Advances in the Management of Patients with Dementia

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Part I: Common Cognitive Diagnoses

Depression and Dementia – A Complicated Relationship
The Relation between Dementia and Depression is a complex one. Depression can cause a mild, sometimes even moderate, cognitive impairment often referred to as pseudodementia of depression, and thus mimic dementia and other cognitive disorders. Depression needs to be screened for and if present, treated, both for the quality of life and functionality of the patient, and also to help clarify the diagnostic picture. If the cognitive complaint goes away with successful treatment of depression, it probably represents pseudodementia of depression. However, depression can also be a harbinger of dementia, sometimes appearing months or more before onset of true dementia. Even if a patient improves with treatment, they may be at further risk for future dementia and thus it is recommended to follow the patient’s cognition over time. Of course, depressive phenomena are also commonly seen symptoms of dementias. Treatment typically is with a Selective Serotonin Reuptake Inhibitor or Serotonin and Norepinephrine Reuptake Inhibitor.¹

Reversible 'Dementias'
One of the largest causes of confusion in the elderly is medication. It is therefore important to remove any medications that may be causing cognitive problems. This in and of itself may restore some patients to their normal cognitive function, though the effects of some drugs may linger far longer than would be expected for their known half-life, and thus weeks or even months may need to be allowed to see the final impact of wash-out on performance. When dealing with potential dementias, there must also be consideration of other toxic/metabolic etiologies such as endocrine abnormalities (with thyroid dysfunction leading the way), electrolyte imbalances (even mild hyponatremia can lead to decreased cognition in older patients). Vitamin deficiencies can also impair cognition with B1, B12, and D being some of the more commonly encountered deficiencies in the United States. Chronic CNS infections can lead to a dementia like presentation, with the most common historically being tertiary neurosyphilis, but HIV dementia is also a possibility, though typically it is a more rapid dementia. Beyond this, some rare cases of autoimmune disorders in the elderly can also lead to cognitive impairment. If correctable or treatable lab abnormalities are detected, then the underlying disease should be corrected and after this cognition should be reassessed. If patient continues to decline even after reversing the suspected problem, it may be that there is another underlying cause.²

Normal Pressure Hydrocephalus (NPH) is another potentially reversible cause of dementia where the problem is with the reabsorption of cerebrospinal fluid. NPH can be primary or secondary, and a history of meningitis or subdural hemorrhage places a patient at greater risk. The classic triad of Normal Pressure
Hydrocephalus is composed of gait apraxia, urinary incontinence, and confusion. The magnetic gait apraxia, where the patient appears almost stuck to the floor is not the only gait abnormality seen; a rigid akinetic parkinsonian gait has also been reported as a variant gait abnormality in this reversible dementia, one that also can respond to treatment. The ultimate treatment for NPH is placement of a ventriculoperitoneal shunt for CSF drainage. This should halt progression, and in selected cases may result in partial to complete reversal of symptoms. Good prognostic indicators include the presence of the classic triad, short duration (several months as opposed to years), or significant improvement after large volume CSF removal (120 – 150) by up to three large volume lumbar punctures over 3 days or drainage by a temporary lumboperoneal shunt up to 72 hours. Note that the patient should be assessed daily for improvement, and if improved the investigation step may be halted and arrangements made for ventriculoperitoneal shunt placement.\[^3,4\]

**The Not Quite Demented**

**Mild Cognitive Impairment**

Mild Cognitive Impairment (MCI) is a syndrome where a patient has a cognitive complaint and detectible cognitive dysfunction on exam in one or more cognitive domain, but with relatively preserved function in real life, independent activities of daily living. MCI is a diagnosis of exclusion, so there should be no other etiology for the cognitive complaint. Especially in Amnestic Mild Cognitive Impairment (aMCI), where patients with MCI has a memory component are at greater risk for developing Alzheimer’s Disease (AD) with conversion to AD occurring at a rate of about 10-15% per year, compared to 2% per year for the general population.\[^5\]

