CHAPTER 20.

SENESCENCE AND DEMENTIA

"An old man is twice a child"
Shakespeare
(Hamlet)

SENESCENCE/AGING

Senescence (Latin, senex: "old man" or "old age") is the combination of processes which follow the period of development of an organism. Aging is generally characterized by declining ability to respond to stress and increased risk of disease. Accordingly, death may be seen as the inevitable consequence of aging. A controversial view is that aging is itself a "disease" which may be curable.

A related and interesting definition: **Aging** represents a state of complex multifactorial pathways that involve and ongoing molecular, cellular, and organ damage causing functional loss, disease vulnerability and eventual death (Fontana et al, 2010).

Memory loss is a less prominent feature of normal ageing than has sometimes been supposed. Healthy older people do not perform quite as well on objective memory tests as healthy younger people. However, **normal aging does not cause functional decline, and ability to perform the normal activities of daily living is maintained.**

As we get older we slow down both physically and mentally. It takes longer to do normal tasks, including mental tasks like calculations and solving puzzles. It also takes longer to interpret new information, particularly visual-spatial information – which explains why older drivers have more accidents at intersections than on the open road.

Executive function and the ability to put together the "big picture" also declines with age. Accordingly, older people may focus on 'insignificant' details. This may explain why some people who have functioned in highly demanding roles are "perfectly happy", in retirement, to occupy themselves with "odd-jobs about the house". In retirement, some people quip, "I'm so busy. I don't know how I ever found time for work". While these people may have filled their lives with many new activities, slowing down of mental functions and greater focus on details may also partly underpin this happy state of affairs.

Mild Neurocognitive Disorder

Mild neurocognitive disorder **(mild-NCD)** was introduced in DSM-5 to indicate conditions which have greater immediate and long term effects than normal aging.

When people with mild cognitive problems are followed up for 5 years, 80% have developed dementia (Godinho et al, 2011).

A recent study of people over 65 years found – cognitive impairment but no dementia, 14.7%; dementia, 4.3% (Rodriguez-Sanchez et al, 2011).

The clustering of white matter lesions (WML) in the temporal region identifies individuals at increased risk of both mild-NCD or dementia (Mortamais et al, 2013).

Apathy in mild-NCD and dementia is associated with abnormalities in the frontal regions and anterior cingulate (Stella et al, 2013).

A Diffusion Tensor Imaging (DTI) study (Fu et al, 2013) shows that individuals with mild-NCD and lower than normal 'fractional anisotropy' (a measure of membrane integrity) of the cingulate fasciculus are more likely to progress to dementia. (The cingulate fasciculus lies within the cingulate gyrus and can be considered part of the superior longitudinal fasciculus.)

There is a suggestion that physical activity may have neuroprotective effects for people with mild-NCD, but this remains to be confirmed (Barber et al, 2011).

DSM-5 criteria Mild-NCD

A. Evidence of mild cognitive decline from a previous level of performance in one or more cognitive domains (language, memory, social cognition etc)
    1. Concern of the individual or informant
    2. Modest impairment on testing
B. Deficits to not interfere with capacity for independence (paying bills, medication – but greater effort and strategies may be necessary).
C. Deficits not limited to periods of delirium
D. Deficits not better explained by another mental disorder

DEMENTIA

Dementia (Latin, de- "away" + mens "mind") causes distress to afflicted individuals and family members. It is costly for the community, and relatively unresponsive to current treatment. It is a common disorder and the prevalence is increasing. Dementia affects >1% of people aged 60-64, and the prevalence doubles every 5 years after 60 years of age, reaching 30-50% of people >85 years. The proportion of people surviving into old age is increasing, and it is this group which provides most cases of dementia.

Dementia is a set of symptoms, and like cough and fever, this set of symptoms may result from various disorders/diseases.

Impaired memory is a central feature of dementia. However, to meet diagnostic criteria, there must also be decline in one other area of cognition. The term cognition (Latin, cogito, "to think") refers to the human processing of information, and includes domains such as language, praxis, gnosis, visuospatial ability and executive function.

