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Dementia: Module 2

Ageing and prevention of age-related cognitive impairment

Based on a talk at the Cipla Psychiatry Forum, Kleinmond, Cape Town, 11-13 October 2019

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LEARNING OBJECTIVES

You will learn to:

1. Understand the causes and neuropathology of dementia
2. Understand the hallmarks of ageing
3. Develop an approach to healthy ageing and preventing or slowing the development of age-related cognitive decline.

Click here – you need to watch the video in order to complete the CPD questionnaire.

Introduction

Every five years, in those between the ages of 50 and 80 years, the prevalence of dementia approximately doubles.[1] The most prevalent form of dementia is Alzheimer's disease (AD), which accounts for 60-80% of cases. However, fewer than half of these patients are expected to have pure AD, and the majority are likely to have mixed dementia.[2] Whereas around 3% of individuals between the ages of 65 and 74 years are estimated to be affected, the prevalence increases to approximately 20% in those aged 75-84 years and can be as high as 47% among people older than 85 years.[2-4] Furthermore, because the world's population is ageing, the prevalence of dementia is expected to increase dramatically in the future. Dementia before the age of 50 is rare, occurring in fewer than one in 4 000 individuals.

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Causes of dementia

In the *DSM-5*, the term 'dementia' has been replaced with 'neurocognitive disorder' (NCD), which begins with delirium, followed by syndromes of major NCD, minor NCD and their aetiological subtypes (Table 1).[5] In South Africa, HIV is the most common cause of NCD.

Table 1. Aetiological subtypes of major and minor NCD according to the *DSM-5*[5]

• Alzheimer's disease	• Prion disease
• Frontotemporal lobar degeneration	• Parkinson's disease
• Lewy body disease	• Huntington's disease
• Vascular disease	• Another medical condition
• Traumatic brain injury	• Multiple aetiologies
• Substance/medication use	• Unspecified
• HIV infection	

Alzheimer's disease

Dementia is a disease of ageing

Neuropathology

AD is a progressive neurodegenerative disease characterised by a mixed proteinopathy (amyloid plaques and tau), neurofibrillary tangles and neuronal loss with atrophy of the cortices, amygdala and hippocampus.[2] The exact aetiology is unclear. However, AD is generally considered a multifactorial disease, resulting from interactions between factors, including age, education, genes and environmental influences.[6] The amyloid cascade hypothesis has been widely accepted to explain the mechanisms of AD pathogenesis. It posits that deposition of amyloid-β protein (AβP), the main component of plaques, is the causative agent of AD pathology and that the neurofibrillary tangles, cell loss, vascular damage and dementia follow as a direct result of this deposition. However, recent research indicates that the pathophysiology is more complicated than this and that AβP accumulation does not correlate with neuronal loss and cognitive decline.[7] Many individuals who do not have memory impairment have a significant amyloid plaque burden that can be demonstrated on a positron emission tomography (PET) scan, and potential treatments that target AβP have proved to be disappointing. In reality, a combination of multiple proteins, protein fragments, inflammation, apoptosis and neuronal loss are likely to play a role in the pathogenesis. Furthermore, AD is frequently associated with other age-related co-pathologies, which together with mixed proteinopathy confound both pathological diagnosis and the development of effective treatments.[2,7]

Genetics

Dominantly inherited familial AD is a rare form of AD, accounting for less than 1% of cases. It presents very early in life, from age 20 years, with a mean age of onset of around 46 years. It is associated with various mutations in three specific genes - amyloid precursor protein (*APP*), presenillin (*PSEN*) *1* or *PSEN2*.[2] *PSEN1* and *PSEN2* are mostly inherited in an autosomal dominant pattern and these genes are associated with an inevitable increase in relative levels of AβP42 peptide and early-onset AD.[8] This is defined as presentation before 65 years of age and

it often has an atypical presentation and aggressive course. It accounts for less than 5% of AD cases.