**Vascular Cognitive Impairment**

Vascular Cognitive Impairment (VCI) is similar in severity to MCI, but in the case of VCI there is associated cerebrovascular damage, commonly seen at this mild level of dysfunction in subcortical vascular disease with ischemic demyelination and/or lacunar strokes, though larger strokes can sometimes be seen causing the milder symptoms of vascular cognitive impairment. While clinical history or exam findings are useful, neuroradiographic evidence for vascular damage is necessary for this diagnosis.\[^6\]

**Alzheimer’s Disease**

Alzheimer’s disease is the most common dementia found in patients age 60 and older. Up to 50% of the population may have AD by their 80s. The first and worst symptom of AD is memory, specifically delayed recall memory that doesn’t improve with cuing. In addition, AD patients should have two more cognitive domains involved. Some common findings on cognitive examination of AD patients include but are not limited to in addition to the memory problems that don’t improve with cuing, animal fluency worse than letter fluency, dysnomia, and visuospatial dysfunction. There are two less common additional initial presentations that have AD pathology as their basis; Posterior Cortical Atrophy (PCA) where the visuospatial abnormalities are the first and worst symptom, and Logopenic Progressive Aphasia where first and worst symptoms are in language, including empty speech, dysnomia, and semantic difficulties. For this and all dementias, patients must have some level of functional impairment in real life, in independent activities of daily living or even in activities of daily living in more severe cases. MRI of the Brain may show atrophy, particular in the hippocampal regions. Other causes of cognitive disturbance must be excluded. Alzheimer’s disease risk factors include the most prominent, age, as well as low education, uncontrolled diabetes mellitus, family history (especially early onset and first degree relatives), and apolipoprotein epsilon genotype. Patients with a Hgb A1C 7.5 or greater have about ten times the risk of developing AD. In some rarer familial cases mutations have been identified in the amyloid precursor protein gene on chromosome 21, presenilin 1 gene on chromosome 14, and presenilin 2 gene on chromosome 1.\[^7\] In late
onset AD, the apolipoprotein epsilon genotype has an interesting relation to risk. The three major alleles are 2, 3, and 4, with relative protection from the 2 allele, average risk with the 3 allele, and increased risk from the 4 allele. It is thus necessary to know the complete genotype to predict risk of late onset Alzheimer’s disease. The rare 2/2 and 2/3 genotypes have less risk, and if AD develops it is usually later onset in the 80s or 90s. The risk and protective alleles have their effects cancel out in the 2/4 genotype who carry average risk of AD with a typical age of onset, just like the most common genotype in the population of 3/3. The 3/4 genotype shows increased risk of developing Alzheimer’s disease, often at younger age of onset more in the 60s to 70s, whereas 4/4 has even greater increased risk, and younger age of onset in the 60s and 70s.\textsuperscript{8,9}

Staging and following Alzheimer’s disease in research has multiple means, but in a busy clinical practice a serendipitous use of the venerable mini-mental state examination (MMSE) can be for this purpose. Some FDA indications make reference to stage of severity in AD. This is where your MMSE score is useful. There are several cut-offs that are used in both research and clinical work, but a useful rough rule of thumb is above 20 is ‘mild’, 20 – 10 ‘moderate’, and below 10 is ‘severe’. Clinicians can also use functional information and clinical judgment to determine where patients fall in the severity spectrum. Though flawed, the MMSE actually follows progression in AD (but not necessarily other dementias) reasonably well. Follow-up visits are generally recommended for every 6 months.