Particular types of dementia (vascular dementia, for example) have additional diagnostic criteria (focal neurological signs, in the case of vascular dementia).

Other diagnostic systems place greater diagnostic importance on the presence of "global deterioration in function" (including self-care and activities of daily living).

The "cognitive paradigm" is the view that memory and language disorders are the primary symptoms of dementia. However, recently much importance has been placed on the **behavioural and psychological symptoms of dementia (BPSD)** (Burns, 2009). The behavioural symptoms include screaming and wandering, the psychological symptoms include change in personality, delusions, hallucinations and depression. The BPSD present major management difficulties, and are frequently the main concern of carers.

The degree to which BPSD are simply manifestations of cognitive impairment remains unclear (Savva et al, 2009).

BPSD often characterise the different sub-types of dementia: vascular dementia (VaD), depression; Dementia with Lewy bodies (DLB), hallucinations and paranoid ideas; frontotemporal dementia (FTD), personality change; subcortical dementia, lack of initiation.

DSM-5 has replaced 'dementia' with the term Major Neurocognitive Disorder (major-NCD) – but 'dementia' as a term and a reality is likely to persist.

DSM-IV criteria Major-NCD

A. Evidence of significant cognitive decline from a previous level of performance in one or more cognitive domains (language, memory, social cognition etc)
    1. Concern of the individual or informant
    2. Substantial impairment on testing
B. The cognitive deficits interfere with independence in everyday activities (paying bills, managing medication.
C. Cognitive deficits interfere with independence in everyday activities
D. Not exclusively in the context of delirium

Treatable dementia

Less than 5% of cases presenting with dementia have a treatable cause. These include:

- Hypothyroidism
- Vitamin B 1 deficiency
- Vitamin B 12 deficiency
- Normal pressure hydrocephalus
- Space occupying lesion
- Pseudodementia (depression presenting as dementia)

Incurable dementia

Common

- Alzheimer's disease
- Vascular dementia
- Dementia with Lewy bodies (DLB)
- Frontotemporal dementia

Less common

- Creutzfeldt-Jacob disease
- Huntington's disease
- Parkinson's disease
- Head trauma

ALZHEIMER'S DISEASE (AD)

AD is characterized by **gradual cognitive decline**. It accounts for at least 60-70% (Lovestone, 2000) of all cases of dementia, and the **prevalence** is 4-8% of people above 65 years of age (Jacobson et al, 2005).

Alois Alzheimer (German; 1864-1915) described the first case of the disorder which bears his name: a middle-aged female who suffered cognitive loss, functional decline, delusions and hallucinations. At autopsy the brain was atrophied and microscopy revealed plaques and neurofibrillary tangles. While AD may occur in middle age, it is more common in old age. The clinical features reported by Alzheimer: cognitive and functional decline often combined with psychotic symptoms remain diagnostically important.

The **psychotic symptoms** of AD are difficult to quantify, they vary with the stage of the disorder, and it can be difficult to communicate satisfactorily with demented people. It is probable that hallucinations and delusions occur in 10-50% of people with AD. Hallucinations are more often visual than auditory, and the delusions are usually that people are entering the house or things are being stolen.

Depression is also common in AD, with major depressive episode being found in 10%, and some depressive symptoms in up to 80% of patients. A history of depression is a risk factor for AD.

There is a loss of awareness and a reduced ability to respond to the environment – thus, a change in **personality** occurs. Relatives often complain about the loss of sensitivity and manners and increased impulsivity in the patient. Aggression can be a problem.

Other **behavioural problems** include wandering (which make it difficult to keep the patient safe), altered sleep pattern (with more disturbed behaviour at night) and incontinence. Grunting and screaming may occur in the late stages.

Classification – Early/Late
Early-onset AD (EOAD) and late-onset (LOAD) are arranged around 65 years of age. They have different genetic contributions, and EOAD tends to have a more rapid course.

