Chapter 5: Alzheimer and Vascular Major Neurocognitive Disorders: Diagnosis and Assessment

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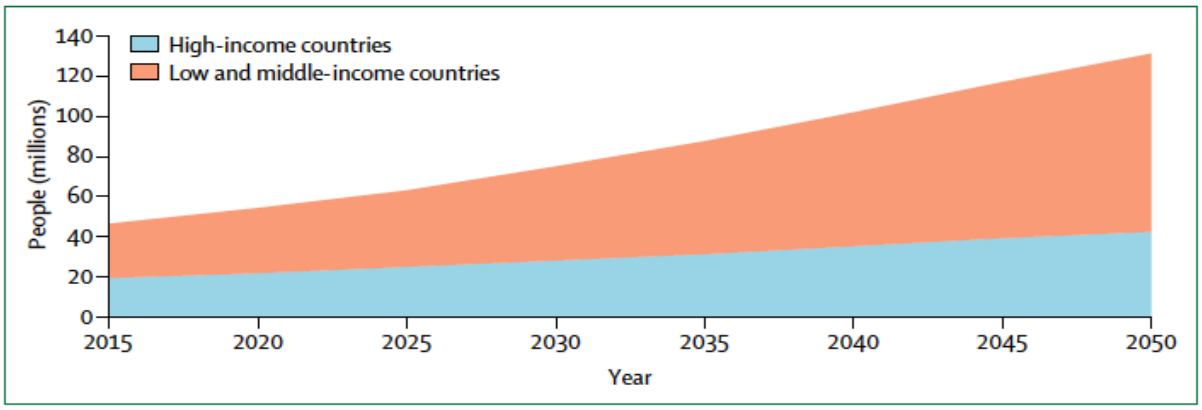
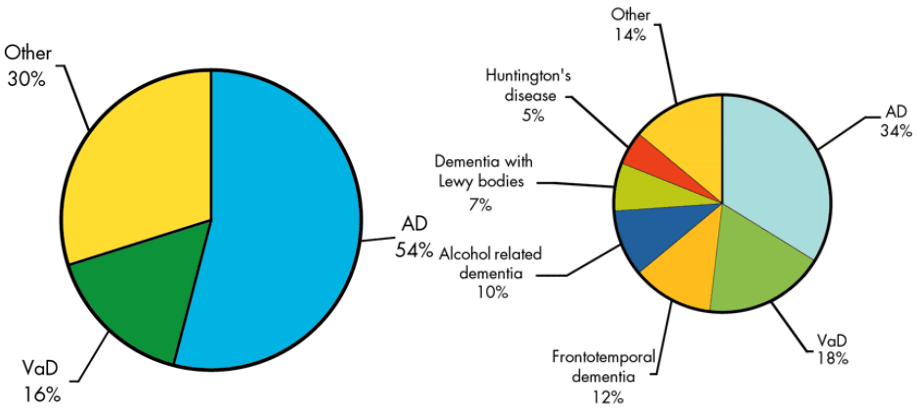
Introduction

- It has been stated that "… dementia is the greatest global challenge for health and social care in the 21st century…" (Livingston et al., 2017). It affects nearly 50 million persons, and that number will triple by 2050, especially in low and middle income countries (see Figure 1 From Prince et al, with permission Alzheimer's Disease International).



- While Major Neurocognitive Disorder (MNCD) (or "dementia") is primarily a disease of older persons (>65 years) but can affect younger persons. The profile of MNCD, though is different in younger persons, and by region. This means that in low- and middle-income countries, NCD caused by external agents or injuries, such as HIV, alcohol, trauma and malnutrition are more common than in high income countries, where so-called "degenerative conditions of younger persons" are the most common cause. These include the syndromes of fronto-temporal dementia, dementia with lewy bodies and Huntington's disease. Note that vascular dementia and Alzheimer's disease do occur in younger persons, but much less commonly than in older persons- see Figure 2 below.