**Vascular Dementias**

Vascular Dementia (VaD) has multiple different subtypes; multiple infarct dementia, subcortical vascular dementia, and strategic infarct dementia. Multiple Infarct Dementia is usually easy to identify clinically and radiographically. It commonly presents with a stepwise deterioration, focal symptoms & signs, and strokes on brain imaging (MRI or CT). Area of stroke(s) should correlate with area(s) of cognition impaired. Subcortical Vascular Dementia is harder to identify clinically since it can mimic the primary neurodegenerative disorders and have a gradual onset and progression though some will still present with stepwise decline. These patients typically do not have a true memory problem, and if they do it will tend to improve with cuing, and in addition have more problems with frontal-subcortical tasks such as letter fluency which may be worse than animal fluency. Neuroimaging (most easy to see with MRI of the Brain) shows lacunes and/or ischemic demyelination. A strategic infarct dementia is simply where a single infarction to the brain results in multiple cognitive domains becoming dysfunctional. The most common risk factors in the older population are high blood pressure, high cholesterol, high blood sugar, smoking, obstructive sleep apnea, and atrial fibrillation.\textsuperscript{10}

**Mixed AD/VaD**

Both Alzheimer’s disease and Vascular Dementia are common in the elderly, so it is not surprising to find that they also co-occur. They also share as a risk factor, diabetes mellitus. Treat both the vascular and the AD components.\textsuperscript{10}

**Lowy Body Dementia**

Lowy Body Dementia is the next most common dementia after AD and Vascular Dementia. It has the same underlying pathology as Parkinson’s disease, but with early predominance in the cerebral cortex. Lowy Body Dementia patients tend to have slightly less problems with memory than AD patients, but with more with executive dysfunction. The classic syndrome is still the best way to diagnose, specifically early hallucinations, rigidity, falls, and fluctuating level of consciousness. Patients should have visuospatial dysfunction; otherwise it is very unlikely to be LBD, though the presence of visuospatial dysfunction is common in several dementias.\textsuperscript{11}
Parkinson Disease Dementia

Parkinson Disease (PD) patients experience subtle cognitive problems that are typically not detected without detailed neuropsychology testing, but about a third of people with PD go on to develop full a full dementia. Compared to Alzheimer’s disease, patients with Parkinson Disease Dementia experience less memory problems, mostly suffering from deficits in the frontal subcortical networks and thus are more likely to show difficulties on tasks like letter fluency than animal fluency. There is overlap between Parkinson Disease Dementia, Lewy Body Dementia, and even Alzheimer’s disease, including pathological overlap.

Other Parkinsonian Syndromes

Beyond Parkinson’s disease and Lewy Body Dementia, there are other parkinsonian syndromes which can lead to dementia, including Progressive Supranuclear Palsy, Corticobasal Degeneration, and Multi-System Atrophy.

Progressive Supranuclear Palsy

Progressive Supranuclear Palsy (PSP) is known for the presence of gaze palsies, especially upon downward gaze. PSP also includes early parkinsonism, especially falls and rigidity, but with little tremor. The cognitive profile of PSP is that of subcortical abnormalities.

Corticobasal Degeneration

This syndrome is characterized by an asymmetric presentation in the classic syndrome of ideomotor apraxia, agraphesthesia, astereognosis, alien hand syndrome, and myoclonic jerks. Again some parkinsonism is present, but gait is often preserved until late in the disease. Brain neuroimaging may show asymmetric frontoparietal atrophy in one hemisphere compared to the other.

Frontotemporal Lobar Degenerations

Frontotemporal Lobar Degeneration as a category includes frontotemporal dementia (behavioral variant), progressive non fluent aphasia, and semantic dementia. The FTLDs have an earlier onset than AD, sometimes as early as the 40s, and onset in the 50s is as common as early onset AD. There is overlap in patients and in families in occurrence of FTLD and amyotrophic lateral sclerosis (ALS).

Frontotemporal Dementia

Frontotemporal Dementia (FTD) is characterized by early odd and inappropriate behavior, food cravings (sweets, chocolate), poor judgment, loss of insight and empathy. Early on, these patients may score perfectly normal on simple tests like MMSE. When cognitive abnormalities are detected, they are in frontal and temporal functions as the name implies, and brain imaging may show more atrophy in right frontal and temporal lobes.

