

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.

As people 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 people 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.

The term “benign senescence” has recently been replaced by mild cognitive impairment (MCI). These terms were coined to describe memory loss which was supposed to accompany normal aging. However, when people with MCI are followed up for 5 years, 80% have developed dementia.

Thus, memory loss is a less prominent feature of ageing than has 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.

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

treatment. It is a common disorder and the prevalence is likely to increase. Dementia affects >1% of people aged 60-64, and the prevalence doubles every 5 years after 60 years, reaching 30-50% of people >85 years. The proportion of people surviving into old age is increasing, and it is this group in 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 be also 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, visuoconstructive ability and executive function.

The DSM has published the following key diagnostic criteria for dementia. Particular types of dementia (vascular dementia, for example) have additional diagnostic criteria (focal neurological signs, in the case of vascular dementia) attached.

The DSM-IV criteria

- A. The development of multiple cognitive deficits manifested by both
 - 1) memory impairment (impaired ability to learn new information or to recall previously learned information)
 - 2) one (or more) of the following cognitive disturbances:
 - a) aphasia (language disturbance)
 - b) apraxia (impaired ability to carry out motor activities despite intact motor function)
 - c) agnosia (failure to recognize or identify objects despite intact sensory function)
 - d) disturbance in executive function (i.e., planning, organizing, sequencing, abstracting)
- B. The cognitive deficits cause significant impairment in social or occupational functioning and represent a significant decline from a previous level of functioning.

Other systems place greater diagnostic importance on the presence of "global deterioration in function" (including self-care and activities of daily living; although these can be conceptualized as a consequence of cognitive deficits). Change in personality (often toward apathy and irritability) and behavioural disturbances are common early symptoms. Delusions (often of people breaking in, or stealing belongings) are also common features.

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)

Untreatable 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.

Experts differ as to whether AD is diagnosed as a “positive process” (Lovestone, 2000) or through the process of exclusion - made only after the exclusion of other forms of dementia (DSM-IV).

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 delusions are usually of 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.

As there is a loss of awareness and a reduced ability to respond to the environment, 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.

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 the presence of large numbers of extracellular amyloid plaques and intracellular neurofibrillary tangles.

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 glutamatergic 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.

Interestingly, a century after first identification, the significance of senile plaques and neurofibrillary tangles to the dementia of AD remains unclear. It is proposed they be the products rather than the cause of a degenerative process (Armstrong, 2006).

A current theory is that interleukin-1 drives the neuropathological changes of AD (and Lewy Body Dementia; Griffin et al, 2006).

Genetics

Three genes (presenilin-1 (PSEN1), PSEN2, and amyloid precursor protein (APP)) are associated with rare forms of Early Onset Familial Alzheimer's disease (EOFAD). Certain mutations in each of these genes are autosomal dominant and cause AD in anyone who carries them. There is a 50% chance that the mutation will be passed from the carrying/affected parent to any child. These mutations have been found in only a few families around the world, and do not account for the majority of AD.

Other genes which increase the risk of AD may be more widely distributed. The ApoE gene directs the production of apolipoprotein E, an agent involved lipid transportation and the removal of dietary fats from the body. ApoE gene normally exists in 3 forms: e2, e3, and e4. Everyone has two copies of the ApoE gene in some combination of the three forms. ApoE e4 has been associated with an increased risk of AD.

There is ethnic variation. The risk of in Hispanics is 2 times greater and that of Americans of African descent is 4 times greater than that of Caucasians.