Genetic risk factors have been associated with sporadic late-onset AD. The most important is apolipoprotein E (APOE). APOE encodes three alleles (ε2, ε3 and ε4). It regulates lipoprotein metabolism and plays important roles in cholesterol transport, neuroplasticity and inflammation in the central nervous system. APOE binds to AβP, influencing the clearance of soluble AβP and the AβP aggregation, and it plays a role in the regulation of AβP metabolism.[9] The ε4 allele has the strongest association with AD risk, where heterozygotes are three times more likely and homozygotes 12 times more likely to develop AD than individuals without the gene.[2] The ε*3* allele is also associated with cerebrospinal fluid (CSF) AβP42 and tau levels, but the ε*2* allele is protective.[9] However, not all people with AD have the APOE4 gene and the population-attributable risk associated with this allele is estimated at 20%.[8] While many other genes that play roles in cholesterol metabolism, immune response, endocytosis and other metabolic processes have been implicated in the risk for AD, their exact role in its pathogenesis remains to be determined.[9]

Biomarkers

Biomarkers for AD have been identified in the CSF and on imaging studies (Table 2). However, their main utility is to determine the specific cause or causes of cognitive symptoms, rather than to diagnose the presence of cognitive decline or dementia.[6]

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Table 2. Biomarkers and imaging for AD diagnosis

• CSF biomarkers – AβP42 and tau proteins – Candidate biomarkers: amyloid-β oligomers and synaptic markers
• Magnetic resonance imaging and fluorodeoxyglucose PET
• Amyloid PET
• Tau PET

Ageing and AD

The most important risk factor for AD is advancing age. Ageing involves a progressive decline in physiological function leading to decreased rates of survival and reproduction and ultimately death. Understandably, in an attempt to slow down ageing, prevent age-related illnesses and increase longevity, much effort is being invested into research on how and why human beings age.

Ageing is polygenic and associated with nine key metabolic characteristics (Table 3).

Cell senescence is a consequence of exposure to intrinsic and extrinsic ageing factors, and is characterised by gradual accumulation of DNA damage and epigenetic changes that affect correct gene expression and lead to altered cell function.

Table 3. Nine metabolic hallmarks of ageing[10]

1.	Damage to the DNA accumulates over time, causing genomic instability (mutations accumulate in nuclear DNA, in mitochondrial DNA and in the nuclear lamina)
2.	Telomere attrition
3.	Epigenetic alterations (DNA methylation)
4.	Loss of proteostasis
5.	Deregulated nutrient sensing
6.	Mitochondrial dysfunction
7.	Cellular senescence
8.	Stem cell exhaustion
9.	Altered intercellular communication

Three main metabolic pathways influence the rate of ageing:

- FOXO3/Sirtuin pathways (involved in genomic stability, trophic and bioenergetics pathways). They are probably responsive to caloric restriction.
- Decline in the growth hormone/insulin-like growth factor 1 signalling pathway.
- Mitochondrial dysfunction (e.g. in the mitochondrial electron transport chain). Free radicals produced by mitochondrial activity damage cellular components.

It is likely that most of these pathways affect ageing separately, because targeting them simultaneously leads to additive increases in lifespan. Various factors, however, regulate ageing at a cellular level.

Ageing is associated with neurodegeneration. The brains of 90-year-olds weigh just over 10% less than those of 50-year-olds. Nevertheless, brain changes associated with ageing and cognitive decline are complex and variable. Abnormal accumulation of tau, amyloid-β or deposits of α-synuclein can be demonstrated in almost all brains of cognitively unimpaired individuals and CSF biomarkers for AβP and tau and PET imaging are positive in approximately 30%. Conversely, in approximately 10% of elderly people with clinically diagnosed dementia, pathological features may be absent (Figure 1).

