

Further reading

- Baddeley AD (1999). *Essentials of human memory*. Psychology Press, Hove.
- Berrios GE, Hodges JR (2000). *Memory disorders in psychiatric practice*. Cambridge University Press, Cambridge.
- Driver J, Mattingley JB (1998). Parietal neglect and visual awareness. *Nat Neurosci*, **1**, 17–22.
- Goodale MA, Westwood DA (2004). An evolving view of duplex vision: separate but interacting cortical pathways for perception and action. *Curr Opin Neurobiol*, **14**, 203–11.
- Hodges JR (2007). *Cognitive assessment for clinicians*, 2nd edition. Oxford University Press, Oxford.
- Hodges JR, Spatt J, Patterson K (1999). 'What' and 'how': evidence for the dissociation of object knowledge and mechanical problem-solving skills in the human brain. *Proc Natl Acad Sci USA*, **96**, 9444–8.
- McCarthy RA, Warrington EK (1990). *Cognitive neuropsychology: a clinical introduction*. Academic Press, San Diego.
- Mesulam MM (1998). From sensation to cognition. *Brain*, **121**, 1013–52.
- Patterson K, Lambon-Ralph MA (1999). Selective disorders of reading? *Current Opin Neurobiol*, **9**, 235–9.
- Patterson K, Nestor PJ, Rogers TT (2007). Where do you know what you know? The representation of semantic knowledge in the human brain. *Nat Rev Neurosci*, **8**, 976–87.
- Rothi LJG, Heilman KM (eds) (1997). *Apraxia: the neuropsychology of action*. Psychology Press, Hove.
- Stuss DT, Alexander MP (2007). Is there a dysexecutive syndrome? *Philos Trans R Soc B*, **362**, 901–15.
- Tulving E, Craik FM (eds) (2000). *The Oxford handbook of memory*. Oxford University Press, New York.
- Walsh K, Darby D (1999). *Neuropsychology: a clinical approach*. Churchill Livingstone, Edinburgh.

24.4.2 Alzheimer's disease and other dementias

John R. Hodges

Essentials

Dementia is defined as a syndrome consisting of progressive impairment in memory and at least one other cognitive deficit (aphasia, apraxia, agnosia, or disturbance in executive function) in the absence of another explanatory central nervous system disorder, depression or delirium.

Epidemiology and classification

Prevalence—dementia is common, affecting about 8% of all people over 65 years, rising to around 20% of those over 85 years. It is estimated that the 18 million people with dementia worldwide will increase to 34 million by the year 2025, with this increase being most marked in the developing countries.

Classification—dementia may be classified in terms of (1) its cause—these are many diseases, some of which are remediable and

thus justify investigation (e.g. vitamin B₁₂ deficiency, thyroid hormone deficiency), but most cases result from Alzheimer's disease, vascular disorders, or subcortical diseases of the brain; or (2) according to the pattern of cognitive loss—this alternative perspective may contribute usefully to diagnosis, to the level of care required, and allow refinement of prognosis.

Particular causes of dementia

Alzheimer's disease—the most common cause of dementia, probably caused by cerebral accumulation of the A β fragment of the amyloid precursor protein. The initial cognitive deficit is impairment of episodic memory (see Chapter 24.4.1), which is thought to reflect the earliest site of pathology in the medial temporal lobe structures. Progression of disease is marked by failing memory, increasing disability in managing complex day-to-day activities, mental inflexibility, and poor concentration, eventually leading on to language and visuospatial impairments, apraxia, and failure of semantic memory. Neuropsychiatric symptoms are common and behavioural problems can be prominent. Agitation, restlessness, wandering, and disinhibition cause considerable carer burden. Terminal stages are characterized by reduced speech, ambulatory difficulties, dependence, and incontinence. The mainstay of treatment is social support and increasing assistance with day-to-day activities. Cholinesterase inhibitors generally achieve modest improvements in cognition in around 25 to 50% of patients.

Frontotemporal dementia—increasingly recognized as a common cause of dementia, particularly in younger patients. Usually associated with tau or ubiquitin-positive interneuronal inclusions. Clinical presentation is with progressive changes in personality and behaviour, or (less commonly) with progressive aphasia. There is no specific treatment.

Dementia with Lewy bodies—a common cause of dementia in the elderly. Typical presentation is with progressive cognitive decline, paralleling that seen in Alzheimer's disease, but with (1) marked spontaneous fluctuations in cognitive abilities; (2) visual hallucinations; (3) spontaneous parkinsonism; and (4) exquisite sensitivity to neuroleptic medication. May respond to treatment with cholinesterase inhibitors, but neuroleptic drugs should be avoided whenever possible.

Vascular dementias—a wide variety of vascular diseases can affect the brain, with the most important vascular syndromes being (1) large infarcts, (2) lacunar infarcts, (3) small-vessel disease (Binswanger's disease), (4) cerebral amyloid angiopathy, and (5) cerebral autosomal dominant arteriopathy with subcortical infarcts and leucoencephalopathy (CADASIL).

Subcortical dementias—these include (1) Huntington's disease, (2) progressive supranuclear palsy, (3) Parkinson's disease, and (4) corticobasal degeneration.

Treatable causes of dementia—these include (1) normal-pressure hydrocephalus—the classic triad of presenting features comprises cognitive impairment, gait disturbance and incontinence; (2) chronic subdural haematomas; (3) benign tumours; (4) metabolic and endocrine disorders—including hypothyroidism, Addison's disease, and hypopituitarism; (5) deficiency states—including vitamin B₁₂ deficiency; and (6) infections—including neurosyphilis and HIV infection.

Introduction

The definition of dementia has evolved from one of progressive global intellectual deterioration to a syndrome consisting of progressive impairment in memory and at least one other cognitive deficit (aphasia, apraxia, agnosia, or disturbance in executive function) in the absence of another explanatory central nervous system disorder, depression, or delirium (according to the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition (DSM-IV)). Even this recent syndrome concept is becoming inadequate, as researchers and clinicians become more aware of the specific early cognitive profiles associated with different dementia syndromes. For instance, in early Alzheimer's disease there may be isolated memory impairment many years before more widespread deficits develop.

Although the incidence of dementia is difficult to establish, community prevalence studies suggest that about 8 per cent of all people over 65 years of age suffer from dementia; this shows a marked increase with advancing age. The prevalence below 65 years is about 1:1000, this rises to 1:50 to the age of 70 and 1:20 from 70 to 80. Over 80 years of age the prevalence is 1:5.

Since dementia is predominantly a disorder of later life, it represents an increasing problem for individuals and society with the projected increase in the elderly population. It is estimated that the 18 million people with dementia worldwide will increase to 34 million by the year 2025. This increase is most marked in the developing countries, where the 11 million people with dementia in the year 2000 will reach 24 million by 2025. In the developed world, the equivalent figures are 7 million in 2000 and 11 million in 2025. In Europe alone, more than 5 million people will be affected by the year 2025.

Dementia may result from many diseases and as a consequence be remediable (e.g. metabolic disorders such as vitamin B₁₂ deficiency, thyroid hormone deficiency), thus justifying extensive investigation, most cases result from Alzheimer's disease, vascular disorders or result from sub-cortical diseases of the brain. Classification of dementias according to the pattern of cognitive loss provides an alternative perspective which may contribute usefully to diagnosis, to the level of care required—and allow prognosis to be refined. At the same time, progress in the study of neurogenetics has greatly enhanced our knowledge of the pathways which lead to neuronal injury in the brain and promises greater understanding of the disease with a more unified view of molecular causation.

Dementia has numerous causes that can be classified in many ways (Table 24.4.2.1 shows a classification by aetiology). Although medical and neurological conditions cause a dementia syndrome, most of these are rare and have other neurological features that suggest the diagnosis, e.g. multiple sclerosis, the AIDS–dementia complex, and the vasculitides. Routine investigation focuses on some of these rarer causes because, although rare, they often result in a reversible dementia. An alternative classification, based on the patterns of cognitive impairment, is that of subcortical and cortical dementias as illustrated in Table 24.4.2.2. This classification shows that disease of diverse cerebral structures can result in dementia but that the resultant patterns of cognitive deficit can be very different. Alzheimer's disease is the prototypical cortical dementia. Subcortical dementias are discussed further below.