Investigations

- Urea and electrolytes
- Thyroid function tests
- B12 and folate
- FBE
- Syphilis serology
- EEG (usually abnormal in early AD, in contrast to frontotemporal dementia)
- CT (not considered essential)
- SPECT (where regional dementias are suspected). SPECT studies have 90-100% sensitivity in discriminating AD patients from healthy controls (Johnson et al, 1993).
- MRI (may help to exclude vascular dementia)

Pathology

The brain is lighter with more prominent sulci and enlarged ventricles. There is progressive loss of neurons and synapses with large numbers of extracellular amyloid plaques and intracellular neurofibrillary tangles.

Plaques are composed of peptides called amyloid beta (Aβ). Aβ is a section taken from amyloid precursor protein (APP). APP is a normal structure which penetrates neuron membranes and is important in neuron growth and post-injury repair. In AD, APP is cut into smaller pieces, including pieces of Aβ, which come together as clumps as senile plaques in the extracellular space.

Neurofibrillary tangles are composed of aggregation of tau protein. Neurons have an internal support structure of microtubules, which function as tracks, sending nutrients from the cell body along the axon and back. Tau is a protein which, when phosphorylated, stabilizes the microtubules. In AD the tau becomes hyper-phosphorylated and clumps together destroying the neuron transport system.

The regions of gray matter with the most marked cell loss are the basal forebrain, hippocampus, entorhinal, and temporal cortices. Research suggests (Braak & Braak, 1991) the neurodegenerative process begins with loss in the glutamaterigic pathways of the entorhinal cortex before extending to the hippocampus and amygdala and then more widely to neocortical and subcortical areas.

Certain neural populations are more vulnerable than others. It was observed, in the 1970s, that acetylcholine containing neurons of the basal forebrain (nucleus basalis of Meynert) are particularly susceptible. This led to the cholinergic hypothesis of AD, and the development of the first 'therapeutic agents' for AD. While still important the cholinergic hypothesis is now regarded as an oversimplification.

Tasting the future -
the details of the pathophysiology of AD remains unclear – many interacting pathways/systems are believed to be involved. The following are a taste and should NOT be learned:
Da Mesquita et al (2016) have suggested the importance of interplay between amyloidogenic pathway, neuroinflammation and the peripheral immune system.
Daulatzai (2016) suggested a fundamental role for inflammation and oxidative-nitrosative pathways.
Giri et al (2016) emphasise the interaction of the inflammatory response, lipid metabolism and endocytosis (a form of active transport in which a cell transports molecules into the cell by engulfing them).
Cardoso et al (2016) propose mitochondrial dysfunction.

Genetics

Genetic variation is an important contributor to the risk for AD, underlying an estimated heritability of about 70% (Avramospulos, 2009).

Early onset
A very small number of the total of AD cases are EOAD; these have autosomal dominant inheritance. The majority have mutations in one of three genes: 1) those encoding amyloid precursor protein (APP) and 2) presenilin 1 & 2 (PSEN1 & 2) – these increase the production of the protein Aβ which is the main component of senile plaques. These mutations have been found in only a few families around the world, and do not account for the majority of AD

Late onset
Most AD cases do not have autosomal-dominant inheritance and are termed sporadic AD (or LOAD), in which environmental and genetic factors play a role. The most prominent risk factor is the inheritance of the ε4 allele of the apolipoprotein E (APOE). The ApoE gene directs the production of apolipoprotein E, an agent involved in lipid transportation and the removal of dietary fats from the body. The ApoE gene exists in 3 forms: e2, e3, and e4. Everyone has two copies of the ApoE gene - some combination of the three forms. 40-80% of people with AD have at least one APOEε4 allele. This allele increases the risk of the disease by 3 times in heterozygotes and by 15 times in homozygotes.

