24.4.2 Alzheimer’s disease and other dementias 583

24.4.2 Alzheimer’s disease and other dementias 5830 Jonathan M. Schott

SECTION 24 Neurological disorders 5830 frontal cortex. Although devastating in their effects on social func- tion, such lesions are notoriously difficult to detect using standard psychometric tests. Patients lack empathy and emotional warmth (e.g. if confronted with something as serious as the admission to hospital of their partner, their primary concern may be that their mealtime routine will be disturbed). They are disinhibited and ob- livious to social mores such that they may be overly familiar with strangers, disregard personal space, and make inappropriate com- ments or gestures (often of a sexual nature). They often make rash and irresponsible decisions such as spending money above their means. They may develop stereotyped and ritualistic behaviours such as insisting on always taking a particular route when shop- ping or repetitively closing doors in the home: these behaviours can be so severe as to constitute a secondary obsessive–compulsive disorder syndrome. A useful clue is often the presence of a change in eating behaviour. Patients may become fixated on one dish; often they develop a pref- erence for sweet foods. A lack of normal satiety means that they may overeat, often with secondary weight gain. Imitation and utilization behaviour are dramatic phenomena related to orbital frontal lobe damage. The patient with imita- tion behaviour unconsciously mimics the examiner’s posture and mannerisms regardless of how absurd they are: raising an arm in the air, placing a leg on the desk, or sitting on the floor. Utilization behaviour is even more striking: patients will use any object placed in their grasp. The classic example is the patient offered multiple pairs of spectacles who attempts to wear them all, one on top of another. Amotivational states Medial frontal lesions are particularly associated with apathy. Patients lack spontaneity, they will not initiate conversation although they can reply to specific questions. In keeping with this observation, per- formance on tests such as the letter fluency task, described earlier, is severely impoverished. If left to their own devices, they may not spontaneously move, preferring to sit in a chair staring blankly into space. This apathy has also been termed ‘abulia’ in the past; in its most extreme form where the individual lies motionless

with no speech, the term ‘akinetic mutism’ has also been applied. The cata- tonic phenomenon of maintaining postures when the limbs are moved by the examiner may also be seen. Patients with depression also show marked apathy, although it is accompanied by both the biological features of depression (anorexia, diurnal variation, and so on) and internal symptoms of mood disturbance (pessimism, suicidal thoughts, anhedonia, and so on). Temporal lobe syndromes In addition to the cognitive deficits that can occur with temporal lobe lesions such as amnesia and loss of semantic knowledge, be- havioural disturbances can also occur. The most severe, secondary to bilateral anterior temporal damage (including the amygdala), is the Klüver–Bucy syndrome, which comprises three characteristic features: placidity, even in threatening situations; indiscriminant hypersexuality; and oral exploration of objects. Other behaviours have been described in temporal lobe dysfunction, particularly, although not exclusively, in association with interictal temporal lobe epilepsy. These include preoccupation with religious or philo- sophical issues and a tendency to excessive writing. FURTHER READING Baddeley AD (1999). Essentials of human memory. Psychology Press, Hove. Berrios GE, Hodges JR (2000). Memory disorders in psychiatric prac- tice. Cambridge University Press, Cambridge. Brok P (2004). Into the silent land: travels in neuropsychology. Atlantic Books, London. Cappa SF, et al. (2008). Cognitive neurology: a clinical textbook. 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 vi- sion: 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. McCarthy RA, Warrington EK (1990). Cognitive neuropsychology: a clinical introduction. Academic Press, San Diego, CA. Mesulam MM (1998). From sensation to cognition. Brain, 121, 1013–52. Miller BL, Boeve BF (2009). The behavioural neurology of dementia. Cambridge University Press, Cambridge. Patterson K, Lambon-Ralph MA (1999). Selective disorders of reading? Current Opin Neurobiol, 9, 235–9. Patterson K, et al. (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, NY. 24.4.2 Alzheimer’s disease and other dementias Jonathan M. Schott ESSENTIALS Dementia is a syndrome of progressive impairment in memory and other cognitive deficits (aphasia, apraxia, agnosia, or disturb- ance in executive function) in the absence of another explanatory central nervous system disorder, depression, or delirium, sufficient to interfere with activities of daily living. In recent years there has been a move to consider and classify patients with less severe forms of cognitive impairment—so-called mild cognitive impairment— and nonmemory presentations, with the latest DSM-V criteria