The most common causes of dementia before and after the age of 65 years are shown in Fig. 24.4.2.1. The relative frequencies of causes of dementia differ depending on age, but it is notable that

Table 24.4.2.1 Causes of dementia

Degenerative disorders
Alzheimer's disease
Frontotemporal dementia
Dementia with Lewy bodies
Parkinson's disease
Huntington's disease
Progressive supranuclear palsy
Corticobasal degeneration
Multisystem atrophy
Progressive myoclonic epilepsies
Vascular diseases
Multi-infarct disease (large vessel and lacunar infarcts)
Binswanger's disease
Primary cerebral amyloid angiopathy
Hypertensive encephalopathy
Vasculitides:
–systemic lupus erythematosus
–polyarteritis nodosa
–Behçet's disease
–giant-cell arteritis
–primary CNS angitis
CADASIL
Anoxia postcardiac arrest
Sickle-cell disease
Infections
Prion dementias:
–sporadic and familial Creutzfeldt–Jakob disease
–Gerstmann–Straussler–Scheinker syndrome
–familial fatal insomnia
AIDS dementia complex
Progressive multifocal encephalopathy
Cerebral toxoplasmosis*
Cryptococcal meningitis*
Neurosyphilis
Subacute sclerosing panencephalitis
Progressive rubella encephalitis
Viral encephalitis
Viral, bacterial, and fungal meningitides
Whipple's disease
Neoplastic causes
Primary intracerebral tumours:
–frontal gliomas crossing the corpus callosum (butterfly glioma)
–posterior corpus callosal or midline tumours (thalamic, pineal, third ventricle)
–cerebral lymphoma

(Continued)

Table 24.4.2.1 (Cont'd) Causes of dementia

Neoplastic causes (Cont'd)
Extracerebral tumours:
–frontal meningiomas
–posterior fossa tumours (acoustic neuromas)
causing hydrocephalus
Multiple cerebral metastases
Malignant meningitis
Paraneoplastic (limbic) encephalitis
Toxic causes
Alcoholic dementia
Heavy metals:
–lead, mercury, manganese
Carbon monoxide poisoning
Drugs:
–lithium, anticholinergics, barbiturates, digitalis, neuroleptics, cimetidine, propranolol
Acquired metabolic disorders and deficiency states
Chronic renal failure
Dialysis dementia
Portosystemic encephalopathy
Hypothyroidism
Cushing's disease
Addison's disease
Panhypopituitarism
Hypoglycaemia (chronic or recurrent)
Hypoparathyroidism
Vitamin B ₁₂ , B ₁ , and folate deficiency
Malabsorption syndromes
Inherited metabolic disorders (that may present in adulthood)
Wilson's disease
Porphyria
Leucodystrophies:
–adrenoleucodystrophy
–metachromatic leucodystrophy
–globoid-cell leucodystrophy
Gangliosidoses
Niemann–Pick disease
Cerebrotendinous xanthomatosis
Adult-onset neuronal ceroid-lipofuscinosis (Kuf's disease)
Mitochondrial cytopathies
Subacute necrotizing encephalopathy (Leigh's disease)
Trauma
Major head injury
Subdural haematoma
Dementia pugilistica

Table 24.4.2.1 (Cont'd) Causes of dementia

Hydrostatic causes
Hydrocephalus:
–communicating (including normal pressure) and obstructive
Inflammatory
Multiple sclerosis
Sarcoidosis
Acute disseminated encephalomyelitis
* Associated with immunocompromisation. CADASIL, cerebral autosomal dominant subcortical infarcts and leucoencephalopathy.

Alzheimer's disease is the most common cause in both groups. The genetic forms of Alzheimer's disease and other rarer causes are more common in the younger age group. Before considering the common and treatable causes of dementia, we discuss the main differential diagnoses to be considered as alternatives to dementia.

Differential diagnosis

Pseudodementia

This term has been used to describe two disorders, namely depressive pseudodementia and hysterical pseudodementia. Cognitive symptoms are common in depression, particularly in the older population. The main complaints are of poor recent memory and concentration with distractibility. There is often a lack of subjective feelings of depression, thereby making the diagnosis difficult. The telltale signs are the so-called biological features of depression, such as sleep disturbance and a loss of appetite and libido. Other common symptoms are low energy and a lack of interest in hobbies and activities. There may be a past personal or familial history of depression. The cognitive picture is of impaired attention and subsequent patchy performance on memory and frontal tasks. There may be some inconsistency in test performance and patients easily give up on a task. Language output may be sparse but paraphasic errors are not present. Even after detailed testing, it may be difficult

Table 24.4.2.2 Cortical and subcortical dementias

Feature Examples	Cortical Alzheimer's disease	Subcortical Parkinson's and Huntington's diseases
Speed of mental processing	Normal	Slowed up
Memory	Severely impaired Recognition and recall affected	Forgetfulness Recognition better
Language	Aphasia common	Normal
Frontal 'executive' abilities	Preserved in early stages	Disproportionately impaired early in disease
Visuospatial and perceptual abilities	Impaired early	Impaired late
Personality	Unconcerned	Apathetic and inert
Mood	Usually normal	Depression common

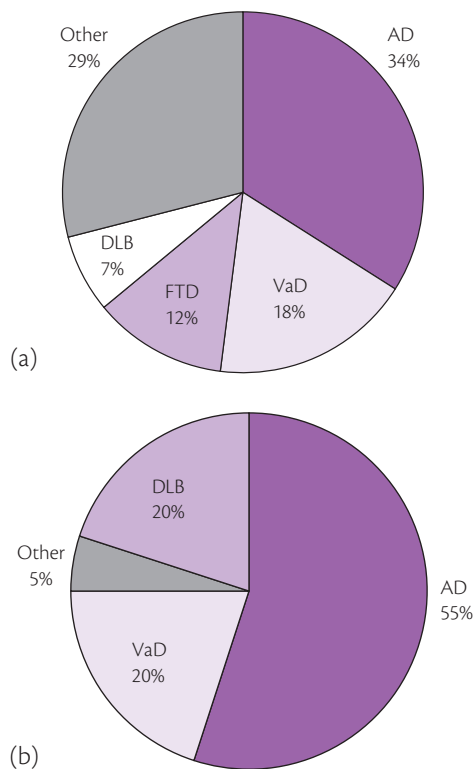


Fig. 24.4.2.1 (a) Relative frequencies of different dementia diagnoses in people under 65 years old. (b) Relative frequencies of different dementia diagnoses in people over 65 years old. AD, Alzheimer's disease; DLB, dementia with Lewy bodies; FTD, frontotemporal dementia; VaD, vascular dementia.

to distinguish depression from dementia; indeed there may also be some overlap between the syndromes in older people. For this reason, ideal practice would be for all newly presenting patients with dementia to undergo psychiatric assessment, and if any doubt remains a therapeutic trial of antidepressants may be warranted.

Hysterical pseudodementia commonly presents with a rapid onset of memory and/or intellectual impairment. There is loss of personal identity and salient personal and life events, which is unlike organic disorders of memory. There may be an obvious precipitant (such as marital problems, financial problems, or trouble with the law) and a past psychiatric history is common. 'Ganser's syndrome' is a name for the condition where the patient gives bizarrely wrong answers to questions, e.g. when asked 'How many legs does a horse have?', they reply three or five. Even with such functional states, the examiner has to be aware of the potential concomitant organic disorder exaggerating the condition, as in other conversion disorders.

Delirium

This clinical syndrome is either caused by a diffuse brain pathology (e.g. intracranial infections, head trauma, epilepsy (postictal states and nonconvulsive status), raised intracranial pressure, subarachnoid haemorrhage) or secondary to a large number of systemic illnesses or insults, including infections, metabolic derangements, hypoxia, and drugs.

The clinical features include the acute onset of attentional abnormalities and disturbance of consciousness (from clouding to coma), perceptual distortions, illusions and hallucinations,

psychomotor disturbance (hypo- or hyperactivity and rapid shifts between the two), disturbance of the sleep-wake cycle, emotional lability, and marked fluctuations in performance and behaviour. The most consistent abnormality is in attention, with a reduced ability to maintain attention to external stimuli leading to distractibility and difficulty answering questions, and to appropriately shift attention to new stimuli, leading to perseverations. The investigation and treatment need to be focused in each case on the likely precipitants (although in about 5 to 20% of older people no cause is found). Although the course and prognosis depend on the underlying diagnosis, if there is resolution of the precipitant there should be cognitive improvement to the baseline state.

Alzheimer's disease

Definition

Alzheimer's disease is the most common cause of dementia. Of the 5 to 10% of the population aged over 65 years who have some kind of cognitive decline, over 50% of cases will be due to Alzheimer's disease and, although accounting for a smaller percentage of presenile cases, Alzheimer's disease is still the single largest cause. The initial disease description by Alzheimer in 1907 was of a woman in her 50s with a progressive dementia and behavioural disturbance, who was found to have neurofibrillary tangles and amyloid plaques throughout her cerebral cortex. The term 'Alzheimer's disease' was then applied to similar cases with a presenile dementia, before it was realized that identical pathological changes were seen in most elderly demented patients. As plaques and tangles are found in a very high proportion of nondemented older individuals, debate continues about whether Alzheimer's disease represents a continuum or a distinct disease process that increases in frequency with age. With recognition of a number of causative gene mutations (see below), Alzheimer's disease is now generally believed to be a multifactorial disease with familial and sporadic forms.

Histological diagnosis remains the 'gold standard', but current research criteria, such as the widely used NINCDS-ADRDA (Table 24.4.2.3), are accurate in up to 90% of cases. Rather than merely being a diagnosis of exclusion, Alzheimer's disease is now recognized as a clinicopathological entity amenable to positive diagnosis. Much recent research has focused on methods of early and accurate diagnosis, which is particularly important in view of the advent of potential disease-modifying treatments.

Epidemiology and risk factors

Age is the most important overall risk factor for Alzheimer's disease. A positive family history is also a risk factor, although autosomal dominant presentations account for less than 5% of cases. To date, three major causative gene mutations have been established: mutations in the presenilin genes I and II on chromosome 14 and 1, respectively, and involving the amyloid precursor protein (APP) gene on chromosome 21. In these families the onset is invariably at an early age (35 to 55 years), with remarkable consistency within families and, as with Huntington's disease, penetrance is complete. Dementia is rapidly progressive and seizures and myoclonus are common. Individuals with Down's syndrome (trisomy 21) develop Alzheimer's disease during their third and fourth decades. This is thought to be due to the extra copy of the amyloid precursor gene on chromosome 21.