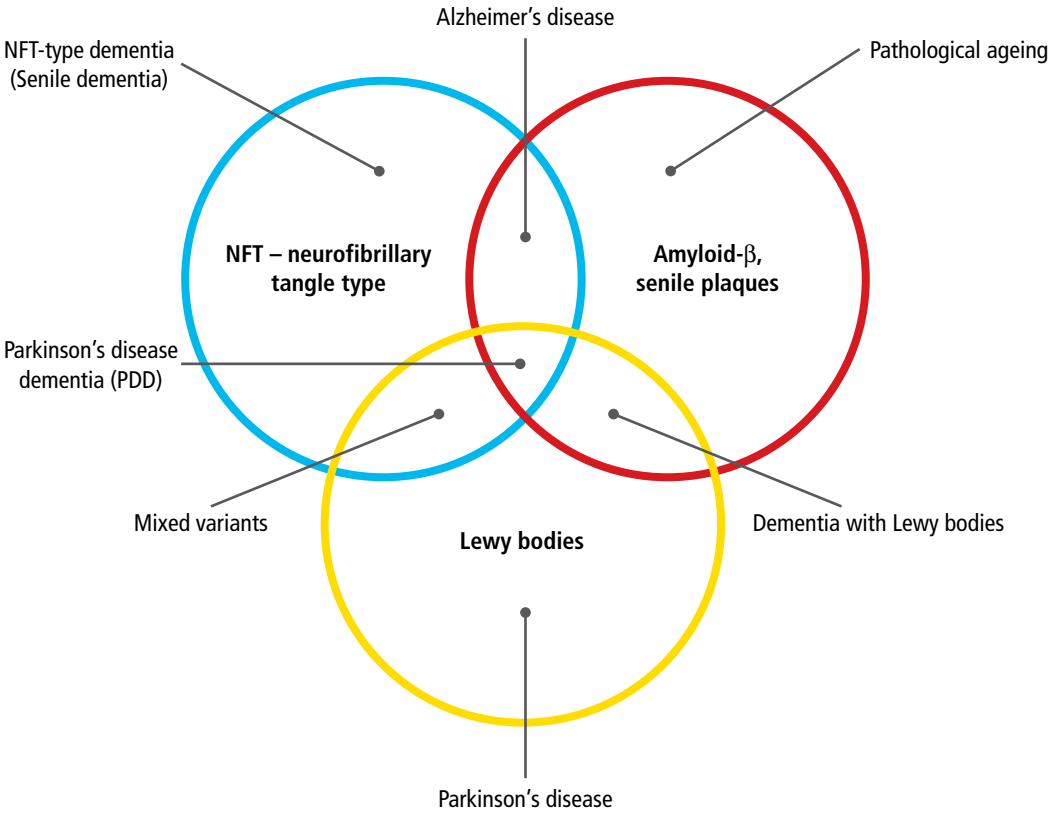

Figure 1. Overlap between ageing and neurodegeneration

Inflammation has long been associated with neurodegeneration. Immune factors that might be part of systemic low-grade inflammation, such as that associated with chronic stress, probably play an important role in ageing – an association that has been termed 'inflammageing'. The use of nonsteroidal anti-inflammatory drugs for several years before onset of clinical symptoms is associated with a reduced risk for AD, although exactly how inflammation contributes to AD is unclear.

Finally, genes play an important role in ageing and longevity. Exceptional longevity has been linked to specific genes including the *TOMM40-APOE-APOC1* locus, and other strong links are observed at genes such as *FOXO3* and *IL6*. Conversely, mutations in the *LMNA* gene are associated with Hutchinson-Gilford progeria, which is characterised by profoundly accelerated ageing.

Early diagnosis and treatment of mild cognitive impairment

Early diagnosis of mild cognitive impairment (MCI) allows timeous intervention to help prevent further damage and slow cognitive decline, as well as time for the family to plan ahead while the patient can still engage in shared decision-making, sign paperwork and appoint a durable power of attorney.

Reversible causes of MCI (Table 4) must be addressed; lifestyle modifications that have been shown to help slow cognitive decline (e.g. mental stimulation, playing an instrument, socialising) should be encouraged and cognitive-enhancing medications (e.g. donepezil, rivastigmine, galantamine, memantine) should be started as early as possible.

Table 4. Reversible causes of mild cognitive impairment

• Polypharmacy	• Dehydration
• Hypotension and orthostatic hypotension	• Sensory loss (visual and hearing impairment)
• Depression	• Obstructive sleep apnoea
• Hypothyroidism	• Normal-pressure hydrocephalus
• Vitamin B_{12} deficiency	• Atrial fibrillation
• Hypo- and hyperglycaemia	• Infection

Future medical therapies

There are a variety of treatments under investigation for the treatment of AD. They include the following:

1. Monoclonal antibodies to prevent amyloid-β from clumping into plaques or to remove amyloid-β plaques.
2. Fyn protein inhibition. Fyn is a protein that interacts with amyloid-β. Overactivation of Fyn that has combined with amyloid-β causes synapse destruction.
3. Amyloid-β production blockers. Amyloid-β is produced in two steps from a parent protein. This process can be blocked by drugs that inhibit β- and γ-secretase.
4. Tau aggregation inhibitors and tau vaccines may be able to prevent tangling of tau.
5. Anti-inflammatory agents, such as sargramostin.
6. Targeting insulin resistance might be a feasible way to reduce cognitive impairment in some individuals, although trials to date have been disappointing.
7. The relationship between old and new drugs and lifestyle factors that modulate cardiovascular risk factors (e.g. hypertension, diabetes, cholesterol, heart disease, stroke) and MCI is under investigation.
8. Hormones. Oestrogen-based hormone therapy for at least a year during early menopause appears to offer some protection against MCI.