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 identifying individuals with major or minor neurocognitive syn- dromes. Ongoing research using biomarkers suggest that there is a long presymptomatic phase for many causes of dementia. Epidemiology and classification Prevalence—dementia is common, affecting about 7% of all people over 65 years, rising to over 20% of those over 85 years. It is esti- mated that there are over 35 million people with dementia

world- wide, and that this will increase to over 65 million by the year 2030, and over 115 million by 2050. Classification—dementia is a syndrome with many causative dis- eases. Most cases of dementia are due to neurodegenerative diseases— including Alzheimer's disease, Lewy body diseases, frontotemporal dementia—and/or vascular syndromes. Some causes of dementia may be at least partially reversible, and these must always be considered and excluded. A very large number of rarer causes of dementia are rec- ognized, often presenting in younger individuals, and with additional, noncognitive clinical features—so-called 'dementia plus'. The various dementias Alzheimer's disease—the most common cause of dementia, is thought to be initiated by cerebral accumulation of the Aβ fragment of
the amyloid precursor protein, followed by deposition and propa- gation of tau through vulnerable neural networks, inflammation, and ultimately irreversible neuronal and neurotransmitter loss. The typical initial cognitive deficit is impairment of episodic memory which is likely to reflect early medial temporal lobe involvement. Progression of disease is marked by failing memory, increasing dis- ability in managing complex day-to-day activities, mental inflex- ibility, and poor concentration, eventually leading to language and visuospatial impairments, apraxia, and failure of semantic memory. Nonmemory presentations with primary language, visual, and be- havioural presentations are also seen, particularly in younger pa- tients. 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, depend- ence, and incontinence. Diagnosis is based on clinical assessment increasingly supported by biomarkers, which allow both for more specific and earlier diagnosis. The mainstay of treatment is social sup- port and increasing assistance with day-to-day activities. Two classes of symptomatic medications—the acetyl-cholinesterase inhibitors and memantine—generally achieve modest improvements in cog- nition in around 25–50% of patients. Several disease-modifying ap- proaches are currently undergoing clinical trials. Frontotemporal dementia—is increasingly recognized as a common cause of dementia, particularly in younger patients. The pathology is usually accumulation of tau or 43 kDa TAR DNA- binding protein (TDP-43) inclusions. Clinical presentation is with progressive changes in personality and behaviour, or with progres- sive aphasia. A significant proportion of patients, particularly with behavioural presentations, have a family history, with mutations in three genes (tau, progranulin, C9orf72) accounting for the majority of inherited forms. There are no specific treatments. Dementia with Lewy bodies—is a common cause of dementia in older people. Typical presentation is with progressive cognitive de- cline, broadly similar to that seen in Alzheimer's disease, but with several characteristic features including: marked spontaneous fluctuations in cognitive abilities; visual hallucinations; and parkin- sonism. Patients may respond to treatment with cholinesterase in- hibitors, but neuroleptic drugs should be avoided whenever possible. Dementia with Lewy bodies is likely to be on the same spectrum as Parkinson's disease dementia, where similar symptoms follow the emergence of motor problems. Vascular cognitive impairment—a wide variety of vascular diseases of the brain can result in cognitive symptoms, the most important syndromes being large vessel infarction; and cerebral small vessel disease which encompasses several different entitites including small subcortical infarcts (lacunes), white matter hyperintensities, and cere- bral amyloid angiopathy.
A range of rare genetic and inflammatory causes of vascular cognitive impairment are recognized. Particularly in older people, combinations of vascular cognitive impairment and Alzheimer's disease or other neurodegenerative dementias are common—so-called 'mixed dementia'. Treatment is that of the underlying vascular or inflammatory disease. Other neurodegenerative conditions associated with dementia in- clude: Huntington's disease, progressive supranuclear palsy, and corticobasal