Table 24.4.2.3 The NINCDS-ADRDA criteria for Alzheimer's disease

Probable Alzheimer's disease
Dementia established by clinical examination, documented by the Mini-Mental State Examination (MMSE) or similar and confirmed by neuropsychological tests
Decline in memory and at least one non-memory intellectual function
Decline from previous level and continuing progression
Onset between 40 and 90 years of age
No disturbance in consciousness
Absence of systemic disorders or other brain diseases that in and of themselves could account for the progressive deficits in memory and cognition
Definite Alzheimer's disease
Clinical criteria of probable AD
Histopathological evidence of AD at postmortem or biopsy
Possible Alzheimer's disease
Patient has dementia syndrome with no other cause but clinical variation from typical for AD
Patient has second disorder that is sufficient to produce dementia but not considered the cause of the dementia
Single gradually progressive cognitive deficit in absence of other cause

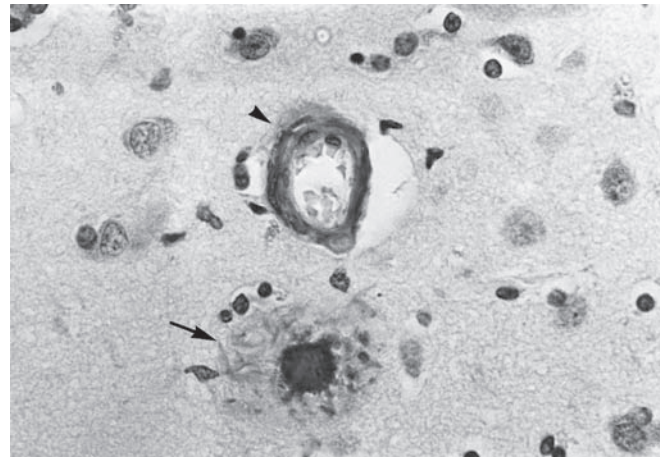
NINCDS-ADRDA, National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association.

Apolipoprotein E (ApoE) is a risk factor rather than a causative gene for Alzheimer's disease in both early and late-onset cases, which at present is thought to be the single most common genetic determinant of a susceptibility to late-onset Alzheimer's disease. ApoE is a component of several classes of plasma and cerebrospinal fluid (CSF) lipoproteins. The brain is the most important site of ApoE production outside the liver, and ApoE is thought to be important in lipid homeostasis in the brain. There are three common alleles for the *ApoE* gene: $\epsilon 2$, $\epsilon 3$, and $\epsilon 4$. One or two $\epsilon 4$ alleles confer an increased risk of Alzheimer's disease and lower the age of onset in a 'dose-dependent' fashion.

Many meticulous epidemiological studies have established that women are at an increased risk for Alzheimer's disease, even after adjusting for confounding factors such as the increased longevity of women and their over-representation in the elderly population, and the increased vascular disease in men. Possible explanations include hormonal effects and the postmenopausal loss of the potentially protective effects of oestrogen. Significant head trauma in earlier life is also a risk factor that may summate with ApoE status, and there appears to be an unexplained protective effect of nonsteroidal anti-inflammatory drugs.

Pathology

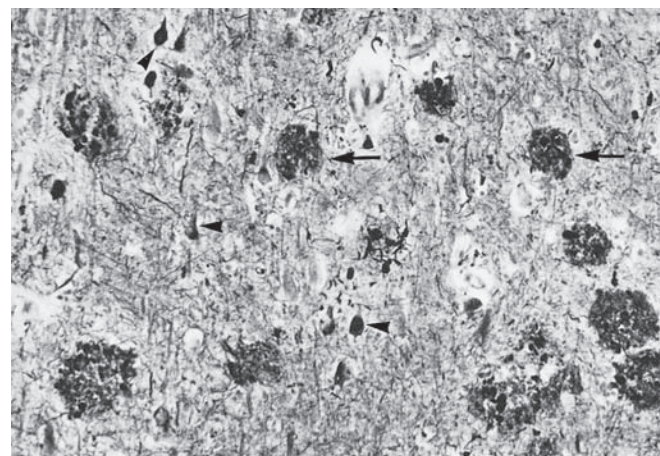
Pathologically, the macroscopic features of Alzheimer's disease are cortical atrophy, particularly involving the medial temporal lobe and parietotemporal association areas, with relative sparing of the primary sensory motor and visual cortices. The pathological process is thought to start in the entorhinal cortex, hippocampus, and other medial temporal lobe structures before spreading to the temporoparietal neocortex and basal frontal cortex, and then to the

**Fig. 24.4.2.2** Amyloid plaque.

other association areas. The histological hallmarks are the senile plaques and neurofibrillary tangles (Figs. 24.4.2.2 and 24.4.2.3). Neither lesion is specific for Alzheimer's disease, as both are found to a lesser extent in the ageing brain; neurofibrillary tangles are also seen in a range of diseases, including progressive supranuclear palsy, encephalitis lethargica, postencephalitic parkinsonism, cerebral trauma, and dementia pugilistica.

Neurofibrillary tangles are formed from bundles of paired helical filaments that replace the normal neuronal cytoskeleton. The central core of the paired helical filaments is the microtubule-associated protein tau. The abnormal phosphorylation of the tau protein causes the microtubular abnormalities and the subsequent collapse of the cytoskeleton. The neurofibrillary tangles are seen as intensely staining intraneuronal inclusions with silver stains or specific anti-tau immunohistochemistry.

The senile or neuritic plaque is the other major lesion found in Alzheimer's disease. Plaques range in size from 50 nm to 200 nm and consist of an amyloid core with a corona of argyrophilic axonal and dendritic processes, amyloid fibrils, and microglia. The amyloid core is composed of 5- to 10-nm filaments made up of a 40 to 43 amino acid peptide referred to as $A\beta$ peptide because of its secondary structure of β -pleated sheets. The use of antibodies against $A\beta$ reveals more widespread deposition of amyloid

**Fig. 24.4.2.3** Neurofibrillary tangle.

throughout the neocortex, especially in layers II, III, and V. The role of microvascular pathology in Alzheimer's disease remains controversial. Cerebral congophilic angiopathy can be seen in a high proportion of cases and almost certainly contributes to the hyperintense lesions commonly seen on T_2 -weighted MRI.

Besides a reduction in synaptic loss from neurons, which may explain some cognitive sequelae of the pathology, there is a major loss of neurotransmitters— especially of acetylcholine. The 'cholinergic hypothesis' of neurotransmitter loss causing attentional and mnemonic dysfunction has been much investigated. There is certainly evidence of severe neuronal loss in the nucleus basalis of Meynert in the basal forebrain, the major site of cholinergic neurons, and the current therapies are aimed at improving cognitive function through inhibition of anticholinesterases. There is also disruption to other neurotransmitters including the serotonin system.

Pathophysiology

Over the past decade a great deal has been learnt about the molecular basis of Alzheimer's disease. The dominant hypothesis to explain the mechanisms leading to Alzheimer's disease is the amyloid cascade model, which states that the $A\beta$ fragment of the APP plays an essential role in the pathogenesis (Fig. 24.4.2.4). $A\beta$ is produced proteolytically from APP by so-called β - and γ -secretases. It is believed that the accumulation of $A\beta$ (in particular the $A\beta$ 42 peptide) in the brain initiates a cascade of events that ultimately leads to neuronal dysfunction, the accumulation of hyperphosphorylated tau, and cell death. The strongest argument supporting a causal role for β amyloid comes from the identification of mutations of the APP gene and the genes for presenilin 1 and 2 responsible for the early onset forms of familial Alzheimer's disease. These mutations modify the generation of $A\beta$ peptides in such a way that the relative proportion of the highly amyloidogenic $A\beta$ 42 form is increased. Recent evidence suggests that, rather than the highly aggregated $A\beta$ species, soluble oligomeric forms of $A\beta$ may represent the neurotoxic entity that causes synaptic dysfunction. Transgenic mice expressing APP mutations have been developed. These animal models, which develop typical plaques, help to understand the role of amyloid and are ideal test beds for the development and trial usage of novel drug compounds.

Clinical features

The earliest cognitive deficit is impairment of so-called episodic memory (memories for events or episodes, including day-to-day

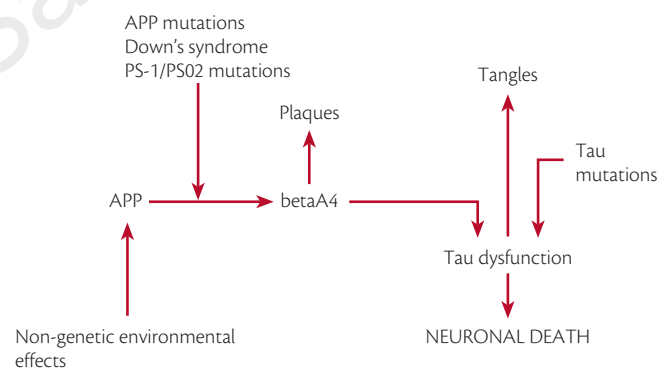


Fig. 24.4.2.4 Proposed pathogenesis of Alzheimer's disease.

memory and new learning), which is thought to reflect the earliest site of pathology in the medial temporal lobe structures. 'Mild cognitive impairment' (MCI) is a term increasingly used for people who are impaired on episodic memory tasks but who do not otherwise fit the criteria for a diagnosis of dementia. It is becoming clear that many, if not all, such people are in the predementia or early stage of Alzheimer's disease, but progression to a full-blown dementia syndrome can take several years. Recent studies indicate a conversion rate to dementia of around 10 to 20% per annum. The main clinical features at this stage are severe forgetfulness, often with repetitive questioning and impairments in social function or job performance, particularly concerning the retention of new information. As the disease progresses to mild Alzheimer's disease, memory function worsens, particularly affecting recall (e.g. forgetting recent visits or family events), increasing disability in managing complex day-to-day activities such as finances and shopping, mental inflexibility, and poor concentration, which reflects involvement of attentional and executive function.

