the goals of therapy. Given that there may be limited clinical benefit based on clinical studies, the goals of the therapy need to be determined as well as thresholds for discontinuing the medication. The condition of the patient taking these drugs may remain stable and the hope is for a slowing of a decline in cognition when compared to untreated patients but patients and caregivers should be realistic about expected benefits. The American College of Physicians and American Academy of Family Physicians recommend that clinicians should base the decision to start pharmacologic therapy on an individual assessment of the risks and benefits. If choosing pharmacotherapy, clinicians should guide their choice of therapy by tolerability, adverse effect profile, ease of use, and cost of the medication (Qaseem, 2008).

CASE ONE CONTINUED:

With the input of your patient, his spouse, and your review of the data, you decide to start Mr. F on donepezil at a starting dose of 5 mg daily. You schedule a follow up visit in one month for a repeat evaluation.

8. **Describe your approach to this follow-up visit.**
    The goal of the follow up visit is to evaluate for development of any side effects of the medication as well as to evaluate for progression of cognitive decline. A repeat MMSE examination would be an appropriate part of the visit as well as review of the changes in the patient's functional status.

    Evaluation of patient safety as it relates to functional activity, medication use, cooking, use of power tools or firearms is important as the disease progresses. The patient should also be evaluated for any wandering away from home.

    The patient and caregiver should be asked about any problems with sleep, behavioral disturbances or psychiatric manifestations of dementia. If these symptoms are present, mild and do not pose any danger to the patient or the caregiver, non-pharmacologic therapy may be sufficient.

Checking in with the patient's spouse around issues of caregiver burnout would be appropriate as well.

CASE TWO:

> **Mrs. F is also your patient. Given her experiences caring for her husband, she asks if she should be screened for dementia. She is 80 years old, she has a history of hypothyroidism treated with levothyroxine, hyperlipidemia on a statin, and osteoarthritis. She is completely independent with her IADLs. She admits to being forgetful at times, particularly with short term memory. For example, at times she misplaces keys or forgets parts of phone conversations. She scores a 5/5 on the mini-Cog testing.**

9. **How would you define her memory impairment, and how would you proceed?**
   Mild cognitive impairment (MCI) is an intermediate state between the normal cognitive decline in aging and the diagnosis of dementia. It can be difficult for clinicians to determine differences between normal cognitive decline in aging and the cognitive decline associated with mild cognitive impairment.   The normal cognitive decline of aging is typically a subtle forgetfulness such as misplacing objects such as keys or some difficulty with word recall. The memory loss in MCI is generally more prominent. The estimated prevalence of mild cognitive impairment ranges from 10 to 20% in community dwelling patients over the age of 65. The memory loss in MCI is characterized by forgetting information a patient would have previously remembered easily such as appointments, telephone conversations, or topics of normal interest to the patient. Mild cognitive impairment, unlike dementia, spares other cognitive capacities and thus use of language, functional activities, visuospatial skills and executive functioning are intact. Patients with MCI may have inefficiencies in performing activities of daily living but still should be able to perform these activities independently (Peterson, 2011).

   In addition to the brief cognitive screening with a test such as the MMSE, review of her independent activities of daily living and functional status, a thorough neurologic examination should be performed. Secondary causes of mild cognitive impairment should be considered, including depression, medication side effects, and sensory impairment.

CASE TWO CONTINUED:

Mrs. F scores 29/30 on a MMSE, her depression screen is negative, and she has a non-focal neurologic examination. You feel her reported memory loss is secondary to mild cognitive impairment.

10. **What is Mrs. F's risk of developing dementia? Does she require treatment?**
    Most patients with mild cognitive impairment are at risk for developing dementia. The annual rate of development of dementia in community-dwelling adults with mild cognitive impairment is 5 to 10% which is higher than the rate in normal community-dwelling adults (Peterson, 2011).

    Currently no medications are approved by the Food and Drug Administration for treatment of mild cognitive impairment. Medications traditionally used to treat dementia (donepezil, galantamine, etc.) have not been shown to be effective in reducing the rate of development of dementia in those with mild cognitive impairment. Some evidence supports the use of cognitive rehabilitation and aerobic exercise in preventing progression to dementia in patients with MCI with few side effects.

    It would be reasonable to instruct your patient to engage in regular exercise and remain involved in intellectually stimulating activities.

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1. **The following are true of dementia except:**

    a. Characterized by an acquired decline in memory with at least one other area of higher cognitive functioning impacted
    b. Characterized by an acute onset and fluctuating course
    c. Symptoms are sufficient to impact function in daily life
    d. Risk factors for dementia include a family history of dementia
    e. All of the above are true

2. **Neuroimaging should be considered part of the work-up for patients with what symptoms of dementia?**
    a. In all patients with memory loss
    b. In patients with a history of onset at or before the age of 70
    c. In patients with focal neurologic signs
    d. In patients with a family history of Alzheimer's disease

3. **All of the following are true regarding treatment for mild Alzheimer's dementia except:**
    a. Non pharmacologic approaches to sleep disturbances are preferred if symptoms are mild and do not pose a threat to the patient or caregivers
    b. Cholinesterase inhibitors are FDA approved for treatment of mild Alzheimer's disease
    c. Cholinesterase inhibitors have been found to improve mortality in Alzheimer's disease
    d. Common side effects of cholinesterase inhibitors include nausea and weight loss.
    e. All of the above are true

Answers:

1. **b**   *An acute onset and fluctuating course are characteristic of delirium*
2. **c**   *Neuroimaging is indicated in patients presenting with symptoms of dementia and focal neurologic signs but not as a routine part of the dementia workup.*
3. **c**   *Cholinesterase inhibitors have not been found to have an impact on mortality in Alzheimer's disease, benefit from clinical trials has mostly been shown on short term (less than six month) markers of cognitive impairment.*