Progressive Nonfluent Aphasia

Progressive Nonfluent Aphasia is where a patient loses fluency and language expression early. Neuroimaging may show increased atrophy in left frontal and temporal lobe.

Semantic Dementia

In Semantic Dementia, while language is fluent, the patient loses the meaning of things, and they may lose empathy much like the FTD patients do. Brain imaging may show increased atrophy in bilateral anterior temporal lobes.
The FTLD-CBD-PSP overlap
All of these diseases overlap to varying degrees in symptoms and in underlying pathology. None have been shown to respond to acetylcholinesterase Inhibitors (though a small study in FTD did suggest rivastigmine might help).

Part Two – Dementia Treatments

Fine Tune the Brain
Remove, change, or reduce medications that may add to confusion in older patients, particularly anti-cholinergics (including bladder control drugs), hypnotics, sedatives, anxiolytics, narcotics, anti-epileptic drugs, chemotherapeutic agents. Reverse any reversible causes such as correcting vitamin deficiencies, Start or maintain healthy physical exercise program, both for the general functional benefits and the possible cognitive benefits. It is also good to try to keep intellectually challenged and artistically engaged.

Finney’s Rules of Thumb for Cognitive Exercise:
Practice what you want to preserve! The closer cognitive exercise comes to the real world activity that is desired to preserve, the more likely it is to have benefit in that activity.

Try learning something completely new! Learning new thing completely outside a person’s domains of experience may serve a similar purpose to enriched environments in animal studies. Examples include learning a foreign language if you’ve never learned one before or taking up an art if you haven’t done art before. Even dementia patients can learn some with enough repetition.

Control Vascular Risk Factors
Keep blood pressure normotensive. Angiotensin Converting Enzyme Inhibitors for essential hypertension with those that cross the blood brain barrier may have additional benefits for dementia; these include lisinopril, monopril, fosinopril, perindopril, and trandolopril. Patients with concomitant obstructive sleep apnea should use properly titrated CPAP. Statins are of use for hyperlipidemia and have evidence in secondary stroke prevention. Despite persistent concerns regarding cognitive side effects from this class of drugs, the actual evidence in the literature does not support concern over cognition in their use, whereas the risk of not controlling hyperlipidemia and preventing strokes is well documented. Smoking cessation is a must in any patient who is continuing the practice as this is a major vascular risk. Tight diabetes control is also necessary, preferably with Hgb A1C kept below 6.5. Antiplatelet agents such as aspirin are also useful in preventing further vascular damage. Anticoagulation is a necessity for almost any patient with a history of atrial fibrillation. Folic Acid can be used for correcting hyperhomocysteinemia.

Primary Neurodegenerative Disorders Treatment

Acetylcholinesterase Inhibitors
Acetylcholinesterase Inhibitors are the major class of medications used to treat dementias. The three most commonly used in the United States are donepezil, rivastigmine, and galantamine. The main side effects gastrointestinal including nausea, diarrhea, and rarely vomiting. Taking the oral formulations of this class of drug on a full stomach helps lower the risk of this side effect. Other side effects include bradycardia, vivid dreaming & sleep disturbance, exacerbation of already existing bleeding ulcers, and muscle cramps. Gradual titration over months helps to limit all these side effects. Taking medication earlier in the day may...
help if patients have dream/sleep side effects. If a patient can’t tolerate one acetylcholinesterase inhibitor it is worth trying another within the class.

**Donepezil (Aricept)**

Donepezil has FDA Indications for mild, moderate, and severe Alzheimer’s disease. There is evidence in the literature for some effect in vascular dementia and other vascular cognitive disorders, Lewy body dementia, Parkinson disease dementia, and mild cognitive impairment. The effect in mild cognitive impairment was noted more for those who also carry the apolipoprotein epsilon 4 allele. Donepezil should typically begin with a dose of 5 mg daily for 4 weeks, which is then increased to 10 mg daily. Both doses have clinical efficacy. For moderate to severe dementia, a 23 mg daily dose now available, which has a modest but statistically significant benefit over 10 mg daily dose.