Insight is variably affected; often patients retain a partial awareness into their difficulties but underestimate the extent of the problem. Remote memory is relatively well preserved with a temporally graded pattern (i.e. sparing of most distant memories). As the disease continues to progress patients often develop impairments in language, most typically word-finding difficulties, a shrinking vocabulary, and poor understanding of complex words and concepts. Visuospatial impairments and apraxia, which may develop at this stage, are particularly disabling, causing difficulty in dressing, cooking, and performing other daily activities. In a small subgroup of patients, language or visuospatial difficulties can be the first or most prominent presenting feature. As the cognitive deficits progress there is worsening of language function and semantic memory, and behavioural problems can be prominent.

Neuropsychiatric symptoms are also common in the earliest stages of Alzheimer's disease, particularly apathy, anxiety, and mood disturbance. Delusions and hallucinations occur in up to 50 and 30% of patients, respectively, in the later stages. Agitation, restlessness, wandering, and disinhibition also cause a considerable burden for carers. The final stages of the disease are characterized by reduced speech output (or mutism), ambulatory difficulties, dependence, and incontinence. Seizures and myoclonus are common late features. There is considerable variation in the time to this stage, but the average time from diagnosis to death is around 10 years.

Neurological examination is unremarkable in the early stages, although increased tone (often frontal resistant, or *gegenhalten*, in type) and mild extrapyramidal features can occur as the disease progresses. Reflex changes such as extensor plantar responses (Babinski's reflex) and—in contrast to frontotemporal dementia—pout, snout, and grasp reflexes occur late. In the final stages, there can be greatly increased rigidity and joint contractures.

Investigations

The aims of neuropsychological, imaging, and laboratory investigations in Alzheimer's disease are twofold: first to exclude other potentially reversible causes of dementia, and second to confirm the diagnosis of probable Alzheimer's disease. The extent and nature of investigation obviously need to be tailored to the individual, but all patients should undergo brain imaging and have a neuropsychological assessment to confirm the diagnosis of dementia.

The neuropsychological profile can also be informative in the differential diagnosis of dementia (see Table 24.4.2.2). Particularly characteristic is early impairment in delayed verbal recall of new material, followed by reduced category fluency (in which individuals are asked to generate exemplars from a given category, e.g. 'animals'), impaired naming of low-frequency words, and difficulty with complex visuospatial tasks such as copying complex figures or block design from the revised Wechsler Adult Intelligence Scale (WAIS-R).

The basic laboratory investigations required in all patients, particularly to exclude treatable causes of dementia, and some of the other investigations that may be indicated in certain cases depending on the patient's age, family history, or specific medical history are shown in Table 24.4.2.4. Research into biological markers of Alzheimer's disease has yet to yield a consistent biological or surrogate marker. Screening for specific gene mutations in young-onset familial cases is available only in specialist centres.

MRI of patients with Alzheimer's disease in the earliest stages (including MCI) show evidence of atrophy of the hippocampus and entorhinal cortex (parahippocampal gyrus) reflecting the pathology (Fig. 24.4.2.5). Unfortunately, the variability in size of these structures in normal older people means that, at present, these imaging abnormalities are not specific enough to be of predictive value. The coregistration of serial MR scans appears

Table 24.4.2.4 Recommended investigations in dementia

Routine
Full blood count and ESR
Biochemical profile: –urea or creatinine, electrolytes, calcium, liver function
Serum vitamin B12 and RBC folate levels
Thyroid function
Serological tests for syphilis
Chest radiography
CT or MRI scan of brain
Other tests which may be indicated in certain cases
EEG (e.g. Creutzfeldt–Jakob disease and subacute sclerosing panencephalitis)
SPECT
Neuropsychological examination (confirm dementia and pattern of disease)
CSF examination
Immunological tests for vasculitides
Screening for cardiac sources of emboli
Slit-lamp examination for Kayser–Fleischer rings and caeruloplasmin estimation (Wilson's disease)
Specific blood and/or urine tests for inherited metabolic disorders
Screening for HIV infection
Genetic screening for HD mutation/ specific AD mutations if familial dementia Cerebral biopsy

ESR, erythrocyte sedimentation rate; RBC, red blood cells; CT, computed tomography; EEG, electroencephalogram; MRI, magnetic resonance imaging; SPECT, single-photon emission computed tomography; CSF, cerebrospinal fluid; HD, Huntington's disease; AD, Alzheimer's disease.

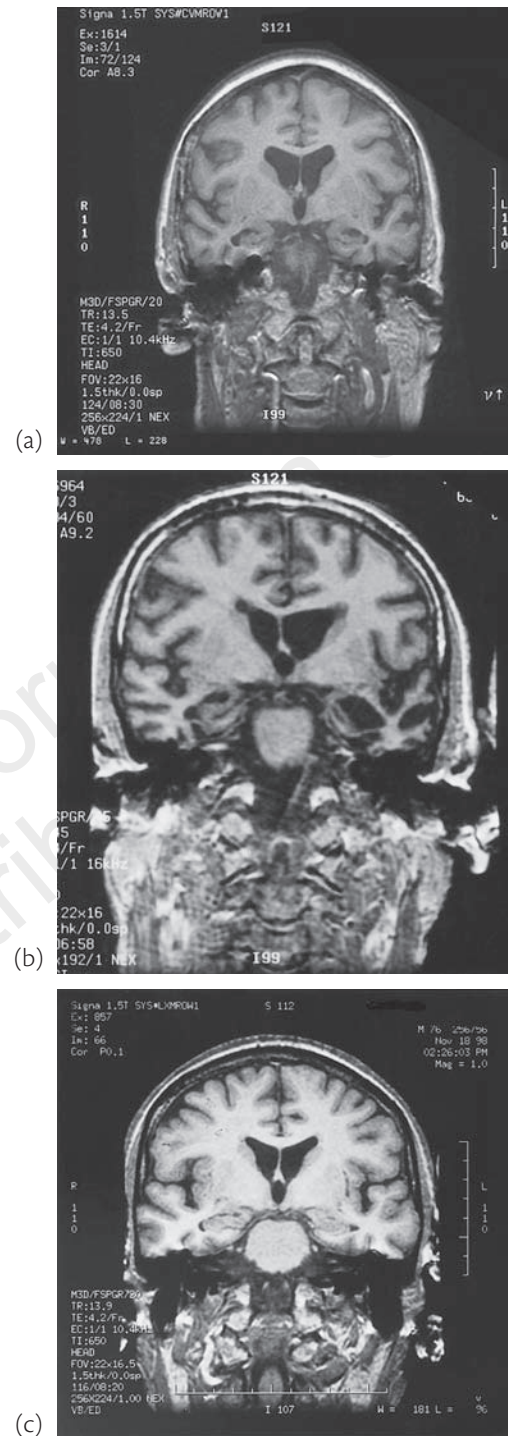


Fig. 24.4.2.5 (a) Coronal T_1 -weighted MRI of a patient with early Alzheimer's disease showing bilateral early hippocampal atrophy. (b) Coronal T_1 -weighted MRI of a patient with frontotemporal dementia (FTD) showing left temporal atrophy. (c) Coronal T_1 -weighted MRI of a normal person.

capable of detecting abnormal rates of brain atrophy, even before the onset of clear-cut cognitive symptoms in at-risk familial cases, but it remains a research instrument. T_2 -weighted MRI often reveals periventricular high-signal changes, even in 'pure' early onset cases. Single-photon emission computed tomography (SPECT) scans similarly demonstrate typical abnormalities in the parietotemporal regions but the specificity is relatively low in individual cases.

Newer technological developments, such as diffusion tensor MRI, MR spectroscopy (MRS), and position emission tomography (PET) may enhance diagnostic accuracy but are expensive and not yet suitable for routine clinical use. Very recently it has become possible to image amyloid deposition *in vivo* using a PET ligand that binds to amyloid.

Management and prognosis

The management of a patient with dementia involves many sensitive issues. It is crucial to provide medical and psychological support to patients as well as to their families and carers. During the progression of the disease there will be different treatment goals at different stages, ranging from aiding failing memory in the setting of independent living to managing behavioural problems and aggression, and eventually full supportive nursing care. There is great variation in the rate of progression, young-onset cases and those with prominent aphasia appearing to deteriorate most rapidly. On average, patients spend several years in the mild or minimal stages (although it can be as long as 5–10 years), between 4 and 5 years in the moderate disease stages, and, depending on the quality of care in the dependent stages, a year or more requiring full nursing care.

