Dementia

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Abstract

Dementia is a general term for a number of progressive, organic brain diseases affecting approximately 670,000 people in the UK. Most neurodegenerative diseases leading to dementia are characterized by processes that result in the aberrant polymerization of proteins, whereas a small proportion of individuals with these diseases develop dementia as a direct result of mutations or polymorphisms in genes influencing these processes. The most common cause of dementia, and the best studied, is Alzheimer's disease. Other important causes include vascular dementia, dementia with Lewy bodies and fronto-temporal dementia. The management of dementia largely focuses on helping carers to cope with the increase in patients' physical dependence as the disease progresses and with the emergence of troublesome neuropsychiatric symptoms. Current pharmacological treatments are based on the neurochemical changes that are found in these diseases. Cholinesterase inhibitors and *N*-methyl-D-aspartate receptor antagonists offer some help in ameliorating the inevitable cognitive decline found in Alzheimer's disease. However, the treatment of neuropsychiatric symptoms in dementia is still largely empirical and is hampered by either limited efficacy or troublesome adverse effects.

Keywords Alzheimer's disease; cognitive deficits; dementia; fronto-temporal dementia; Lewy body dementia; vascular dementia

Key points

- Alzheimer's disease is a diagnosis of exclusion
- Neurodegenerative causes of dementia have an important genetic component
- A large number of rare genetic polymorphisms affecting cholesterol metabolism and inflammatory pathways have been identified as risk factors for the development of late-onset Alzheimer's disease
- Early advice regarding lasting power of attorney, financial aid and local support networks for carers is an essential part of management
- Cholinesterase inhibitors and *N*-methyl-D-aspartate receptor antagonists have an important role in the treatment of Alzheimer's disease
- The drug treatment of neuropsychiatric symptoms is empirical but should follow the maxim 'start low, go slow'

Definition

Dementia is a general term for a range of progressive organic brain diseases characterized by problems of short-term memory and other cognitive deficits.

Epidemiology

In 2013 it was estimated that there were some 670,000 people with dementia in the UK.[1] The main risk factor for dementia is age, with prevalence increasing exponentially >60 years of age to around 20% at age 85 years. However, the prevalence of dementia in the UK may now be reducing, possibly as a result of improved prevention of vascular disease and higher levels of education.

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Diagnoses

There are a large number of causes of dementia (Table 1), the most common being Alzheimer's disease (AD; approximately 60% all causes), vascular dementia (VaD; 20%), dementia with Lewy bodies (DLB; 5%) and fronto-temporal dementia (FTD; 2%). Importantly, although they are considered as discrete entities, these diseases are not mutually exclusive, and mixed pathologies are common.

Causes of dementia

- Alzheimer's disease
- Vascular dementia
- Dementia with Lewy bodies
- Fronto-temporal dementia
- Parkinson's disease
- Alcohol
- Huntington's disease
- Creutzfeldt–Jacob disease
- HIV
- Multiple sclerosis
- Neurosyphilis
- Normal-pressure hydrocephalus
- Chronic subdural haematoma
- Cerebral tumours
- Hypothyroidism
- Progressive supranuclear palsy
- Tuberculosis
- Wilson's disease

Table 1

Aetiology

The aetiology of dementia is determined by the underlying causative disease. However, it has become increasingly clear that most neurodegenerative diseases that lead to dementia are often characterized by processes resulting in the aberrant polymerization of proteins, and that a proportion of subjects with these diseases develop dementia as a direct result of mutations or polymorphisms in genes influencing these processes.

Alzheimer's disease

Apart from increasing age, the clearest associated risk factor for AD is a positive family history, amounting to an approximately threefold higher risk in the first-degree relatives of patients with AD. Direct support for a genetic component to AD comes from the recognition of a small number of patients who develop the disease largely before the age of 65 years in an autosomal dominant pattern.

To date, a number of mutations in three genes (amyloid precursor protein, presenilin 1 and presenilin 2) have been described that lead to this early form of AD. These mutations have the same effect, which is the increased production of a longer version of β-amyloid peptide (42 amino acids compared with normal 40 amino acids); this aggregates to form a condensed core of amyloid protein that becomes surrounded by degenerating neurites. These relatively large extracellular structures are known as plaques and are a characteristic feature of both sporadic and inherited AD.