There appears to be ethnic variation. The risk was initially thought to be higher in Hispanics than in Americans of African descent, and lowest of all among Caucasians. This observation is now being greatly qualified, perhaps because of the appearance of racism. Cognitive decline was found to be greater among African Americans than among Caucasians – when education and literacy were taken into account, the difference declined, but remained significant (Sachs-Ericsson & Blazer, 2005). On the other hand, some evidence indicates that the rate of cognitive decline in AD is slower in African Americans than non-African Americans (Barnes et al, 2005). In an epidemiology study of brain morphology, Hispanic and African American participants had larger relative brain volume and more severe white matter hyperintensity burden than white participants (Brickman et al, 2008).

Epigenetics

Not surprisingly, this relatively new field is promising much in the detection and treatment of AD (Veerappan et al, 2013; Maloney and Lahiri, 2016).

Treatment

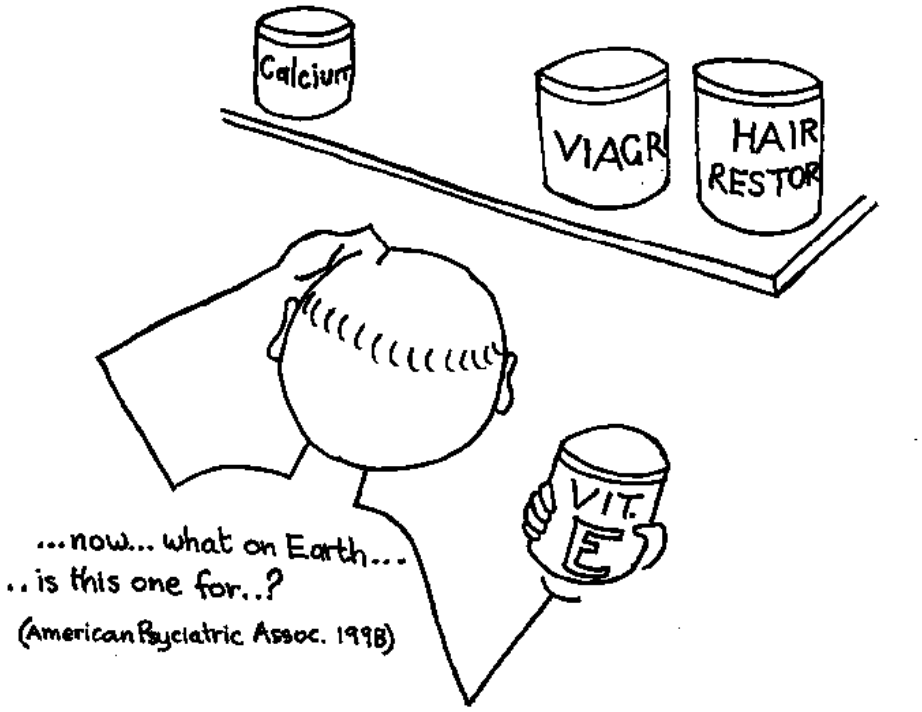
The aim of treatment, at this point is to improve/maintain the quality of life. Services seek to provide an environment which is comfortable, stimulating and safe. Optimally, behavioural disturbances can be managed by non-pharmacological means. Pharmacological agents may be helpful for some symptoms or behaviours. Specialist day-care is appropriate for many patients. It is important to help the family deal with their physical and emotional load. Carer driven organizations may provide support and resources, and they are politically effective.

Pharmacological treatment has been very disappointing. There was great interest in developing pharmacological agents to prevent the breakdown of acetylcholine (cholinesterase inhibitors). The first agents appeared 20 years ago, but had severe, potentially fatal side-effect profiles.

Donepizil became widely available more than a decade ago, and has more acceptable side effects (nausea, vomiting, diarrhoea, abdominal pain, anorexia, dizziness). Studies have indicated that donepezil improves cognitive function, activities of daily living and behaviour, and may delay the progress of dementia. However, debate continues as the treatment effects are small and not always apparent in practice (Rodda and Walker, 2009).

