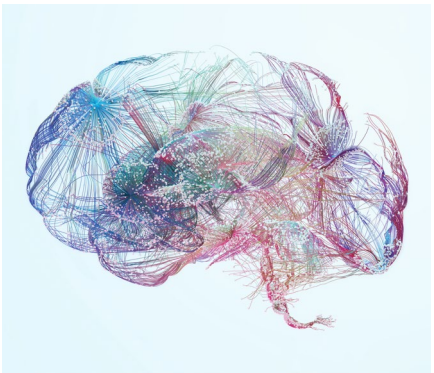
Pathophysiology of dementia



CPD

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Background
Dementia is a debilitating neurological condition that affects millions of patients and families worldwide and remains a significant public health concern. Understanding the underlying neurobiology and pathophysiology of dementia is an important step towards finding effective treatment options.

Objective
This article provides an overview of the pathophysiological processes of the most common types of dementia in older adults and highlights some of the developments in the research of biomarkers.

Discussion
The most common forms of late-onset dementia are Alzheimer's disease, dementia with Lewy bodies, vascular dementia and frontotemporal dementia. The pathophysiology of dementia is broadly characterised by the aggregation of misfolded proteins (such as amyloid-β plaques and neurofibrillary tangles in Alzheimer's disease) and cerebrovascular disease. Mixed neuropathologies are frequently detected in the brains of older people with dementia and have important clinical implications.

DEMENTIA is a common neurological condition affecting older people that is associated with progressive cognitive impairment, functional dependence, reduced quality of life and adverse health outcomes. An estimated 40 million people have dementia worldwide, and this figure is projected to double in the next 20 years.[1] In Australia, it was estimated that more than 400,000 Australians were living with dementia in 2022, and dementia was listed as the second leading cause of death in 2021.[2,3] In addition to being a burden to patients and their families, dementia has significant economic and public healthcare system effects. For instance, Australian data from 2016–17 revealed that people living with dementia had more general practitioner consultations and an increased number of medication management reviews than people without dementia.[2]

To date, there is no effective disease-modifying therapy available clinically for patients living with dementia and there remain substantial gaps in the understanding of the neuropathological and aetiological complexity of the disease. Our understanding of the exact mechanism and pathophysiology of dementia has continued to evolve over the years. This article provides an overview of the pathophysiological processes in the most common types of dementia in older adults and highlights some of the important developments in the use of biomarkers in the clinical diagnosis of dementia.

Risk factors

Most cases of late-onset dementia are sporadic and the development of dementia is likely to be influenced by the complex interplay between genetic risk factors, medical comorbidities and environmental and lifestyle factors. Advancing age is regarded as one of the biggest risk factors for the development of dementia. Based on Australian Institute of Health and Welfare estimates, the rate of dementia in Australia rises significantly from less than 1 per 1000 people among those aged <60 years, to 68 per 1000 people for those aged 75–79 years and then to 399 per 1000 people for those aged ≥90 years.[2] These Australian data are also in keeping with global data, as reported in a previous systematic review and meta-analysis.[4] Genetic risk factors have been described for late-onset dementia, particularly Alzheimer's disease (AD). The ε4 allele of the apolipoprotein E (*APOE*) gene is the strongest established genetic risk factor for sporadic AD, whereby carrying at least one *APOE* ε4 allele was

associated with a 2.3-fold increased risk (95% confidence interval [CI]: 1.49, 3.53) of dementia compared with non-carriers.[5] Traditional vascular risk factors, such as hypertension and diabetes, have long been recognised as playing an important role in the pathogenesis of cognitive impairment and dementia (both AD and vascular dementia).[5–7] Late-life depression has also been shown to be associated with increased risks for all-cause dementia and AD.[7] Other factors, such as the use of benzodiazepines, a low frequency of social contacts and sleep disturbances, have also been linked to increased risks of dementia.[7,8]

Pathophysiology of dementia

The pathophysiology of dementia is broadly thought to be related to the aggregation and accumulation of misfolded proteins (termed proteinopathies) and/or associated with cerebrovascular disease (CVD). The most common cause of late-onset dementia is AD, followed by dementia with Lewy bodies (DLB), vascular dementia and frontotemporal dementia (FTD).