Nonpharmacological treatment

The mainstay of treatment is social support and increasing assistance with day-to-day activities. Issues such as driving and planning for future financial affairs are important and should be discussed early in the course of the disease. Throughout the course of the illness there will be different requirements for the support services listed below:

- ◆ information and education
- ◆ carer support groups
- ◆ community dementia team, including home nursing and personal care
- ◆ community services such as meals-on-wheels, community transport services, home maintenance assistance
- ◆ sitter service
- ◆ day centre
- ◆ respite care
- ◆ residential/nursing home
- ◆ diet, exercise, mental activity.

Pharmacological treatment

Pharmacological treatments can be divided into symptom- and disease-oriented approaches. Symptom modification relates to the treatment of depression, agitation, and psychotic phenomena, and requires the input from a specialist psychiatrist. The cholinesterase inhibitors donepezil, galantamine, and rivastigmine are licensed for use in the United Kingdom as is the *N*-methyl-D-aspartate (NMDA) receptor antagonist memantine. The importance of acetylcholine depletion in Alzheimer's disease is established; these cholinesterase inhibitors generally achieve modest improvements in cognition in around 25 to 50% of the patients studied. The disease-modifying effects of these drugs remain controversial. Antioxidants (such as vitamin E), ginkgo biloba, and monoamine oxidase B (MAO-B) inhibitors have shown minor benefits in some

clinical trials, although again their long-term benefit has yet to be established. Pilot trials and experimental studies are being conducted at present in this area. Ideally, the goal is to prevent patients developing further cognitive deficits and to prevent those with MCI from progressing to dementia. The epidemiological findings of protection from cognitive decline in women using hormone replacement therapy (HRT) are of interest in developing preventive strategies. Trials to look at the effect of HRT in preventing or delaying the onset of dementia have been disappointing. A number of disease-modifying drug and other therapeutic approaches have been developed based on the amyloid cascade hypothesis, ranging from inhibitors of β - and γ -secretase, anti-A β immunization, and tau kinase, to aggregation inhibitors.

Frontotemporal dementia

Definition

Frontotemporal dementia (FTD) is now preferred to the older term 'Pick's disease', to describe patients with focal frontal and/or temporal focal atrophy, because the underlying pathology of these syndromes is heterogeneous. Arnold Pick (1851 to 1924) first described patients with both progressive aphasia and associated severe left temporal cortical atrophy *post mortem*, and patients with behavioural disturbances associated with frontal lobe atrophy. In 1910, Alzheimer described the histological changes in patients with focal lobar degeneration as distinct from the syndrome that bears his name. Alzheimer described both argyrophilic intracytoplasmic inclusions (Pick bodies) and diffusely staining ballooned neurons (Pick cells). More recently it has become clear that the spectrum of pathology that accompanies the clinical syndromes of frontal and temporal dementias is much broader, with a range of distinct inclusions as described below. There is also considerable overlap between FTD and two categories of motor disorders: motor neuron disease (MND, also referred to as amyotrophic lateral sclerosis) and corticobasal degeneration, in terms of both clinical features and pathology.

Epidemiology

FTD is increasingly recognized as a common cause of dementia, particularly in the younger age groups (see Fig. 24.4.2.1a)—the peak incidence of onset being 45 to 65 years of age. In hospital series, the ratio FTD:Alzheimer's disease has been found to vary from 1:5 to 1:20, with men and women being equally affected. Many cases are familial, with up to 40% having an affected family member.

Pathology and genetics

The gross pathological appearance of FTD is that of profoundly atrophied frontotemporal regions which may be so severe as to produce the so-called knife-edged gyri and deep widened sulci. The histopathological hallmarks are widespread cortical and subcortical gliosis, loss of large cortical nerve cells, and microvacuolation. Immunohistochemical staining reveals two major patterns based on the presence of interneuronal inclusions. The first pattern is a build-up of either tau in the form of classic Pick bodies, diffuse neuronal and glial, and pathology typically seen in patients with mutations of the tau gene, or corticobasal degeneration. The second major pattern consists of ubiquitin-positive but tau-negative pathology, first identified in patients with MND without dementia, but then later found in those with MND-associated FTD, and more

recently in patients with progranulin gene mutations. A small proportion of patients have neither tau- nor ubiquitin-positive inclusions.

About 20 to 30% of patients with FTD have a positive family history, although in some cases this may be coincidental. Two major causative gene mutations occur on chromosome 17. The first mutation, found in the late 1990s, involves the microtubule-associated protein tau gene (*MAPT*). In 2006, the second major locus close to *MAPT* was discovered, the progranulin gene. Familial MND with FTD has been linked to chromosome 9 although no gene has yet been identified.

Clinical features

The presentation of FTD mirrors the distribution of neuropathological changes; in the early stages two major presentations can be distinguished.

Frontal or behavioural presentations

Patients present with insidiously progressive changes in personality and behaviour that reflect the early locus of pathology in orbital and medial parts of the frontal lobes. There is often impaired judgement, an indifference to domestic and professional responsibilities, and a lack of initiation and apathy. Social skills deteriorate and there can be socially inappropriate behaviour, fatuousness, jocularity, abnormal sexual behaviour with disinhibition, or theft. Many patients are restless with an obsessive-compulsive and ritualized pattern of behaviour, such as pacing or hoarding. Emotional lability and mood swings are seen, but other psychiatric phenomena such as delusions and hallucinations are rare. Patients become rigid and stereotyped in their daily routines and food choices. A change in food preference towards sweet foods is very characteristic. Of importance is the fact that simple bedside cognitive screening tests such as the Mini-Mental State Examination (MMSE) are insensitive at detecting frontal abnormalities. More detailed neuropsychological tests of frontal function (such as the Wisconsin Card Sorting Test or the Stroop Test) usually show abnormalities. Speech output can be reduced with a tendency to echolalia (repeating the examiner's last phrase). Memory is relatively spared in the early stages, although it does deteriorate as the disease advances. Visuospatial function remains remarkably unaffected. Primary motor and sensory functions remain normal. Primitive reflexes such as snout, pout, and grasp develop during the disease process. Muscle fasciculations or wasting, particularly affecting the bulbar musculature, can develop in the FTD subtype associated with MND.

Language presentations

Less common than the behavioural variant is a presentation with progressive aphasia which can be of a fluent or nonfluent type. In progressive fluent aphasia, also known as semantic dementia, there is a profound loss in conceptual knowledge (or semantic memory), causing anomia and impaired comprehension of words, objects, or faces. The patient typically complains of 'loss of memory for words' and has fluent, empty speech with substitutions such as 'thing' and 'one of those', but the grammatical aspects are preserved. Naming is impaired with semantically based errors (such as 'animal' or 'horse' for zebra). Patients are unable to understand less frequent words and fail on a range of semantically based tasks such as matching words to pictures and matching pictures according to their meaning. Repetition of words and phrases is normal even though

patients are unaware of their meaning. Unlike patients with Alzheimer's disease, day-to-day memory (episodic memory) with good visuospatial skills and nonverbal problem-solving ability is relatively preserved, at least in the early stages. As the disease progresses behavioural changes often emerge.

In progressive nonfluent aphasia, by contrast, there is a gradual loss of expressive language abilities with impairments in the phonological (sound based) and grammatical aspects of language production. This leads to nonfluent, agrammatical, and poorly articulated speech with phonological errors (e.g. sitter for sister or fencil for pencil). Repetition of multisyllabic words and phrases is impaired but, in contrast to semantic dementia, word comprehension and object recognition are well preserved. Orobuccal apraxia is common and some patients develop parkinsonism and limb apraxia.

Diagnosis

The diagnosis of FTD is based on the clinical, neuropsychological, and imaging assessments. The consensus broad clinical criteria are shown in [Table 24.4.2.5](#). The differences between the various syndromes described above are obvious early in the disease, but there is increasing overlap between the temporal and frontal syndromes as the disease progresses. MRI demonstrates a characteristic pattern of frontal and/or temporal lobe atrophy: in contrast to Alzheimer's disease, the changes involve the polar and lateral temporal structures and are asymmetrical, commonly involving the left side to a greater extent (see [Fig. 24.4.2.5](#)). The functional imaging (SPECT or PET) findings mirror the structural imaging results, with reduced frontotemporal perfusion and hypometabolism.

Management and prognosis

There is no curative treatment at present, so the general management of the person with dementia and their family, as discussed above, is of prime importance. Patients with a family history of dementia should be screened for tau or progranulin mutations after appropriate genetic counselling. The prognosis can be variable with different rates of progression between individuals. The disease is progressive and the average duration from diagnosis is around 5 to 10 years.

Dementia with Lewy bodies

Definition

Since the discovery in the 1960s that patients with Lewy bodies (ubiquitin-positive inclusions) in the cortex have a distinctive pattern of dementia with features of both Parkinson's and Alzheimer's diseases, it has been increasingly recognized as an important cause of dementia. The terminology has been confusing, with multiple designations including: Lewy body dementia, dementia of Lewy body type, diffuse Lewy body disease, and cortical Lewy body disease. The consensus clinical criteria for 'dementia with Lewy bodies' (DLB), the term now preferred, are shown in [Table 24.4.2.6](#).

Epidemiology

Dementia with Lewy bodies is a common cause of dementia in the elderly population, although the true prevalence remains unclear. As many as 12 to 36% of patients with a clinical diagnosis of Alzheimer's disease reach the pathological criteria for a diagnosis of dementia with Lewy bodies.