Ravastignine, a cholinesterase inhibitor in transdermal patch and capsule form, appears to be useful (Farlow et al, 2011).

Memantine, an NMDA receptor (a glutamate receptor) antagonist/blocker appears to provide benefit in AD (Winblad & Jelic 2003).



Vitamin E may have a preventative role (American Psychiatric Association, 1998). Confirmation is awaited.

Non-steroidal anti-inflammatory drugs may have a preventative function, but a large recent study was discontinued because of unacceptable cardiovascular side effects.

Estrogen therapy has also been suggested as a prophylactic, particularly in menopausal women, but the evidence is not convincing (Barrett-Connor and Laughlin, 2009).

VASCULAR DEMENTIA (VaD)

The **diagnosis** of vascular dementia (VaD) depends on the cognitive disturbances listed above and the presence of significant cerebrovascular disease. What is "significant" is not always straightforward, however, as >90% of healthy elderly individuals have evidence of vascular pathology on MRI (Kertesz et al, 1988).

Cerebral vessel disease is also frequently present in AD (Arvanitakis et al, 2016).

The **prevalence** of VaD is 1.2-4.2% in people above 65 years (Hebert and Brayne, 1995). AD is more common in Western countries, with VaD being more common in Japan, China and Russia.

Dementia is diagnosed in >30% of people three months after acute stroke (lesion location is important). Left hemisphere strokes are more likely to produce dementia. However, VaD may develop in the absence of clinical stroke (Sachdev et al, 1999).

Brain parenchymal **pathology** may occur through ischaemia, haemorrhage or oedema. The vascular pathology may include atherosclerosis, arteriosclerosis, lipohyalinosis, amyloid angiopathy, and senile arteriolar sclerosis. Systemic causes include inflammatory diseases, hyperviscosity syndromes and embolic disorders.

The **clinical** diagnosis of VaD vs AD is based on:

- Sudden onset
- Occurrence of one or more strokes
- Neurological abnormalities
- Tendency to fluctuating course with day-to-day improvement
- Stepwise progression
- Labile emotional state
- Tendency for retained insight
- Hypertension
- Evidence of coronary or other major arterial disease

The **prognosis** of VaD is less favourable than AD, with a 5 year mortality of >63% (compared to AD <32 %; Brodaty et al, 1993).

Treatment and prevention are major tasks. Reduction in the prevalence of vascular dementia will require reduction in the rate of cerebrovascular disease. The following are indicated:

- Treat hypertension effectively
- Treat diabetes effectively
- Control hyperlipidemia
- Cease smoking and reduce alcohol intake
- Prescribe anticoagulants for atrial fibrillation
- Antiplatelet therapy for high risk patients
- Carotid endarterectomy for severe carotid stenosis
- Weight loss
- Regular exercise
- Reduce salt intake
- Reduce stress
- Intervene early for stroke and transient ischaemic attack
- Intensive rehabilitation following stroke

DEMENTIA WITH LEWY BODIES (DLB)

Dementia with Lewy bodies (DLB) is incompletely understood. On histological examination, all patients with Parkinson's disease (PD) and DLB, and 40% of patients with AD have Lewy bodies.

Frederick Lewy first described Lewy bodies, eosinophilic, round, cytoplasmic inclusions, in the cells of the substantia nigra in patients with PD in 1914.

Autopsy studies indicate the DLB accounts for around 5% of all dementias in older patients (Hogan et al, 2016a). Similar rates have been observed in the US, Europe and Japan. DLB is slightly more common in males.

Symptoms range from parkinsonian features, such as loss of spontaneous movement (bradykinesia), rigidity (muscle stiffness), tremor, and shuffling gait, to AD-type symptoms including memory loss, acute confusion, and fluctuating cognition. Visual

hallucinations may be one of the first symptoms (44%), other psychiatric symptoms include delusions and depression (34%, Auning et al, 2011).

At the present time a 1 year rule is used to differentiate patients with DLB from PD with dementia. If PD has been present for 1 year or longer before cognitive impairment, the disorder is termed PD with dementia, otherwise it is designated DLB.