degeneration. Prion diseases are rare but important causes of dementia which can occur on a sporadic, inherited or acquired basis, and are dis- cussed in Chapter 24.11.5. Potentially treatable causes of dementia include: hydrocephalus; chronic subdural haematomata; benign tumours; metabolic and endocrine disorders—including hypothyroidism, Addison's disease, and hypopitu- itarism; deficiency states—including vitamin B12 deficiency; infections— including neurosyphilis and human immunodeficiency virus infection; transient epileptic amnesia; and inflammatory/autoimmune disorders. Introduction Concepts of dementia have evolved considerably over time. Moving from an initial formulation as progressive global intellectual de- terioration, for many years the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) criteria prevailed, defining dementia 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 an- other explanatory central nervous system disorder, depression, or delirium, resulting in symptoms sufficient to interfere with daily living. As researchers and clinicians became more aware of the spe- cific early cognitive profiles associated with different dementia syn- dromes, for example, that in early Alzheimer's disease there may be isolated memory impairment many years before more widespread deficits develop, the concept of mild cognitive impairment was intro- duced, latterly refined to include amnestic and nonamnestic forms, and single and multidomain impairments. More recently, DSM-V has proposed the use of the terms minor and major neurocognitive syndromes to reflect both the range of severity and causes of cogni- tive impairment. While still currently only within the research do- main, the advent of disease-specific biomarkers has led to the field increasingly moving towards attempts to define individuals with prodromal or presymptomatic forms of dementia. For the purposes of this chapter, the term dementia will be used to discuss all causes of symptomatic cognitive decline.

 Importantly, dementia is not a diagnosis, but a syndrome that may result from many diseases. Some causes may be at least par- tially remediable, and therefore always warrant consideration and exclusion. However, most are due to neurodegenerative diseases, cerebrovascular disease, or combinations of both. While for most diseases post-mortem brain examination is the only means of definitively determining the cause of an individual's dementia, careful clinical assessment based on the pattern and progression of cognitive loss and allied clinical features, supplemented by investigations, allows for a specific diagnosis to be reached with a high degree of accuracy in most cases. This in turn allows for appropriate treatments to be instigated, bespoke care plans to be designed, and can guide prognostication. At the same time, advances in genetics, cellular biology and the development of novel biomarkers have greatly enhanced our understanding of the processes that lead to the development of specific dementia syn- dromes. These advances pave the way for rational treatments aiming to modify the underlying pathophysiology, with the ultimate aim of slowing, or ideally preventing, the development of cognitive impairment. Not least given the changes in definitions, the incidence of dementia is difficult to establish, but community prevalence studies suggest that about 7% of all people over 65 years of age suffer from dementia. This shows a marked increase with advancing age: between the ages of 65–69 the prevalence is c.1.7%, approxi- mately doubling every five years such that more than 1/3 individ- uals over the age of 90 will be affected. While much rarer in younger patients, current estimates suggest that there are over 40 000 people in the United Kingdom with young onset dementia (onset before 65 years). Since dementia is predominantly a disorder of later life, the pro- jected increase in the older population, represents an increasing problem for individuals and society. In 2018 it was estimated

that there were c.50 million people with dementia worldwide, and this would increase to c.152 million by 2015. This increase is predicted to be most marked in low or middle income countries who represent 58% of the total number of cases now, a figure predicted to rise to 71% by 2050. The annual costs of dementia are currently estimated to be $1 trillion dollars, rising to over $ 2 trillion by 2030. Causes of dementia The dementias can be classified in several ways, the most common being based on aetiology (Table 24.4.2.1). The most common causes of dementia before and after the age of 65 years (the arbi- trary cut-off usually used to define late vs. young onset dementia) are shown in Fig. 24.4.2.1. The relative frequencies of causes of de- mentia differ depending on age, but it is notable that Alzheimer's disease is the most common cause in both groups. The genetic forms of neurodegenerative dementias and other rarer causes are more common in the younger age group. Clinical assessment Accurate diagnosis of the dementias starts with a detailed clin- ical assessment. This should aim to determine if there is indeed evidence for cognitive impairment, and if so, whether it is life-long Table 24.4.2.1 Causes of dementia Neurodegenerative diseases Alzheimer's disease Frontotemporal dementia (behavioural variant and primary progressive aphasias)a Dementia with Lewy bodies Parkinson's disease dementia Huntington's disease and Huntington's disease-like syndromes 1–3 Progressive supranuclear palsy Corticobasal degeneration Multiple system atrophy Primary age-related tauopathy Argyrophilic grain disease Spinocerebellar ataxias (especially types 2, 12, 17) Fragile-X tremor ataxia syndrome Familial British and Danish Dementia Dentato-rubro pallidolusyian atrophy (DRPLA) Neurodegeneration with brain iron accumulation Vascular diseases Large vessel ischaemia Cerebral small vessel disease Hypertensive encephalopathy Vasculitides: • systemic lupus erythematosus • polyarteritis nodosa • Behçet's disease • giant-cell arteritis • primary CNS angiitis • cerebral amyloid angiopathy-related inflammation Inherited vascular cognitive disorders: • CADASIL • cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy • retinal vasculopathy with cerebral leukodystrophy • hereditary cerebral amyloid angiopathies anoxia postcardiac arrest sickle-cell disease superficial siderosis Infections HIV infection Progressive multifocal encephalopathy Cerebral toxoplasmosis Cryptococcal meningitis Neurosyphilis Subacute sclerosing panencephalitis Progressive rubella encephalitis Viral encephalitis Viral, bacterial, and fungal meningitides Whipple's disease (continued)