Figure 2: Profile of MNCD's in Older vs Younger Persons



Adapted from (Lobo et al., 2000)

- As can be seen, Alzheimer's disease (AD), followed by Vascular Dementia, are the most common MNCD's of old age. Mixed MNCD is now also thought to be very common. With aging comes co-morbidities, which contribute to frailty and dementia risk.
- Most of the costs associated with MNCDs are related to the family and social costs, not medical direct costs.
- While there are currently NO truly disease-modifying treatments for dementia (and AD in particular, data suggest that modifiable risk factors do exist, and that be addressing them, the onset may be delayed. These include early life factors (education), mid-life factors (vascular risk factors and hearing loss) and late life factors (smoking, depression, physical inactivity, social isolation and diabetes).
- In addition to risk factor prevention and delaying onset, the use of currently available medical treatments, together with multi-modal interventions, may afford improved patient-outcomes, and probably improved care-giver burden outcomes.
- Multi-modal interventions with varying degrees of evidence include management of hypertension, Mediterranean diet, cognitive interventions, exercise, and social engagement. A detailed discussion of these is beyond the scope of these notes.

<u>Diagnosis of MNCD's</u>

- The diagnosis of MNCD in 2022 remains largely clinical, with support from blood/CSF and imaging where appropriate and available.
- The Diagnostic and Statistical Manual- 5th edition (DSM5) and ICD describe the features of all-cause MNCD in the category of neurocognitive disorders, with a decline in cognitive function the main criterion.
- In DSM 5 six domains of cognitive function are addressed, and the inclusion of social cognition is a key change from DSM4. It also presumes that the clinician has been able in

some way or other, to measure these domains either through bedside testing or by the administration of a neuropsychological test battery where available. In addition to cognitive decline (usually involving at least 2 domains) is accompanied by interference in ability to function at work or usual activities; and it is not better explained by another psychiatric or medical condition, such as delirium.

- In order to tap the domains affected, the Mini-Mental State Examination (MMSE) is probably of limited use. The Montreal Cognitive Assessment has become more widely used as it taps not only these domains, but is also useful in the diagnosis of Mild Cognitive Impairment (MCI) (Nasreddine et al., 2005).
- The value of key informant / care-giver accounts is not only critical to the diagnostic assessment, but also in ascertaining needs for care, as well as care planning.

Table 1: Domains Affected by MNCD in DSM5

Complex attention	includes sustained attention, divided attention, selective attention and information processing speed
Executive function	includes planning, decision making, working memory, responding to feedback, inhibition and mental flexibility
Learning and memory	includes free recall, cued recall, recognition memory, semantic and autobiographical long term memory, and implicit learning
Language	includes object naming, word-finding, fluency, grammar and syntax, and receptive language
Perceptual-motor function	includes visual perception, visuo-constructional reasoning and perceptual-motor coordination
Social cognition	includes recognition of emotions, theory of mind and insight

- In ICD11, Neurocognitive disorders are characterized by primary clinical deficits in cognitive functioning that are acquired rather than developmental. NCD's do not include disorders characterized by deficits in cognitive function that are present from birth or that arise during the developmental period, which are classified in the grouping neurodevelopmental disorder. NCD's represent a decline from a previously attained level of functioning.
- It is VERY important to note that although cognitive deficits are present in many mental disorders (e.g., schizophrenia, bipolar disorders), only disorders whose **core features** are cognitive are included in the Neurocognitive Disorders grouping. In cases where the underlying pathology and etiology for neurocognitive disorders can be determined, the identified etiology should be classified separately.