Table 24.4.2.5 The clinical diagnostic features of frontotemporal dementia (FTD)

Frontal syndrome
<i>I Core features</i>
A Insidious onset and gradual progression
B Early decline in social contact
C Early impairment in personal conduct
D Early emotional blunting
E Early loss of insight
<i>II Supportive features</i>
A Behavioural
i. Decline in personal hygiene and grooming
ii. Mental rigidity and inflexibility
iii. Distractibility and impersistence
iv. Hyperorality and dietary changes
v. Perseverative and stereotyped behaviour
vi. Utilization behaviour
B Speech and language
i. Altered speech output: –spontaneity and economy of speech –pressure of speech
ii. Stereotypic speech
iii. Echolalia
iv. Perseveration
v. Mutism
C Physical signs
i. Primitive reflexes
ii. Incontinence
iii. Akinesia, rigidity, and tremor
iv. Low and labile blood pressure
D Investigations
i. Neuropsychology: significant impairment on frontal lobe tests in the absence of severe amnesia, aphasia or perceptuospatial disorder
ii. Electroencephalography: normal on conventional EEG despite dementia
iii. Brain imaging (structural and or functional): predominant frontal and/or anterior temporal abnormality
Semantic dementia
<i>I Core features</i>
A Insidious onset and gradual progression
B Language disorder characterized by:
i. Progressive, fluent, empty spontaneous speech
ii. Loss of word meaning, manifest by impaired naming and comprehension
iii. Semantic paraphasias;
<i>and/or</i>

Table 24.4.2.5 (Cont'd) The clinical diagnostic features of frontotemporal dementia (FTD)

C Perceptual disorder characterized by:
i. Prosopagnosia: impaired recognition of identity of familiar faces; <i>and/or</i>
ii. Associative agnosia: impaired recognition of object identity
D Preserved perceptual matching and drawing reproduction
E Preserved single word repetition
F Preserved ability to read aloud and write to dictation orthographically regular words
<i>II Supportive diagnostic features</i>
A Speech and language
i. Pressure of speech
ii. Idiosyncratic word use
iii. Absence of phonemic paraphasias
iv. Surface dyslexia and dysgraphia
v. Preserved calculation
B Behaviour
i. Loss of sympathy and empathy
ii. Narrowed preoccupations
iii. Parsimony
C Physical signs
i. Absent or late primitive reflexes
ii. Akinesia, rigidity, and tremor
D Investigations
E Neuropsychology
i. Profound semantic loss, manifest in failure of word comprehension and naming, and/or face and object recognition
ii. Preserved phonology and syntax, and elementary perceptual processing, spatial skills, and day-to-day memory
F Electroencephalography normal
G Brain imaging (structural and/or functional): –predominant anterior temporal abnormality (symmetrical or asymmetrical)
Progressive non-fluent aphasia
<i>I Core diagnostic features</i>
A Insidious onset and gradual progression
B Non-fluent spontaneous speech with at least one of the following: –agrammatism, phonemic paraphrasias, anomia
<i>II Supportive diagnostic features</i>
A Speech and language
i. Stuttering or oral apraxia
ii. Impaired repetition
iii. Alexia, agraphia
iv. Early preservation of word meaning
v. Late mutism

(Continued)

Table 24.4.2.5 (Cont'd) The clinical diagnostic features of frontotemporal dementia (FTD)

B Behaviour
i. Early preservation of social skills
ii. Late behavioural changes similar to FTD
C Physical signs:
–late contralateral primitive reflexes, akinesia, rigidity, and tremor
D Investigations
i. Neuropsychology: non-fluent aphasia in the absence of severe amnesia or perceptuospatial disorder
ii. Electroencephalopathy: normal or minor asymmetrical slowing
iii. Brain imaging (structural and/or functional): asymmetrical abnormality predominantly affecting dominant (usually left) hemisphere

(Adapted with permission from Neary *et al.* (1998). Frontotemporal lobar degeneration: a consensus on clinical diagnostic criteria. *Neurology* **51**, 1546–54.)

Pathology

Pathological criteria require the presence of cortical and subcortical Lewy bodies. Confusingly, there is considerable overlap with the histological features of both Parkinson's and Alzheimer's diseases, although the distribution of pathology is the key to distinguishing these conditions. Lewy bodies are intracytoplasmic eosinophilic neural inclusions formed from altered cytoskeleton components that can be seen on haematoxylin and eosin staining, but are more prominently shown using anti-ubiquitin immunohistochemistry. The major component of the Lewy body is α -synuclein and anti-synuclein immunohistochemistry is the method of choice for detecting these lesions. Cortical Lewy bodies are found in the temporal lobe, insular cortex, and cingulate gyrus, and are always accompanied by typical 'core-and-halo' Lewy bodies in the substantia nigra (the pathological hallmark of Parkinson's disease). Dystrophic ubiquitin-positive neurites are also seen in the hippocampus, amygdala, nucleus basalis of Meynert, and other brainstem nuclei.

Changes of Alzheimer disease—neurofibrillary tangles and amyloid plaques—are seen in up to 50% of cases, raising nosological

Table 24.4.2.6 Clinical features of dementia with Lewy bodies

Dementia in association with:
Fluctuations in cognition (especially attention and alertness)
Visual hallucinations (typically well formed)
Mild spontaneous parkinsonism
Supportive features:
Repeated or unexplained falls, syncope, or transient loss of consciousness
Neuroleptic sensitivity syndrome
Hallucinations in other modalities
Systematized delusions

(Adapted with permission from McKeith *et al.* (1996). Consensus guidelines for the clinical and pathologic diagnosis of dementia with Lewy bodies (DLB): report of the consortium on DLB International Workshop. *Neurology* **47**, 1113–24.)

issues with Alzheimer's disease. The distribution of changes is of importance in distinguishing the conditions, e.g. neurofibrillary tangles in DLB commonly spare the hippocampus, which is severely affected in Alzheimer's disease.

The neurotransmitter changes in DLB reflect the areas of pathology, with severe dopamine depletion in the basal ganglia and marked reduction in acetylcholine throughout the cortex.

Clinical features

Patients typically present with a progressive cognitive decline paralleling that seen in those with Alzheimer's disease. There are, however, a number of characteristic and distinguishing features. First, there is a tendency to marked spontaneous fluctuations in cognitive abilities, particularly alertness and attention, producing a delirious state lasting days or even weeks. Second, visual hallucinations, illusions, and fleeting misidentification phenomena occur in 50 to 80% of those with the condition even at an early stage and without drug provocation. The hallucinations are commonly well-formed images of people or animals. The marked cholinergic deficit is postulated to be the cause of their tendency to visual hallucinations. Third is the occurrence of spontaneous parkinsonism, which is usually mild in the early stages. Rigidity, gait disturbance, and bradykinesia are all common, although in contrast to patients with Parkinson's disease the tremor is usually mild, atypical (with postural and action components), and symmetrical. Repeated falls also occur. In the later stages the akinetic rigid syndrome can cause severe disabilities in mobility and swallowing, and an increase in the number of falls. Fourth, there is often an exquisite sensitivity to neuroleptic medication, producing the malignant neuroleptic syndrome (delirium, hyperpyrexia, muscle rigidity, massive elevation of creatine phosphokinase, and renal failure).

Diagnosis

Neuropsychologically there is a mixture of subcortical and cortical features, with prominent cognitive slowing plus impairment of executive (planning and organizational) abilities and visuospatial abilities. Compared with patients with Alzheimer's disease, those with DLB tend to have greater deficits in attention and visuospatial processing. Memory loss may be less prominent than in Alzheimer's disease. There is no diagnostic test for this condition and the diagnosis *in vivo* relies on the clinical features described above and in Table 24.4.2.6. MRI shows similar changes to Alzheimer's disease, although there is a suggestion that medial temporal lobe atrophy is less pronounced. SPECT shows occipitoparietal hypoperfusion.

Management

The symptomatic management of this disorder is complicated by the presence of both hallucinations and an akinetic rigid syndrome. Patients are notoriously sensitive to the side effects of dopamine-enhancing medications used for the treatment of the akinetic rigid syndrome. However, although dramatic motor improvements are not to be expected, a cautious medication trial is worth attempting. Even though neuroleptic drugs should be avoided whenever possible, neuropsychiatric features, if severe, can be ameliorated with the newer atypical neuroleptics such as clozapine and olanzapine, without exacerbation of the parkinsonism. Thus, the main aim is to maintain a balance between the patient being mobile and the patient being lucid.

Marked improvement in attentional cognitive deficits in response to treatment with cholinesterase inhibitors, such as donepezil and rivastigmine, has been reported. Although there have been few controlled trial reports patients with DLB may respond better than those with Alzheimer's disease to this drug therapy.

Vascular dementia

Definition and epidemiology

Vascular dementia can be defined as a dementia resulting from a cerebrovascular disorder. This is obviously a broad categorization and many different aetiologies may be included in this rubric, e.g. multiple infarcts from cardiac emboli, vasculitides including systemic lupus erythematosus, primary cerebral amyloid angiopathy, and cerebral autosomal dominant arteriopathy with subcortical infarcts and leucoencephalopathy (CADASIL). The term 'multi-infarct dementia' was introduced in the 1970s to emphasize the contribution of multiple cerebral infarcts to clinical dementia syndromes, and to replace the older label of 'atherosclerotic dementia', although it is now apparent that diffuse small-vessel disease contributes significantly in the absence of clinically overt strokes. Traditionally regarded as the second most common cause of dementia, it is increasingly difficult to estimate the true contribution of vascular disease. Postmortem studies of patients with multi-infarct dementia show that Alzheimer's disease changes commonly coexist. Conversely, the advent of sensitive instruments for detecting cerebral vascular lesions *in vivo* (MRI) has revealed that presumed vascular changes are common in patients with the clinical diagnosis of Alzheimer's disease, even in young patients with known gene mutations, and that the presence of vascular lesions may be contributing to the severity of Alzheimer's disease. Finally, it is increasingly apparent that traditional risk factors for vascular dementia—including hypertension, diabetes, and hypercholesterolaemia—are also factors that increase the likelihood of developing both vascular dementia and Alzheimer's disease.