Alzheimer's disease

The pathological hallmarks of AD are the accumulation of extracellular amyloid-β (Aβ) plaques and intraneuronal neurofibrillary tangles.[9] The amyloid cascade hypothesis, first described in 1992, suggested that the accumulation of Aβ plaques was driven by an imbalance between the Aβ production (by cleavage of amyloid precursor protein [APP] by β- and γ-secretase) and Aβ clearance.[10,11] The strongest evidence for the role of Aβ pathology in AD came from studies of individuals with dominantly inherited AD, in whom mutations in one of three different genes (*APP*, presenilin 1 [*PSEN1*], presenilin 2 [*PSEN2*]) led to the overproduction and aggregation of Aβ, with subsequent development of AD at an early age (~30–50 years).[9,12] Unlike *APOE*, which is a susceptibility gene more commonly seen in sporadic AD, mutations in *APP* and *PSEN* genes are associated with early onset AD.[9] Neurofibrillary tangles formed by phosphorylated (p-) tau proteins are one of the cardinal features of AD. Tau hyperphosphorylation causing microtubule destabilisation is generally thought to be the main pathological process driving downstream neurodegenerative damage resulting in microglial activation, synaptic loss and neuronal death.[9,13] In AD, according to the Braak system, tau pathology typically originates in the temporal cortices and tau, rather than Aβ, has been shown to be the main determinant of brain atrophy, cognitive changes and clinical decline in patients.[14,15]

The amyloid cascade hypothesis has remained the main pathological model in AD for decades; however, there is increasing evidence that supports multicausality of the pathophysiology of AD.[10] In addition to Aβ and tau, coexisting neuropathologies are commonly detected in individuals with AD. For example, in a previous autopsy study of patients with neurodegenerative disease, pure AD only represented a minority of the cases, with α-synuclein being detected in 41–55% of patients and TAR DNA-binding protein-43 (TDP-43) present in 33–40% of patients, depending on the severity of their AD-related pathologies.[16] CVD and AD share many vascular risk factors and often coexist in older people with dementia. Findings from previous autopsy and imaging studies showed that cerebrovascular lesions were present in more than half of those with AD.[17–19] To that end, the term 'mixed dementia' has been traditionally and widely used to denote the co-occurrence of AD and vascular dementia, although the use of this term has been increasingly discouraged due to its ambiguity. CVD, when present in AD, has been found to be associated with more rapid cognitive decline and an accelerated rate of hippocampal atrophy in the presence of Aβ proteinopathy.[20] In addition, cerebral amyloid angiopathy (CAA), associated with lobar intracerebral haemorrhages found frequently in the occipital lobes, is also more prevalent in AD than in healthy controls, which is likely to be related to the deposition of Aβ in the cerebrovascular wall.[21–23] Neuroinflammation with microglial activation has been increasingly recognised to play an important role in the pathogenesis of AD and is involved in Aβ deposition, neuronal damage and cell death.[24] Cholinergic transmission, implicated in modulating cognitive processes such as learning, memory and arousal, also plays an integral part in AD.[25] Cholinergic neurons located in the basal forebrain, including the nucleus basalis of Meynert, are significantly depleted in AD and cholinesterase inhibitors (eg donepezil) remain the mainstay of symptomatic treatment for mild-to-moderate AD.[25]

AD biomarkers

The development of positron emission tomography (PET) and lumbar punctures has enabled the in vivo measurement of Aβ plaques and neurofibrillary tangles, and allowed the progression of these pathologies to be studied in humans. The temporal progression model of AD biomarkers proposes that Aβ accumulation (reduced cerebrospinal fluid [CSF] Aβ and positive Aβ PET) begins 20–30 years before the onset of clinical symptoms.[26,27] This process is then followed by tau dysregulation (elevated CSF tau and abnormal tau PET), which leads to neurodegeneration, as evidenced by abnormal glucose metabolism on fluorodeoxyglucose (FDG)-PET, and brain atrophy, typically in the medial temporal lobes, on structural imaging such as magnetic resonance imaging (MRI).[27] The typical clinical manifestation is impairment in episodic memory, particularly in the early stage of the disease. Recent advances in AD biomarkers include the advent of blood biomarkers. The various forms of plasma p-tau have all been shown to have high specificity and accuracy in detecting AD-specific pathologies, including in the early stages of the disease, to correlate strongly with Aβ and tau and to be able to predict future cognitive decline.[13,28–30] Given the invasiveness and costs associated with PET and lumbar punctures, blood biomarkers show promise as a reliable clinical tool to be implemented widely, but will need to be tested in large clinical samples, including in community and primary care settings.