- Moving on from the all-cause approaches of DSM5 and ICD11, with aetiology specifiers, there are Working Group Approaches for most common dementias, including AD and VaD.
  - Alzheimers Disease: National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) and the Alzheimer's Disease and Related Disorders Association (ADRDA) 1983; National Institute on Aging and the Alzheimer's Association workgroup 2011
  - Vascular Dementia: Neuroepidemiology Branch of the National Institute of Neurological Disorders and Stroke (NINDS) - Association Internationale pour la Recherche et l'Enseignement en Neurosciences (AIREN) NINDS-AIREN 1993

Challenges to AD Diagnosis

The following points have been raised as concerns / challenges to Ad diagnosis by the working group of the NIA in the USA (See (McKhann et al., 2011). Notably:

1. Histological pathology of AD (or surrogates for this pathology) may be found across a broad clinical spectrum (including individuals who are cognitively normal, those with MCI, and those with dementia)
2. Lack of acknowledgement of distinguishing features of other dementing conditions that occur in a similarly aged population, EG Dementia with Lewy bodies, vascular dementia
3. No inclusion of results of magnetic resonance imaging, positron emission tomography (PET) imaging, and cerebrospinal fluid (CSF) assays in diagnostic systems
4. The implication that memory impairment is always the primary cognitive deficit in all patients with AD dementia
5. Lack of information about genetics of AD (other then known single gene defects)
6. Proposed age cut-offs for the diagnosis of AD dementia. Work over the past decades has established that AD dementia in those aged <40 years, although rare, does not differ in its pathophysiology from older persons
7. Extreme heterogeneity of the "Possible" AD dementia category, including a group of patients who would now be diagnosed as "Mild cognitive impairment (MCI)

Vascular Dementia: Criteria and Clinicopathological Types

The NINDS-AIREN Criteria as noted above:

- Meets criteria for dementia; and *Exclusion criteria*: disturbance of consciousness, delirium, psychosis, severe aphasia, or major sensorimotor impairment precluding neuropsychological testing. Also excluded are systemic disorders or other brain diseases (such as AD) that in and of themselves could account for deficits in memory and cognition.
- *Cerebrovascular disease*, defined by **the presence of focal signs on neurologic examination…** and **evidence of relevant CVD by brain imaging (CT or MRI)**

including *multiple large vessel infarcts* or a *single strategically placed infarct* (angular gyrus, thalamus, basal forebrain, or PCA or ACA territories), as well as *multiple basal ganglia* and *white matter lacunes*, or *extensive periventricular white matter lesions*, or combinations thereof- see Table 2.

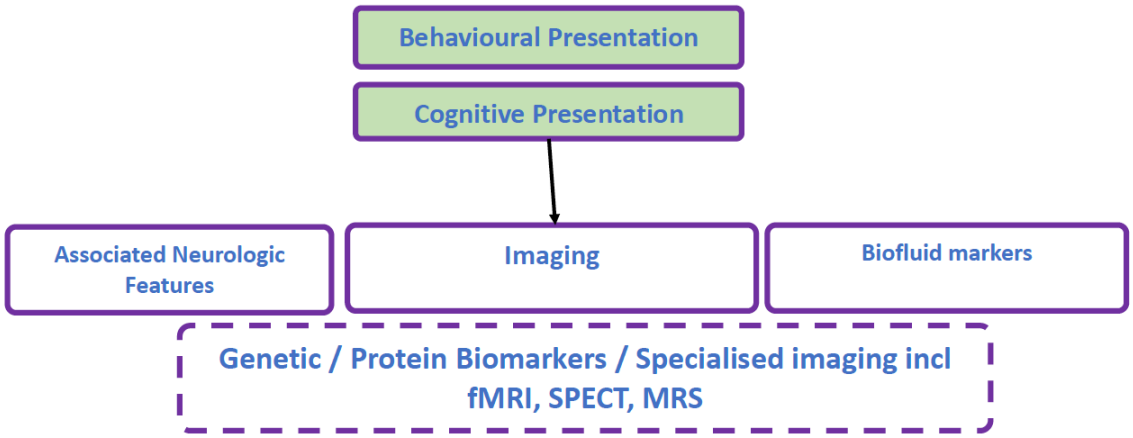
- *A relationship between the above two disorders*, manifested or inferred by the presence of one or more of the following: (a) onset of dementia within 3 months following a recognized stroke; (b) abrupt deterioration in cognitive functions; or fluctuating, stepwise progression of cognitive deficits.