Clinicopathological vascular syndromes

The varieties of vascular diseases that affect the brain are legion, and the resultant clinical features and underlying pathology widely different (see Table 24.4.2.1). The most important vascular syndromes are considered below.

Large infarcts

Recurrent cerebral infarcts involving multiple main arterial territories (e.g. posterior or middle cerebral artery territories), resulting from thrombosis or embolism, can cause dementia with a stepwise cognitive decline. There is commonly a history of atherosclerotic risk factors (e.g. hypertension, smoking, and hypercholesterolaemia), other evidence of atherosclerotic cardiac or peripheral vascular disease, and neurological signs on examination (e.g. spasticity, hyperreflexia, extensor plantar responses, and a pseudobulbar palsy). There are often asymmetries on the neurological examination, and gait apraxia and/or bladder dysfunction can be early features. The cognitive picture is characterized by cortical features and is dependent on the sites of the lesions. There is often severe language impairment, visuospatial disturbance, amnesia, and dyspraxia, related to lesions in the middle and posterior cerebral artery distributions. Specific syndromes can result from discrete lesions, e.g. lesions of the left angular gyrus result in a fluent aphasia,

agraphia, acalculia, right–left disorientation, and finger agnosia known as Gerstmann's syndrome.

Lacunar infarcts

The small multiple lacunar lesions are caused by occlusion in the deep penetrating arterial branches. The underlying pathogenic mechanism is a distinct small-vessel arteriopathy with replacement of the muscle and elastin in the arterial wall by collagen, leading to tortuous vessel and microaneurysm formation as a result of long-standing hypertension. The basal ganglia, thalamus, and deep white matter are common sites for lesions, due to the nature of the arterial supply. These lacunes may coexist with the larger infarcts (described above), thereby contributing to a mixed picture. However, the typical presentation of the lacunar state is with a more subcortical syndrome causing impaired attention and frontal executive malfunction, forgetfulness, apathy, and emotional lability. Thalamic lacunes can result in a speech disorder and, if bilateral, in amnesia. Examination features are similar to those seen with larger infarcts, with rigidity, gait disturbance, and extrapyramidal and pyramidal signs.

Small-vessel disease (Binswanger's disease)

'Binswanger's disease' (or 'diffuse leucoarystosis') is the term applied to the radiologically defined syndrome of confluent subcortical and corpus callosal demyelination and loss of the cerebral white matter, which again typically complicates severe or accelerated hypertension. The clinical features are similar to those of the lacunar state described above. On CT there is symmetrical, diffuse, low-density periventricular hypodensity, which can be accompanied by ventricular dilatation. This is visualized with great sensitivity on T_2 -weighted MRI as a diffuse white matter of high intensity. Pathologically, there is demyelination, axonal loss, and gliosis, thought to be due to diffuse ischaemia in the territory of the long perforating arteries.

Cerebral amyloid angiopathy

Amyloid is deposited in the cerebral vessels both with increasing age and in a proportion of cases with ordinary Alzheimer's disease. However, there is also a rare and sometimes familial form of cerebral amyloidosis that produces recurrent cerebral haemorrhages and an Alzheimer's disease-type dementia. Amyloid deposition in the vessel walls causes structural weakness leading to intracerebral haemorrhages and narrowing of the vessel to produce ischaemia. The haemorrhages tend to be lobar and can be recurrent.

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leucoencephalopathy (CADASIL)

This recently established disorder may be a more common cause of vascular dementia than previously realized. Patients present in their early 20s with migraine-like headaches and subsequently develop stroke-like episodes, which are sometimes ascribed to migraine or may mimic the attacks of acute demyelination. A subcortical dementia syndrome develops during their fifth and sixth decades. MRI shows multiple subcortical infarcts and diffuse white-matter disease. Other clues to the diagnosis are the absence of risk factors for atherosclerotic disease and the strong family history. Pathologically there is a distinctive, nonamyloid, nonatherosclerotic angiopathy of the leptomeningeal and perforating arteries of the brain, with eosinophilic granular substance replacing smooth muscle. The diagnosis can also be confirmed with the finding of the same pathological changes in the cutaneous blood

vessels in a skin biopsy. Mutations in the *notch3* gene on chromosome 19 have been reported in patients with CADASIL.

Treatment of vascular dementia

The treatment should be directed to the amelioration of any underlying cause of the vascular disorder, such as reducing cardiac embolism and treating vasculitides and hypertension. The potential for altering the progression of the disease is alluring. Nevertheless, efforts directed at altering atherosclerotic risk factors tend to produce disappointing results. The course of vascular dementia can be as severe as or even more rapid than that of Alzheimer's disease.

Subcortical dementias

Despite shortcomings, the differentiation between cortical and subcortical dementias continues to be useful in clinical practice. This classification highlights the fact that, although disease of diverse cerebral structures can result in dementia, the resultant patterns of cognitive deficits are very different. Alzheimer's disease is the prototypical cortical dementia; vascular syndromes can present with a spectrum of features from cortical to subcortical, as can dementia with Lewy bodies. Purer forms of subcortical dementia result from pathology of the basal ganglia and white matter, the prototypical examples being Huntington's disease and progressive supranuclear palsy (Steele–Richardson–Olszewski syndrome). The typical cognitive pattern is that of attentional and executive dysfunction with marked cognitive slowing (bradyphrenia), causing problems with mentation and information retrieval. Memory is moderately impaired due to reduced attention and poor registration, but is not as severely impaired as in Alzheimer's disease. There is often an associated personality change and mood disturbance with prominent apathy. Spontaneous speech is impoverished and slow.

Huntington's disease

Huntington's disease is an autosomal dominant inherited disorder with an incidence of about 4 per 100 000. The mutation is an expansion of the trinucleotide repeat (CAG) in the IT-15 gene on chromosome 4, which encodes the polyglutamine protein, huntingtin, essential for nervous system development. There is a clear dose–response relationship between the length of the CAG repeat and the age of onset of the disorder. Psychiatric symptoms, such as depression, irritability, and personality changes, often precede the motor disorder, which is typically choreiform. The other cognitive changes that develop over the next 10 to 20 years are of a subcortical pattern, with deficits in attention and concentration, executive function, and retrieval from memory.

Progressive supranuclear palsy

Progressive supranuclear palsy (PSP) is a rare, but increasingly recognized, disorder with an incidence of 1 to 2 per 100 000. The subcortical dementia is accompanied by an atypical parkinsonian syndrome. The motor deficits are symmetrical in onset, with severe rigidity in the axial muscle groups and bulbar symptoms. A supranuclear gaze palsy invariably develops, but in the early stages the only feature may be slowing of fast downward movement (saccadic slowing). Another early feature is a marked tendency to falls. The pathological features are neurofibrillary tangles, neuropil threads, and neuronal loss and gliosis in the subthalamic nucleus, red nucleus, substantia nigra, and dentate nucleus. The main

neurotransmitter deficit is in dopamine. Unlike Parkinson's disease, PSP does not respond well to levodopa. The disease progresses rapidly with an average time course of around 5 years.

Parkinson's disease

Subcortical dementia occurs in about one-third to one-half of patients with Parkinson's disease, which develops at a late stage in the motor disorder in contrast to dementia with Lewy bodies.

Corticobasal degeneration

Corticobasal degeneration is a rare cause of a dementia and motor signs. Patients present with an asymmetrical akinetic rigid syndrome, together with limb apraxia, and the almost pathognomonic feature of alien limb phenomenon in which the hand(s) acts as if 'with a will of its own'. Myoclonus and dystonia also occur. Dementia is common in the later stages and there is considerable overlap with frontotemporal dementia. The pathology is focused in the frontal and parietal cortices as well as the substantia nigra, basal ganglia, and thalamus.

Treatable causes of dementia

Normal-pressure hydrocephalus

Normal-pressure hydrocephalus has a classic triad of presenting features: cognitive impairment, gait disturbance, and incontinence. The cognitive features are typically those of a subcortical dementia with frontal features and psychomotor slowing. The gait disorder is a dyspraxia and may show the pathognomonic feature of 'being stuck to the floor', although there is an absence of signs when the patient is examined in the supine position. The condition may be secondary to a prior disturbance of CSF flow (resulting from, for example, a head injury, meningitis, or a subarachnoid haemorrhage), but often no cause is found in older people. Neuroimaging shows ventricular enlargement disproportionate to the degree of cortical atrophy. The presence of periventricular lesions can make the distinction from vascular dementia difficult. The investigation and management of these patients should be undertaken by neurosurgeons, the definitive treatment being ventricular shunting. If treated early the prognosis is good.