 Prion diseases: • sporadic Creutzfeldt–Jakob disease • familial prion diseases • iatrogenic prion disease • variant Creutzfeldt–Jakob disease Neoplastic causes Primary intracerebral tumours: • frontal gliomas • posterior corpus callosal or midline tumours (thalamic, pineal, third ventricle) • cerebral lymphoma Extracerebral tumours: • frontal meningiomas • posterior fossa tumours (acoustic neuromas) Tumours causing hydrocephalus multiple cerebral metastases malignant meningitis Toxic causes Alcoholic dementia Heavy metals: • lead, mercury, manganese • carbon monoxide poisoning • drugs: illicit and prescribed Acquired metabolic disorders and deficiency states Chronic renal failure Dialysis dementia Porto-systemic encephalopathy Hypothyroidism Cushing's disease Addison's disease Panhypopituitarism Hypoglycaemia (chronic or recurrent) Hypoparathyroidism Vitamin B12, B1, and folate deficiency Malabsorption syndromes Inherited metabolic disorders (that may present in adulthood) Wilson's disease Porphyria Leucodystrophies: • adrenoleucodystrophy • metachromatic leucodystrophy • globoid-cell leucodystrophy • Alexander's disease • vanishing white matter disease • polyglucosan body disease Gangliosidoses Niemann–Pick Type C Cerebrotendinous xanthomatosis Adult-onset neuronal ceroid-lipofuscinosis (Kuf's disease) Mitochondrial cytopathies Subacute necrotizing encephalopathy (Leigh's disease) Fabry's disease Trauma Major head injury

Subdural haematoma Dementia pugilistica Hydrocephalus: communicating and obstructive Inflammatory/autoimmune Multiple sclerosis Sarcoidosis Acute disseminated encephalomyelitis Lgi1 and CASPR2 antibody mediated limbic encephalitis NMDA-antibody associated encephalitis Paraneoplastic (limbic) encephalitis Miscellaneous Polycystic lipomembranous sclerosing leukoencephalopathy (Nasu Hakola disease) Neuroferritinopathy Hereditary diffuse leukoencephalopathy with spheroids Fragile-X tremor ataxia syndrome Neuroacanthocytosis Giant axonal neuropathy Progressive myoclonic epilepsy syndromes a Several different underlying pathologies (see text). (a) Other 29% DLB 7% FTD 12% VaD 18% AD 34% (b) DLB 20% Other 5% VaD 20% AD 55% Fig. 24.4.2.1 Relative frequency of different causes of dementia (a) before 65 yrs and (b) after 65 yrs. DLB refers to all Lewy body dementia, and to pathologically confirmed rather than clinically diagnosed cases Table 24.4.2.1 Continued