Table 2: Sub-types of Vascular Dementia

Subtype	Types of Lesions	Descriptor
I	Large Infarct(s) 0.5ml tissue loss; multi-infarct dementia	Large / medium vessel disease
II	Multiple small infarcts minimum diameter 5mm- includes CAA, lacunes, PVD	Small vessel disease
III	Infarcts in critical areas (thalamus, hippocampus, forebrain)	Strategic infarct
IV	Incomplete or diffuse infarction- hippocampal sclerosis, anoxic damage	VaD due to Hypoperfusion
V	Multiple cerebral haemorrhages	
VI	Any of the above with concurrent AD pathology	Mixed dementia

<u>The Clinical Assessment in MNCD</u>

- With regards to clinical presentation in old age psychiatry and dementia, we are then often faced with a patient with either or both of a behavioural or cognitive presentation- see Figure 3
- Following clinical assessment of these clusters, we would normally complete the clinical assessment by adding in a brief neurologic examination, and then the “routine” investigations of neuro-imaging and serum blood tests. In specialized centres and in research projects, there is opportunity to assay genetic or protein markers, and to conduct specialized imaging studies such as PET studies of amyloid, or alpha synuclein.



- Some guidelines for features of the behavioural presentation that may be useful include: the age of onset and course of the syndrome; whether or not there is a family history of dementia or other neurological condition; how any aggression features present themselves in terms of timing, relation to triggers or to the absence of inhibition; the nature of broadly-termed “psychotic features”- in this instance visual hallucinations, for example, carry a specific meaning; and then associated behavioural features which may in fact overlap with non-specific cognitive and neurologic signs; these include apathy and social withdrawal, or hypofrontal behavioural features such as coarse behaviour and inappropriate jocularity.
- A useful aid to detailing the Neuropsychiatric / Behavioural / Psychological features of MNCDs is the Neuropsychiatric Inventory (NPI)- see (Cummings et al., 1994).
- Bedside cognitive testing will depend on the time and resources available. The MMSE and MOCA are common bedside tests. Clinicians may add in other brief tests to better characterize different domains, including social cognition and praxis which are not well capture by the MMSE and MOCA.
- Once cognitive testing has been completed, and the extent and nature of deficits may also be useful to distinguish WHERE the bulk of the pathology lies. For instance:
  - Predominant impairment in attention/concentration may point to a diffuse pathology or delirium
  - Predominant social cognitive and disinhibition may point to fronto-temporal dementia
  - Language and semantic impairment may suggest FTD of the semantic type, and slowed processing, together with executive dysfunction and impaired free memory recall with preserved cued recall may suggest a sub-cortical vs left cortical process. See Table 3 below

Table 3: Domains, Tests/sub-tests and Clinical Significance

Domain	Test	Significance
Orientation	MOCA / MMSE	Early SDAT day date, delirium
Delayed recall	MOCA 5 words with clues / MMSE 3 words	Amnestic disorders, cued recall preserved VaD
Abstraction	MOCA similarities	Frontal/EF, education sensitive
Language	MOCA (rep, fluency) / MMSE (reading, writing, rep, comprehension)	SDAT, aphasic disorders
Attention	MOCA digits, letters, 7's / MMSE 7's	VaD, delirium, moderate SDAT
Memory / registration	MOCA 5 words / MMSE 3 words	VaD, moderate amnestic disorders
Naming	MOCA animals / MMSE watch, pen	aphasias
Visuospatial / Executive	MOCA trails, cube, clock / MMSE pentagons	Early VaD, dysexecutive disorders
Speed of processing	IHDS, trail-making part A and B	Sub-cortical disorders

- The brief neurologic examination can provide a wealth of information and can be done inside of 5 mins. It is crucial to be able to assess eye movements through the vertical and horizontal planes, as well as the pupils. Be able to assess tone well, and to differentiate pyramidal and extra-pyramidal tone. Sensory examination is more subjective and time-consuming but may be key in problems such as vitamin deficiency or functional neurologic conditions. The cerebellar and gait functions can also provide a lot of information on frontal, spinal and posterior brain functions.
- You will need a basic knowledge of imaging in neuropsychiatry. Imaging is often non-specific in psychiatry, but in old age, you should be able to notice whether there is a lobar pattern to atrophy, the presence and severity of white matter disease and strokes, ventricular size and symmetry, and possibly patterns of white matter disease. In reality, we are often left wondering whether there is a fronto-temporal pattern of change vs generalized atrophy; and also we commonly see mild to moderate white matter disease in patients with clinical Alzheimers disease.