**Rivastigmine (Exelon)**

Rivastigmine has FDA Indications for mild to moderate Alzheimer’s disease and mild to moderate Parkinson disease dementia. It has the strongest evidence based medicine for effect in Lewy body dementia. There is evidence in the literature for some effect in vascular dementia and other vascular cognitive disorders. There was one very small open label study in Frontotemporal Dementia. Rivastigmine is available in both oral and patch forms. While it was originally recommended as a 2 week titration schedule for the oral form, in clinical practice, a very slow titration from 1.5 mg BiD for 4 weeks then 3 mg BiD for 4 weeks, then 4.5 mg BiD for 4 weeks to the target of 6 mg BiD best avoids side effects, and the beginning dose is not effective. Oral effective doses are 3 mg BiD, 4.5 mg BiD and 6 mg BiD, with more effect seen for higher doses. The patch form has three different 24 hour doses, 4.6 mg, 9.5 mg, and 13.3 mg. The 4.6 mg/25 hour dose is a starting dose only, the 9.5 mg dose is equivalent in efficacy to the 6 mg BiD oral dose. The higher dose of 13.3 mg /24 hours is available for severe dementia and those who decline on the 9.5 mg/24 hour dose. Note that lower doses may need to be used for those who have low body weight (below 50 kg) as well as those with mild to moderate liver dysfunction or moderate to severe renal impairment.

**Galantamine (Razadyne, formerly Reminyl)**

Galantamine has FDA Indications for mild to moderate Alzheimer’s disease. There is evidence in the literature for some effect in vascular dementia and other vascular cognitive disorders. One study of Galantamine and MCI showed lower mortality rate in those in the placebo arm than those treated with galantamine, so off-label use at this time for MCI is discouraged, though this difference in mortality may be a statistical fluke. Galantamine comes in oral form, originally BiD dosing but now also has an extended release version (Razadyne ER). There is about two month titration. For the immediate release this would be 4 mg BiD for four weeks, 8 mg BiD for four weeks, then 12 mg BiD as target. For extended release the titration is 8mg daily for four weeks, then 16 mg daily for four weeks, then 24 mg daily thereafter. The first dose in both is subtherapeutic, with higher doses suggested to be more beneficial.

**Memantine (Namenda)**

Memantine is a weak NMDA antagonist with a FDA indication for moderate to severe Alzheimer’s disease. There is evidence in the literature for some effect in mild Alzheimer’s disease and vascular dementia and other vascular cognitive disorders. There is little information in Lewy body dementia. Memantine has two forms, immediate and extended release (XR). Titration of immediate release memantine is increased by 5 mg weekly to target of 10 mg BID, and titration of extended release memantine is increased by 7 mg weekly to target of 28 mg daily.
Ergoloid Mesylates (Hydergine)
Ergoloid Mesylates is a sympatholytic and metabolic ‘enhancer’. It is the third category of drug recognized by Center for Medicare and Medicaid Services for treatment of dementia. The FDA indication for ergoloid mesylates is Idiopathic cognitive decline in the elderly. There is some evidence in the literature for effect in vascular dementia and other vascular cognitive disorders, Alzheimer’s disease (less certain). In the United States it comes in 1 mg oral form. Original FDA indicated dose 1 mg PO TiD, but most studies suggesting efficacy have doses of 6.5 mg/day or higher.\(^\text{34}\) Beers Report suggested it is not proven useful, and may cause confusion. Main side effects are bradycardia, feeling of stuffy nose.

Medium Chain Tryglycerides (Axona)
Axona is a medical food FDA approved for ApoE 4 negative patients with Alzheimer’s disease. It is theorized to bypass glucose by raising levels of ketone bodies in the brain. The most common side effects are gastrointestinal – flatulence, diarrhea. The best way to avoid side effects is to take the supplement on a full stomach, mix it with a drink or soft food, and take slowly over 30 minutes.

References