Dementia with Lewy bodies

After AD, DLB is the second most common form of neurodegenerative dementia in older adults. Clinically, people with DLB typically present with progressive cognitive impairment, accompanied by one or more of the four DLB core clinical features, namely spontaneous motor parkinsonism, recurrent well-formed visual hallucinations, cognitive fluctuations and rapid eye movement (REM) sleep behaviour disorder.[31] The clinical diagnosis of DLB is often challenging, and the international consensus diagnostic criteria (McKeith's criteria) were revised in 2017 with the aim of improving the clinical diagnostic accuracy of DLB. McKeith's criteria include the four core clinical features of DLB and three diagnostic/indicative biomarkers, namely reduced dopamine transporter (DAT) uptake in the basal ganglia, confirmation of REM sleep without atonia on polysomnography and an abnormal metaiodobenzylguanidine (MIBG) myocardial scan.[31,32] Pathologically, DLB is characterised by the accumulation of the synaptic protein α-synuclein into Lewy bodies and Lewy neurites in the brain.[32] DLB can be categorised as brainstem-predominant, limbic or transitional and diffuse neocortical DLB, based on the regional distribution of Lewy body pathology. These categories correspond to the likelihood of manifesting a typical DLB clinical syndrome, with more diffuse pathology corresponding to a higher likelihood of manifesting the clinical syndrome.[31] A previous study suggested that the distribution of Lewy body pathology may influence prognosis because those with diffuse Lewy body pathology were found to have shorter disease duration.[33] Studies investigating biomarkers for α-synuclein have so far yielded conflicting and inconclusive results.[34,35] Recent research has included the detection of phosphorylated α-synuclein deposits in autonomic skin nerves[36] and, more recently, the use of a real-time quaking-induced conversion assay for the ultrasensitive detection of α-synuclein aggregates in the CSF and potentially other biospecimens.[37]

Apart from α-synuclein, the neuropathology of DLB is characterised by neuronal loss in the substantia nigra, although the deficits tend to be less severe than those seen in Parkinson's disease.[38] Clinically, the use of ^{123}I-N-fluoropropyl-2b-carbomethoxy-3b-(4-iodophenyl) nortropane (^{123}I-FP-CIT) imaging shows reduced DAT uptake in the caudate and anterior and posterior putamen, which is one of the indicative biomarkers of DLB.[31] However, it is important to note that approximately 15–20% of people with DLB have normal DAT scans and often present with none or milder motor symptoms.[39,40] The absence of motor parkinsonism does not rule out DLB. Despite being a highly specific and relatively sensitive biomarker, ^{123}I-FP-CIT scans are not currently licenced for use in Australia. Similar to DAT, dopaminergic activity in the basal ganglia can be evaluated using PET scans targeting vesicular monoamine transporter type 2, which is currently only available for research use in Melbourne, Australia.[32,41]

DLB versus Parkinson's disease dementia

DLB and Parkinson's disease dementia (PDD) are both termed 'Lewy body dementia' and are both α-synucleinopathies. There are ongoing debates with regard to the classification of DLB versus PDD.[38] The arbitrary 'one-year rule' continues to be used, whereby DLB is diagnosed when the onset of cognitive impairment occurs prior to or within one year of the onset of motor impairment, whereas PDD is diagnosed when cognitive impairment happens in the setting of well-established Parkinson's disease.[31]

Comorbid AD-related proteinopathies (Aβ plaques and neurofibrillary tangles) are frequently detected in people with DLB. A previous systematic review found that Aβ-PET positivity was reported in 51% (95% CI: 33%, 69%) of people with DLB, with the prevalence increasing with age and *APOE* ε4 carriership.[42] Similarly, approximately 66% (95% CI: 60%, 73%) of people with DLB had significant tau burden detected at autopsy, which may be associated with more severe cognitive impairment.[43] In a large observational study using a national dementia database, 73% of participants with either transitional or diffuse Lewy body disease had significant Aβ and tau burden at autopsy, sufficient to meet the international neuropathological criteria for a high or intermediate likelihood of AD dementia.[33] Similar to AD, CVDs, including CAA, have been investigated in people with DLB, but their prevalence and clinical implications in DLB are not well understood.[44]

Vascular dementia

Cognitive disorders of vascular aetiology are a heterogeneous group of disorders and CVD encompasses a spectrum of processes including multiple cortical infarcts, strategic infarcts, small vessel disease, hypoperfusion and cerebral haemorrhages (including CAA).[45,46] The concept of 'vascular dementia' (used interchangeably with 'vascular major cognitive disorder' or 'vascular cognitive impairment') has evolved substantially over the years. Several sets of diagnostic criteria have been published with the aim of standardising the clinical diagnosis of vascular dementia.[47–49] The contribution of CVD to cognitive impairment and dementia is well appreciated, but establishing whether the vascular pathology seen on neuroimaging or neuropathology is sufficient to account for the observed cognitive deficits can be challenging because some degree of cerebrovascular change, particularly small vessel disease, is very common in the brains of older people without any apparent cognitive symptoms.[47] Clinically, people with vascular dementia typically present with cognitive deficits temporally related to a cerebrovascular event (described as stepwise or fluctuating course) or, in the absence of a history of stroke, impairments in processing speed and executive functions together with early gait disturbance and/or urinary symptoms.[47] In addition, the presence of neuroimaging evidence of significant CVD, such as two or more large vessel infarcts, strategically placed single infarct and extensive and confluent white matter lesions, is generally required to support a diagnosis of probable vascular dementia.[47]