Chronic subdural haematomas

This treatable cause of dementia is caused by head trauma. It is common in individuals at risk of recurrent head injuries, such as older people, those with alcohol problems, and people with epilepsy. Risk is also increased by coagulation disorders, either pathological or iatrogenic. The clinical features are of a subacute dementia with symptoms of raised intracranial pressure, fluctuating cognitive performance, and focal neurological signs. Diagnosis is confirmed by neuroimaging, the peripheral mass lesions may be of varying signal density on CT, depending on the age of the lesion. If the lesions are isodense with the brain tissue, the diagnosis can be easily overlooked. Treatment is by neurosurgical evacuation, except in clinically insignificant collections. Although the outcome is good, about 10 to 40% of patients have a recurrence that may require further drainage.

Benign tumours

Subfrontal meningiomas are the classic tumours that present with features of a frontal dementia. The onset is usually insidious with

personality changes and other frontal features. Besides the neuropsychological abnormalities there may be anosmia or unilateral visual failure and optic atrophy. Other relatively benign midline tumours occasionally present with hydrocephalus and cognitive impairment secondary to this (e.g. colloid cysts of the third ventricle and nonsecretory pituitary tumours).

Metabolic and endocrine disorders

Metabolic derangements can give rise to acute-onset cognitive impairments, but the features are invariably those of a delirium rather than a dementia. Chronic hypocalcaemia and recurrent hypoglycaemia can result in a dementia often accompanied by ataxia and involuntary movements. Endocrine disorders can more frequently present with a dementia syndrome, with or without psychiatric features (e.g. hypothyroidism, Addison's disease, and hypopituitarism). The prominent complaints common to most disorders are mental slowing, apathy, and poor memory. Cushing's disease can present with psychiatric features, although a dementia syndrome is rarer. Although not strictly an endocrine disorder, Hashimoto's encephalopathy is a recently recognized cause of chronic delirium or dementia, often accompanied by seizures and fluctuating focal neurological signs. The diagnosis is made by finding extremely high levels of antithyroid antibodies despite a euthyroid state. Patients respond well to high-dose steroid therapy.

Deficiency states

Vitamin B₁₂ deficiency can cause the classic picture of subacute combined degeneration of the spinal cord and a dementia. The dementia can be variable in severity and it is unusual to present without some features of peripheral neurological disease, at least diminished vibration sense in the lower limbs and/or sensory ataxia. Reflexes can be increased, decreased, or mixed. Although most patients have a macrocytic anaemia, neurological manifestations can occasionally occur in the absence of haematological features. Severe thiamine (vitamin B₁) deficiency results in the Wernicke-Korsakoff syndrome, with delirium, ataxia, and ophthalmoplegia. The most common causes are alcoholism and recurrent prolonged vomiting, such as hyperemesis gravidarum. If not promptly treated a chronic amnesic syndrome can occur.

Infections

Neurosyphilis, once a common cause of dementia, is now rare. The associated neurological features include pupillary abnormalities, optic atrophy, ataxia, and pyramidal signs. The diagnosis is confirmed with serology and examination of CSF. Treatment with penicillin can result in some improvement. Those at increased risk are people inadequately treated for syphilis and those infected with the human immunodeficiency virus (HIV). HIV infection is an increasingly common cause of dementia in some parts of the world. The encephalopathy (AIDS-dementia complex) is characterized by psychomotor slowing, personality change, and other features of a subcortical dementia. Examination of the CSF can show a pleocytosis and increased protein and oligoclonal bands. White-matter changes are visible on neuroimaging. Cognitive changes in patients with HIV may also be due to opportunistic infections such as cerebral toxoplasmosis and cryptococcal meningitis, and progressive multifocal leucoencephalopathy, which all require specific treatment.

Further reading

- American Psychiatric Association (1994). *Diagnostic and statistical manual of mental disorders*, 4th edition (DSM-IV). American Psychiatric Association, Washington DC.
- Bak TH, Hodges JR (1998). The neuropsychology of progressive supranuclear palsy. *Neurocase*, **4**, 89–94.
- Berrios GE, Markova IS, Giralda N (2000). Functional memory complaints: hypochondria and disorganisation. In: Berrios GE, Hodges JR (eds) *Memory disorders in psychiatric practice*, pp. 384–99. Cambridge University Press, Cambridge.
- Braak H, Braak E (1991). Neuropathological staging of Alzheimer-related changes. *Acta Neuropathol (Berlin)*, **82**, 239–59.
- Goedert M, Spillantini MG, Davies SW (1998). Filamentous nerve cell inclusions in neurodegenerative diseases. *Curr Opin Neurobiol*, **8**, 619–32.
- Greene JDW, Hodges JR (2000). The dementias. In: Berrios GE, Hodges JR (eds) *Memory disorders in psychiatric practice*, pp. 122–63. Cambridge University Press, Cambridge.
- Gregory CA, Hodges JR (1996). Frontotemporal dementia: use of consensus criteria and prevalence of psychiatric features. *Neuropsychiatry Neuropsychol Behav Neurol*, **9**, 145–53.
- Harvey J *et al.* (1998). Genetic dissection of Alzheimer's disease and related dementias: amyloid and its relationship to tau. *Nat Neurosci*, **1**, 355–8.
- Harvey RJ (2001). Epidemiology of pre-senile dementia. In: Hodges JR (ed.) *Early onset dementia*, pp. 1–23. Cambridge University Press, Cambridge.
- Hodges JR, Patterson K (1995). Is semantic memory consistently impaired early in the course of Alzheimer's disease? Neuroanatomical and diagnostic implications. *Neuropsychologia*, **33**, 441–59.
- Hodges JR *et al.* (1992). Semantic dementia: progressive fluent aphasia with temporal lobe atrophy. *Brain*, **115**, 1783–806.
- Hodges JR *et al.* (1999). The differentiation of semantic dementia and frontal lobe dementia (temporal and frontal variants of fronto-temporal dementia) from early Alzheimer's disease: a comparative neuropsychological study. *Neuropsychology*, **13**, 31–40.
- Hodges JR (2007). *Frontotemporal demential syndromes*. Cambridge University Press, Cambridge.
- Jellinger K *et al.* (1990). Clinicopathological analysis of dementia disorders in the elderly. *J Neurol Sci*, **95**, 239–58.
- Kalaria RN, Ballard C (1999). Overlap between pathology of Alzheimer's disease and vascular dementia. *Alzheimer's Disease and Associated Disorders*, **13**, S115–23.
- Kaliki HW *et al.* (2006). Therapeutic approaches to Alzheimer's disease. *Brain*, **129**, 2840–55.
- Klunk WE *et al.* (2004). Imaging brain amyloid in Alzheimer's disease with Pittsburgh Compound-B. *Ann Neurol*, **55**, 303–5.
- Linn RT *et al.* (1995). The 'preclinical phase' of probable Alzheimer's disease. *Arch Neurol*, **52**, 485–90.
- McKeith IG *et al.* (1996). Consensus guidelines for the clinical and pathologic diagnosis of dementia with Lewy bodies (DLB): report of the consortium on DLB International Workshop. *Neurology*, **47**, 1113–24.
- McKeith IG. (2006). Consensus guidelines for the clinical and pathologic diagnosis of dementia with Lewy bodies (DLB): report of the Consortium on DLB International Workshop. *J Alzheimer's Dis*, **9** Suppl 3, 417–23.
- McKhann G *et al.* (1984). Clinical diagnosis of Alzheimer's disease: report of the NINDS-ADRDA Work Group under the auspices of the Department of Health and Human Services Task Force on Alzheimer's disease. *Neurology*, **34**, 939–44.
- Mackenzie IR (2007). The neuropathology and clinical phenotype of FTD with progranulin mutations. *Acta Neuropathol*, **114**, 49–54.
- Masters CL, Beyreuther K (2006). Alzheimer's centennial legacy: prospects for rational therapeutic intervention targeting the Abeta amyloid pathway. *Brain*, **129**(Pt 11), 2823–39.

- Mesulam MM (1982). Slowly progressive aphasia without generalized dementia. *Ann Neurol*, **24**, 17–22.
- Neary D *et al.* (1998). Frontotemporal lobar degeneration: a consensus on clinical diagnostic criteria. *Neurology*, **51**, 1546–54.
- Rahman S *et al.* (1999). Specific cognitive deficits in early frontal variant frontotemporal dementia. *Brain*, **122**, 1469–93.
- Reisberg B *et al.* (1997). Diagnosis of Alzheimer's disease. Report of an International Psychogeriatric Association Special Meeting Work Group Under the Cosponsorship of Alzheimer's Disease International, the European Federation of Neurological Societies, the World Health Organization, and the World Psychiatric Association. *Int Psychogeriatr*, **9**, S11–38.
- Rockwood K *et al.* (1999). Subtypes of vascular dementia. *Alzheimer's Disease and Associated Disorders*, **13**, S59–65.
- Roman GC *et al.* (1993). Vascular dementia: diagnostic criteria for research studies. Report of the NINDS-AIREN International Workshop. *Neurology*, **43**, 250–60.
- Snowden JS, Neary D, Mann DMA (1996). *Fronto-temporal lobar degeneration: fronto-temporal dementia, progressive aphasia, semantic dementia*. Churchill Livingstone, Hong Kong.
- van Swieten J, Spillantini MG (2007). Hereditary frontotemporal dementia caused by Tau gene mutations. *Brain Pathol*, **17**(1), 63–73.

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