The amyloid cascade hypothesis postulates that β-amyloid peptide aggregates are the underlying cause of all the other neuropathological features of both sporadic and inherited AD. These include the formation of intracellular tangles made up of hyperphosphorylated tau protein, inflammatory features, widespread neurochemical changes (including loss of acetylcholine and impaired glutamatergic neurotransmission) and ultimately neuronal cell death. However, there is increasing evidence that soluble monomers of β-amyloid peptide, rather than aggregates in plaques, are the neurotoxic species.

In late-onset AD, developing >65 years of age, no clear autosomal dominant patterns have been established. However, prevalence studies suggest that a presence of one copy of the apolipoprotein E ε4 allele is associated with a three times increased risk of developing late-onset AD, although possession of the apolipoprotein E ε4 allele is neither a necessary nor a sufficient condition for the development of AD.

Recent, large-scale genome-wide association studies have shown that, in addition to apolipoprotein E ε4, a large number of rare genetic polymorphisms involved in cholesterol and inflammatory processes are also appreciable risk factors for developing late-onset AD. One of these rarer polymorphisms is in *TREM2* (triggering receptor expressed on myeloid cells 2), which causes a threefold increase in risk of late-onset AD. *TREM2* is highly expressed on microglial cells and might play a role in regulating inflammatory processes in the brain. There is thus a growing body of evidence from animal, clinical and epidemiological studies that inflammation may play a key role in the aetiology and progression of late-onset AD.

Studies investigating environmental risk factors provide support for possible associations with head injury, a family history of depressive illness, mid-life hypertension, diabetes and obesity, and for a possible inverse association with long-term non-steroidal anti-inflammatory use and years of education.

Vascular dementia

VaD usually develops from the cumulative effect of multiple cerebral infarctions (multi-infarct dementia) with an accumulating loss of neurones or axons. Less commonly, dementia can arise from single focal lesions or from widespread subcortical ischaemia affecting the white matter. A rare form of VaD, CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy), has been found to be caused by inheritance of mutations in the *NOTCH3* (neurogenic locus notch homolog protein 3) gene. However, most cases of VaD are sporadic and associated with the same risk factors as stroke, i.e. smoking, diabetes mellitus, hypercholesterolaemia and hypertension.

Dementia with Lewy bodies

Individuals with DLB have Lewy bodies in both the cortex and subcortical regions. Lewy bodies are intracellular structures composed of filamentous protein made up primarily of α-synuclein and ubiquitin. Patients with DLB also have a variable burden of amyloid plaque pathology and, to a lesser extent, tau pathology. Like AD, DLB shows widespread neuronal degeneration. However, unlike AD, there is also neuronal loss in the substantia nigra.

Fronto-temporal dementia

FTD is characterized by focal cerebral atrophy, principally in the cerebral hemispheres and involving mostly the frontal, anterior parietal and temporal regions. All of the variable clinical and pathological phenotypes share, to a greater or lesser degree, a non-Alzheimer-type histological profile. Approximately 25–50% of FTD is familial, making the genetic contribution to these diseases substantial. Two major genetic loci are situated on chromosome 17, one linked to the tau gene and the other linked to progranulin.

Clinical features

Cognitive symptoms

A wide variety of cognitive symptoms occur in dementia, but the exact clinical presentation can differ depending on the disease causing the dementia. Memory loss is the most common cognitive symptom, and indeed is a core feature of any dementing illness. Short-term memory loss is usually the presenting complaint, with patients having difficulty learning new information, such as names, shopping lists and details of conversations. Later on in the disease, remote memories are also affected. Other cognitive deficits include aphasia, apraxia, agnosia and executive deficits. Cognitive deficits relate more clearly to disease progression than any other symptoms, leading to the widespread use of cognitive scales such as the mini-mental state examination (MMSE) to monitor disease progression (see Table 5 of *Clinical assessment and investigation in psychiatry* on pp 630–637 of this issue).

In most dementias, including AD, the onset of memory problems is insidious and gradually progressive. In VaD, cognitive changes are classically of sudden onset with a stepwise progression. A marked temporal variability in cognitive function, with pronounced