In vascular dementia, atherothromboembolic disease (causing multiple infarcts and single strategic

infarct) and small vessel disease (associated with lacunar infarcts, cortical microinfarcts and microhaemorrhages) are two common neuropathological findings.[47,50] However, the direct mechanisms by which CVD causes pathological damage and cognitive symptoms remain to be elucidated and may depend on the nature, location and extent of the vascular pathology. Given the challenges in the clinical diagnosis and variability in the interpretation of vascular pathology, neuropathological guidelines have also been developed that propose the use of a combination of three determinants (moderate-to-severe occipital leptomeningeal CAA, at least one large infarct and moderate-to-severe arteriolosclerosis in the occipital white matter) to determine the likelihood of CVD contributing to cognitive impairment,[51] but these will require further validation in larger cohorts.

Frontotemporal dementia

FTD, a common cause of early onset dementia (ie onset before 65 years of age), is a term used to describe a group of clinical syndromes and encompasses behavioural variant FTD, non-fluent variant primary progressive aphasia and semantic variant primary progressive aphasia.[52] The clinical diagnosis of FTD is challenging owing to the heterogeneous clinical presentations, typically manifesting as progressive changes in behaviour, language and/or executive functions, and the overlaps between different clinical entities, as well as with other neurodegenerative disorders, often causing missed and/or delayed diagnoses.[52] As suggested by the name, the common neuropathological feature of FTD is the relatively selective degeneration of the frontal and temporal lobes (frontotemporal lobar degeneration) associated with characteristic protein inclusions, such as microtubule-associated protein tau (MAPT) and TDP-43.[53] Genetic factors play an important role in the pathogenesis of FTD. A family history of dementia has been implicated in up to 40% of cases of FTD and approximately 20% of cases of FTD are attributed to a genetic mutation, with the most common mutations being associated with the *MAPT*, progranulin and chromosome 9 open reading frame 72 (*C9orf72*) genes.[54]

Cerebral multimorbidity

Traditionally, dementia was thought to be attributed to a single neuropathological process, but the coexistence of multiple neuropathologies, sometimes termed 'cerebral multimorbidity' or 'mixed neuropathologies', is frequently detected and may even be the norm in the brains of older people with dementia.[55] The high prevalence of cerebral multimorbidity has been consistently demonstrated in many previous studies, including in autopsy series, but there remain no international consensus guidelines with regard to the definition of mixed neuropathologies.[16,33,55,56] A better understanding of cerebral multimorbidity in people with dementia is essential because the synergistic interactions between these different neuropathological changes may potentially contribute to lowering the clinical threshold for the diagnosis of dementia, affect the clinical picture and influence disease trajectories.[57,58] For instance, in DLB, those with a significant tau burden have been shown to have a reduced likelihood of manifesting the core clinical features of DLB and were less likely to be diagnosed with DLB or may take longer to exhibit their DLB symptoms, potentially leading to missed diagnoses.[43,59] Longitudinally, individuals with multiple neuropathological processes were also reported to have more aggressive disease trajectories and a worse prognosis than those with a single brain pathology.[60–62] Although the extent to which each of these neuropathologies contributes to the clinical syndrome and cognitive decline in patients is an important consideration, it would be extremely difficult to determine.[57]

Conclusion

In conclusion, dementia is a debilitating illness for patients and their families and continues to be a large global public health issue. Unravelling the pathophysiological complexity of dementia is becoming imperative. Future work should include large longitudinal studies incorporating comprehensive phenotyping and pathology-specific biomarkers with neuropathological confirmation to help enhance our understanding of the pathophysiology of dementia and provide insights into the development of potential therapeutic targets.

Key points

- The pathophysiology of dementia is complex and our understanding of it has continued to evolve over the years.
- AD, characterised by amyloid-β plaques and neurofibrillary tangles, is the most common form of dementia.
- DLB is an α-synucleinopathy and is associated with neuronal loss in the substantia nigra.
- CVD is strongly linked with cognitive impairment, and often coexists with other forms of neurodegenerative dementia.
- Cerebral multimorbidity is increasingly recognised as having important pathological and clinical implications in older people with dementia.

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