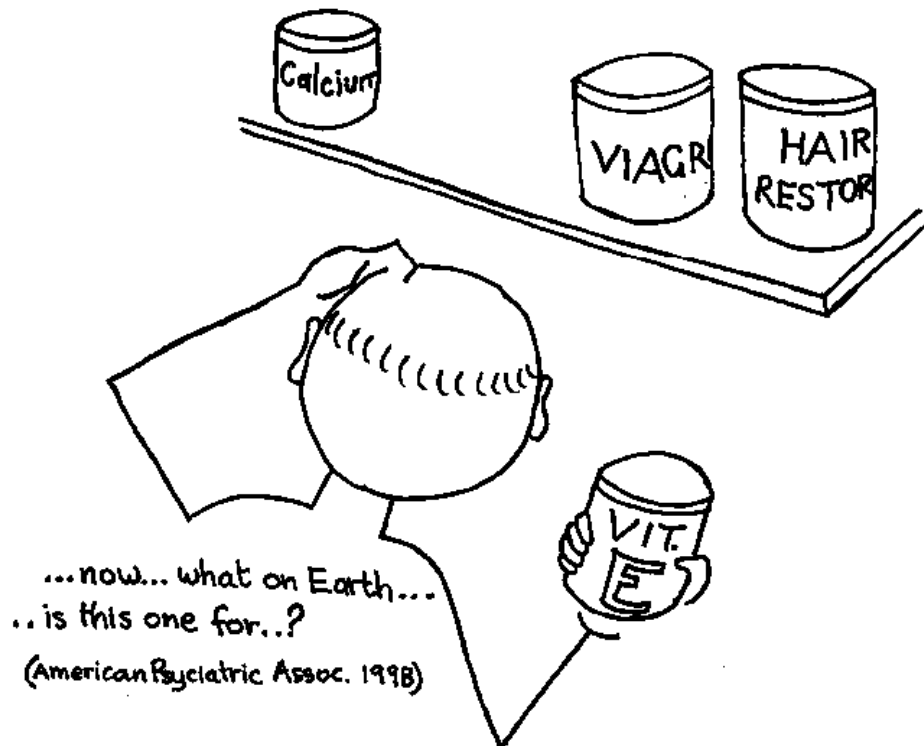
Treatment

The aim of treatment, at this point in time is to improve/maintain the quality of life of the patient. 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.

There has been great interest in developing pharmacological agents to prevent the breakdown of acetylcholine (cholinesterase inhibitors). A number have become available. Donepezil and galantamine are examples. Studies have indicated that for patients with dementia, donepezil improves cognitive function, activities of daily living and behaviour. However debate continues as the treatment effects are small and not always apparent in practice (Birks & Harvey, 2006).

Glutamate induced excitotoxicity is thought to play a critical role in the neurodegenerative process in AD (and other disorders, including PTSD). Memantine, an NMDA receptor (a glutamate receptor) antagonist appears to provide benefit in AD (Winblad & Jelic 2003).

There is some evidence non-steroidal anti-inflammatory drugs and vitamin E have a preventative role (American Psychiatric Association, 1998). Confirmation is awaited.



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).

25-35 % of patients with dementia have cerebral ischaemic lesions that are a major factor in the dementing process.

The **prevalence** of VAD is 5.6% in people above 60 years. 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. Not all stroke patients develop dementia, indicating that lesion location is important. Left hemisphere strokes are more likely to produce dementia. 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 a topic of controversy. It is not yet understood whether DLB is a distinct clinical entity or perhaps a variant of Parkinson's disease (PD) or AD. On histological examination, all patients with PD and DLB, and 40% of patients with AD have LBs.

Frederick Lewy first described Lewy bodies, eosinophilic, round, cytoplasmic inclusions, in the cells of the substantia nigra in patients with PD in 1914. Later that century LBs were described in the cortex of a small number of patients. However, a couple of decades ago, advanced pathological methods revealed LBs are common in people with dementia.

Autopsy studies indicate the DLB accounts for around 15% of dementias. 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. Other psychiatric symptoms include delusions and depression.

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.

In **pathological** studies, LBs are found in both PD and DLB, in the substantia nigra (and often other structures including the locus ceruleus, substantia innominata and the dorsal motor nucleus of the vagus). LBs are found in the cortex of many people with PD and all people with DLB.

In DLB, LBs are found in nonpyramidal cells in layers V and VI of the cortex.

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)

Frontotemporal dementia (FTD) is a heterogeneous group of disorders, with some clinical features in common. The first was described by Pick (Pick's disease) in 1892, and has characteristic histopathology ("ballooned" neurones (Pick's cells) and argentophilic globes (Pick's bodies)). This archetypal FTD is, however, quite rare, representing about 1% of post-mortem verified dementia. The prevalence of FTD is not clear, but it may be responsible for 5 % of all dementia. The onset may be early (35), 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.

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 of 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.	

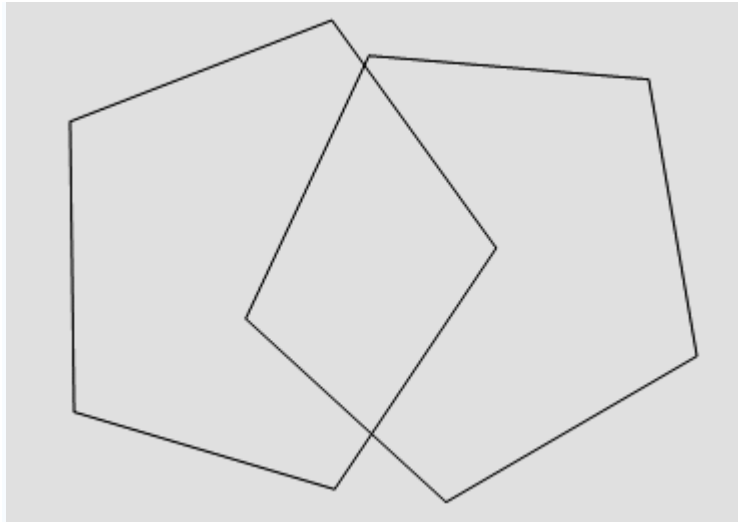
Mini mental state examination (MMSE)

The mini mental state examination (MMSE; Folstein et al, 1975) is the most commonly used cognitive screening test. It is a 30-point questionnaire test 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

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