Olfactory tests may be a useful tool in predicting dementia in Parkinson's disease (Takeda et al, 2013).

In **pathological** studies of DLB, LBs are found in nonpyramidal cells in layers V and VI of the cortex. LBs are also found in both DLB and PD, in the substantia nigra (and often other structures including the locus ceruleus, substantia innominata and the dorsal motor nucleus of the vagus).

Genetics: approximately 25% of cases carry a pathogenetic mutation or risk variant of APP, glucosylceramidase beta **(**GBA) or PSEN1 (Geiger et al, 2016).

Prognosis is poor. DLB is a slowly progressive disorder for which there is no cure.

Treatment also offers challenges. Antiparkinsonian medication which may help reduce tremor and improve movement may worsen hallucinations and delusions. Antipsychotic drugs which may reduce psychiatric symptoms may markedly worsen movement symptoms. There is evidence the acetylcholinesterase inhibitors may decrease psychiatric symptoms, including apathy, anxiety, hallucinations and delusions. Depression may respond to SSRIs, which do not appear to introduce particular complications.

FRONTOTEMPORAL DEMENTIA (FTD)

FTD is a heterogeneous group of disorders, with some clinical features in common. It was described by Pick (Pick's disease) in 1892, and has characteristic histopathology ("ballooned" neurones - Pick's cells, and argentophilic globes - Pick's bodies). It is quite rare, representing about 1% of post-mortem verified dementia – however, the prevalence is not clear, and FTD may be responsible for 2.7% % of all dementia (Hogan et al, 2016b). The onset may be early (35 years), and is rarely after 70 years of age.

The frontal and temporal lobes control personality and speech. Accordingly, early **clinical presentation** is characterized by changes of personality and behaviour, affective symptoms and progressive reduction of expressive speech.

There is loss of personal and social awareness, with neglect of personal hygiene and grooming, tactlessness and antisocial behaviour. There may be inappropriate sexual advances, impulsive shopping and shoplifting. There is inattentive and carelessness and driving should cease.

There may be stereotyped and perseverative behaviour: wandering, clapping, humming, dancing and hoarding of objects. There may be imitative behaviour, seen as the repetition of other people's gestures and utterances. There may be a strong urge to explore the environment by touching and placing objects in the mouth.

Spontaneous speech reduces, and there is frequent word finding difficulty. There is over use of particular phrases, and there may be echolalia. Eventually, the patient becomes mute.

Epigenetic factors are likely important (Veerappan et al, 2013; Banzhaf-Strathmann et al, 2013).

Treatment: patients may be extremely sensitive to psychotropic medication; disturbing side-effects and paradoxical reactions are relatively common. There is a need for physical activity and the memory is comparatively preserved, so that supervised outings may be possible. Time needs to be well-structured, with consideration to the patient's premorbid personality and interests.

A middle-aged well-to-do man in the author's home city developed FTD. He continued to wear expensive suits and was often seen, up to his shoulder, feeling around in rubbish bins on street corners. When one asked if he had lost something and whether one could be of any assistance, he would look back blankly, but utter no words. This was disinhibited, out or character behaviour. It had elements of "a strong urge to explore the environment" and perhaps, hoarding. Needless to say, it was humiliating for the individual's family to have him behaving in this manner. The man himself, however, did not appear to be self-conscious or distressed. He was later met by the author in a specialized dementia unit.

INITIAL COGNITIVE TESTING

Neuropsychological testing has a place in the comprehensive assessment of many people with dementia. In the initial assessment, a simple tool allows a degree of quantification.

Abbreviated mental test score (AMTS)

The AMTS (Hodkinson, 1972) is probably the briefest. It consists of 10 questions. If the patient scores 6 or less correctly, there is a need for further assessment. Make sure the patient is not delirious and is able to attend to the task.