<u>MNCDs as Proteinopathies</u>

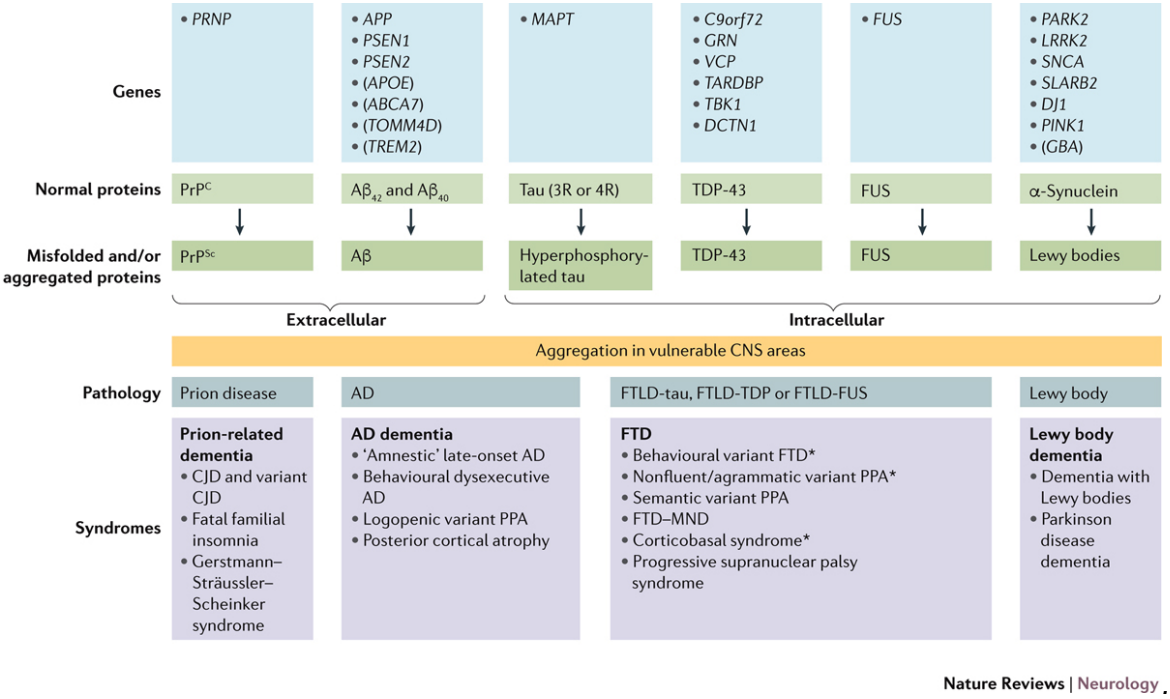
Many of the degenerative diseases of the brain that result in neurocognitive disorders are associated with abnormal protein formation and deposits. It is important to note that proteinopathy may precede clinical disease by years; we still don't know whether protein abnormalities are signal markers of disease or residues of a final common pathway of disease. For instance, there is some controversy that the amyloid hypothesis of AD has been a red herring, rather than an appropriate prevention and treatment target. Also, protein changes often arise in a focal or lobar pattern first, then are followed by spread then to a generalized pattern. Lastly, while we know that dementia rises with age, so too does mixed disease and mixed proteinopathy

Figure 4 below presents an overview of the clinicopathological spectrum of neurodegenerative proteinopathies.