Lifestyle factors associated with longevity

The Blue Zones project was a joint project between *National Geographic* and the National Institute on Ageing (USA). The aim was to find the five demographically confirmed, geographically defined areas with the highest percentage of centenarians and to identify the lifestyle characteristics that might explain longevity.[11] The specific areas were Loma Linda, California, USA; Nicoya, Costa Rica; Sardinia, Italy; Ikaria, Greece; and Okinawa, Japan. They shared nine specific characteristics (Table 5).

Table 5. Blue Zones: Lifestyle factors common to geographic areas with the greatest longevity[11]

1.	Environment requiring an unavoidable natural physical activity (e.g. growing gardens) and an absence of mechanical conveniences for house and yard work;
2.	Sense of purpose ('Why I wake up in the morning);
3.	Routines to relieve stress (e.g. meditation, prayer, napping, happy hour); work less, slow down, take vacations;
4.	80% rule: discontinue eating when stomach is 80% full; the last meal of the day is the smallest;
5.	Most diets are predominantly plant-based, including beans in particular; meat is eaten sparingly, on an average no more than five times a month;
6.	Alcohol in moderation, preferably red wine;
7.	Membership of a faith-based community;
8.	Putting family first: keeping ageing parents nearby, having a life partner and investment in children with time and love;
9.	Healthy social network, long-standing friends.

Exercise is an important part of a healthy lifestyle. It is cardioprotective, improves cardiorespiratory fitness, prevents sarcopenia, improves bone mass and bone mineral density, and may preserve telomere length.

Healthy eating habits can not only reduce obesity and the development of lifestyle-associated diseases, such as cardiovascular disease and type 2 diabetes mellitus, but may also help to preserve cognitive function. Patients should be given practical dietary instructions on how to implement a culturally acceptable, practical, affordable and sustainable anti-inflammatory, Mediterranean-type or MIND (Mediterranean-DASH Intervention for Neurodegenerative Delay) diet. These diets encourage consumption of fresh fruit and vegetables and avoidance of processed foods (Table 6). Specific dietary factors that might be associated with a reduced risk for AD are listed in Table 7.

More information about healthy eating can be found at: http://www.nutritious-foodculture.com.

Table 6. Examples of foods appropriate to an anti-inflammatory eating plan[12]

Consume more of:	Consume less of:
• Green leafy vegetables	• Red meats
• Other colourful vegetables, including beans, squash, broccoli, carrots, celery	• Omega-6 (vegetable oils)
• Nuts and seeds	• Saturated and trans fats
• Fruit and berries (fresh fruit is encouraged)	• Butter and stick margarine
• Whole grains	• High-glycaemic and refined carbohydrates (e.g. grains and starches)
• Omega-3, fish	• Pastries, chips and sweets
• Yoghurt, fresh cheese (e.g. ricotta, mozzarella, cottage cheese)	• Processed meats
• Poultry, lean meat, eggs	• Fried/fast foods
• Extra-virgin olive, canola oils	• Alcohol
	• Caffeine
	• Foods with added sugar/fructose syrup and/or salt

Table 7. Specific nutrients and foods that may reduce the risk of cognitive decline and AD

1. Antioxidants
   - Vitamins E, C and β-carotene
   - Polyphenols (figs, blackberries, black currants, blueberries, strawberries, bilberries, mulberries)
   - Red wine
   - Resveratrol
   - Ginkgo biloba
2. Polyunsaturated fatty acids: omega-3 fatty acids (fish)
3. Extra-virgin olive oil
4. Coffee
5. Magnesium and calcium
6. *Crocus sativus* (saffron)
7. Curcumin
8. Genistein (soy isoflavone)
9. Folate and vitamins B_6 and/or B_{12}
10. Luteolin
11. Caprylidene and coconut oil
12. Selenite
13. Rosmarinic acid and methyl caffeate

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Conclusions

A healthy lifestyle can not only prevent chronic illness, but also reduce the risk for and slow the decline of age-related cognitive impairment. The Blue Zones project in particular has provided an insight into what the world's oldest people are doing to stay healthy and live longer. For the most part, these habits are simple and should be encouraged in everybody. It may, however, be even more important to teach them to children so that they can be started early and continued throughout life.

KEY LEARNINGS

- There are different aetiological subtypes of major and minor NCD
- The exact aetiology of AD is unclear, but it is generally considered to be multifactorial with advancing age being the most important risk factor
- Ageing is associated with neurodegeneration; early diagnosis of MCI allows timeous intervention to help prevent further damage and slow cognitive decline
- Reversible causes of MCI must be addressed, along with lifestyle intervention and the use of cognitive-enhancing medication
- A variety of treatments are currently under investigation for future AD therapy.

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Click on references to access full article for additional reading

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