Question	Score
What is your age?	
What is the time to the nearest hour?	
Give the patient an address, and ask him or her to repeat it at the end of the test	
What is the year?	
What is the name of the hospital or number of the residence where the patient is situated?	
Can the patient recognize two persons (the doctor, nurse, home help, etc.)?	
What is your date of birth?	
In which year did the First World War begin (adjust this for a world event the patient would have known during childhood)?	
What is the name of the present monarch (head of state, etc.)?	
Count backwards from 20 down to 1.	

Mini mental state examination (MMSE)

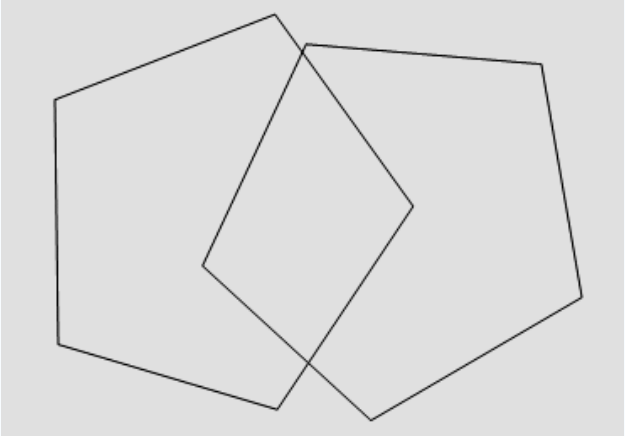
The mini mental state examination (MMSE; Folstein et al, 1975) is the most commonly used cognitive screening test. It is a 30-point questionnaire which samples memory and orientation, language and constructional skills. A printable version is freely available at www.cnsforum.com.

Any score over 24 is considered normal. Take schooling and background into account. A score below 24 suggests cognitive impairment. Make sure the patient is not delirious (can attend to the task at hand) and has no visual, hearing or physical difficulties.

The MMSE

- *Orientation in time:* what is the year, month, date, season, day of the week?(1 point each, total 5)
- *Orientation in place:* in which state, county, town/city, hospital/street, floor/number are you now? (1 point each, total 5)
- *Registration:* repeat these three words - e.g. car, ball, key (1 point for each, total 3)
- *Arithmetic:* "serial sevens" -- take 100 and subtract 7 in 5 iterations - 100, 93, 86, 79, 72, 65 (1 point for each, total 5)
- *Recall/memory:* repeat the three words from before (1 point each, total 3)
- *Language:* (total 8)
    - name these objects - e.g. key, watch (1 point for each, maximum 2).
    - repeat "NO IFS, ANDS OR BUTS" (1 point for correctly repeating)
    - follow a three-stage instruction - take this sheet of paper, fold it over once, and put it on your lap (1 point each, total 3)
    - read and obey "CLOSE YOUR EYES" (1 point for closing eyes)
    - write a sentence (1 point for a grammatically correct sentence)

- *Spatial insight*: copy out a drawing of two interlocking pentagons (1 point for correct drawing)



Interlocking pentagons used for the last question

SUMMARY OF DIFFERENTIAL FEATURES

Alzheimer's disease (AD)	Cognitive impairment: Anterograde amnesia (inability to learn and retain new information), Plus impairment in one of the following: Reasoning Visuospatial ability Orientation Language
Dementia with cerebrovascular disease (VaD)	Cognitive impairment as for AD Plus evidence of cerebrovascular disease
Dementia with Lew bodies (DLB)	Cognitive impairment as for AD, Plus to of the following: Parkinsonism Visual hallucinations Fluctuations in arousal REM sleep behavior disorder. Also, there may be delusions
Frontotemporal dementia (FTD)	Either of the following: 1. Decline in regulation of personal or interpersonal conduct (loss of empathy for others; socially inappropriate behavior that are rude, sexually explicit; mental rigidity; decline in personal hygiene; obsessional behaviors), or 2. Impaired reasoning or handling of complex tasks, out of proportion to impairments of recent memory or spatial ability. Also, there is often rapid decline in language skills

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