- It is a schematic representation of the molecular underpinnings of neurodegenerative diseases and their main clinical manifestations.
- The figure lists genes with full penetrance that are considered causative and risk genes (in parentheses) that influence molecular processes culminating in the misfolding and/or aggregation of six fundamental proteins: cellular prion protein (PrP^C), $A\beta_{42}$ (and, to a lesser extent, $A\beta_{40}$), tau, TAR DNA-binding protein 43 (TDP-43), fused in sarcoma (FUS), and α-synuclein.

- These normal proteins misfold and/or accumulate in intracellular or extracellular compartments in specific areas of the CNS.
- Four major pathological disease categories are recognized: prion disease, AD, frontotemporal lobar degeneration (FTLD) and Lewy body diseases (LBD).
- The pathologies can involve multiple molecules; for example, AD is a dual proteinopathy with Aβ and tau aggregates. Also, in some cases of prion disease, Aβ in seen in addition to the principal aggregates of misfolded scrapie prion protein (PrP^{Sc}). The majority of FTLD cases are associated with three different proteinopathies: tau, TDP-43 and FUS.
- Each pathological entity can in turn manifest as a variety of clinical syndromes, sometimes featuring symptoms that bridge syndromes. Asterisks indicate frontotemporal dementia (FTD) syndromes that, in addition to FTLD, can be associated with AD neuropathology. Genetic pleiotropy also occurs: mutations in certain genes — for example, *GRN* — have full penetrance for one pathology (FTLD-TDP) and associated FTD syndromes, while representing a risk factor for another pathology (AD). The rich and diverse clinical expression of neurodegenerative processes is best illustrated in FTLD, a pathological category with six distinct clinical syndromes. Of note, FUS pathology causing FTLD is typically not associated with *FUS* mutations, which more often cause amyotrophic lateral sclerosis.

Figure 4: Spectrum of Proteinopathy (from Elahi, F. M. & Miller, B. A clinicopathological approach to the diagnosis of dementia. *Nat. Rev. Neurol* (Elahi & Miller, 2017))



Alzheimer's Disease as a Dual Proteinopathy

- In Alzheimers disease we are aware of two possible proteinopathies: the Amyloid pathway, from the precursor protein and its abnormal cleavage and accumulation of the Ab42 fragments. This pathway may be triggered by various genetic and environmental factors as illustrated here.
- Tau protein accumulates once hyper-phosphorylated and forms tangles. Both of these intra-and extra-cellular proteins lead to neuronal and synaptic dysfunction, oxidative stress, and ultimately neuronal loss and apoptosis.
- Bringing together imaging and fluid biomarkers leads to a best-fit picture of pre-morbid and active Alzheimer's disease. Using a combination of CSF amyloid beta 42, PET amyloid PET are the best markers of early disease, followed by more routine FDGPET and MRI; these markers offer the best opportunity to confirm whether a clinical syndrome, especially in its early stages, is in fact Alzheimers disease. This may be very important going forward for prevention and early treatment trials.
- The major AD biomarkers:
  - Biomarkers of brain amyloid-beta (Aβ) protein deposition are low CSF $A\beta_{42}$ and positive PET amyloid imaging.
  - Biomarkers of downstream neuronal degeneration or injury. The three major bio-markers in this category are elevated CSF tau, both total tau and phosphorylated tau (p-tau); decreased ^{18}fluorodeoxyglucose (FDG) uptake on PET in temporo–parietal cortex; and disproportionate atrophy on structural magnetic resonance imaging in medial, basal, and lateral temporal lobe, and medial parietal cortex. Total tau and p-tau are treated equivalently in this study, although p-tau may have more specificity for AD than other dementing diseases.
  - This Amyloid, Tau and Neurodegeneration approach is now referred to as the ATN approach.
- In persons who meet the core clinical Criteria for probable AD dementia, biomarker evidence may **increase the certainty that the basis of the clinical dementia syndrome is the AD pathophysiological process** but the value in probable clinical diagnosis remains limited.

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