SECTION 24 Neurological disorders 5834 and nonprogressive (i.e. not due to dementia) or acquired. It is im- portant to distinguish between dementia and delirium (see next) as they are associated with different causes, although commonly coexist. Exclusion of potentially treatable forms of cognitive im- pairment is vital, as is the identification of significant psychi- atric morbidity that can mimic or complicate organic forms of dementia. The history—supplemented wherever possible by an informant—should include ascertainment of the onset, progres- sion, and current cognitive impairments as well as prior medical, medication and family history, and use of illicit drugs, tobacco, and alcohol. The cognitive examination allows for the extent and focality of cognitive function to be assessed, which is diagnos- tically helpful as different dementia syndromes target different brain regions. Physical examination may reveal important clues to the diagnosis (e.g. the presence of parkinsonism in dementia with Lewy bodies, or patchy upper motor neuron signs in vas- cular cognitive impairment). This is particularly important in patients with younger onset or atypical dementias where the dif- ferential diagnosis is large, and any additional symptoms and signs—so-called ‘dementia plus’—may provide important clues to the diagnosis. Investigation has historically focused on excluding ‘treatable’ causes of dementia, with a range of blood tests to exclude major metabolic, infectious, or inflammatory processes, and structural brain imaging to rule out lesions potentially amenable to neurosur- gery (e.g. tumours, subdural haematomata, and hydrocephalus). Increasingly, however, investigations are directed to determining dementia subtypes. Formal neuropsychology provides quantita- tive information about the extent and pattern of an individual’s performance relative to their expected cognitive performance and age-related normative ranges, and can be very informative both in determining whether there is objective impairment, and in differ- ential diagnosis. Magnetic resonance imaging (MRI) allows for the assessment of specific patterns of brain atrophy which have posi- tive predictive pattern for many of the major neurodegenerative forms of dementia; the presence of white matter lesions can indi- cate cerebrovascular disease, inflammation, or suggest a range of rarer causes of dementia; and the diagnosis of prion diseases has been revolutionized by the advent of diffusion weighted imaging. In selected cases, cerebrospinal fluid examination may not only be helpful in excluding infection or inflammation in atypical cases, but also in making a positive diagnosis of Alzheimer’s disease and diagnosing prion disease. Molecular imaging can provide evidence for central dopaminergic depletion in Lewy body diseases and other conditions associated with parkinsonism; and the advent of specific positron emission tomography (PET) ligands binding fi- brillar amyloid allows for the demonstration of Alzheimer-related pathology in vivo. In the appropriate clinical context, and with suitable counselling and consent, genetic testing—increasingly performed using next generation sequencing which allows for multiple different genetic mutations to be assessed in

parallel— may allow for autosomal dominant forms of dementia to be def- initely diagnosed during life. In unusual or atypical forms of dementia, a very wide range of investigations (Table 24.4.2.2), ranging from blood testing, advanced imaging, and tissue biopsy may be required to reach the diagnosis, with brain biopsy reserved for the very few individuals in whom a potentially treatable cause (e.g. central nervous system vasculitis) is possible, yet cannot be diagnosed by other means. Management of the demented patient depends on the cause, se- verity, and social situation. Specific medications are available for certain diseases (discussed next). Appropriate management of comorbidities (e.g. vascular risk factors and depression) is important. The extent to which additional care or other interventions are re- quired will depend on the individual patient and their circumstances, and needs to be re-evaluated as the disease progresses over time. In the sections that follow, the main differential diagnostic alter- natives to dementia are considered; the major neurodegenerative causes of dementia and vascular cognitive impairment are reviewed; and other important and 'treatable' causes of dementia are discussed. Prion diseases are discussed in Chapter 24.11.5. Differential diagnosis of dementia Psychiatric causes of cognitive impairment A wide variety of psychiatric disorders are associated with cognitive symptoms. Cognitive symptoms are common in depression, particu- larly in the older population. The main complaints are of poor recent memory and concentration, and distractibility. There may be a lack of subjective feelings of depression, thereby making the diagnosis Table 24.4.2.2 Investigation of dementia Routine Full blood count and ESR Biochemical profile (urea and creatinine, electrolytes, calcium, liver function) Vitamin B12 and folate levels Thyroid function Chest radiography Structural brain imaging (MRI preferred over CT) Neuropsychological examination Other tests which may be indicated in certain cases Electroencephalography Fluorodeoxyglucose PET or SPECT Amyloid PET Whole body FDG-PET CT CSF examination (including measures of Aβ1-42 and tau) Screening for autoimmune/inflammatory disease Screening for cardiac sources of emboli Slit-lamp examination Specific blood and/or urine tests for inherited metabolic disorders Screening for HIV and other infections Genetic testing – with suitable consents Sleep study Tissue biopsy Cerebral biopsy ESR, erythrocyte sedimentation rate; RBC, red blood cells; CT, computed tomography; EEG, electroencephalogram; MRI, magnetic resonance imaging; PET, positron emission tomography; SPECT, single-photon emission computed tomography; CSF, cerebrospinal fluid; HIV, human immunodeficiency virus.

 difficult. Although not always present, the so-called biological fea- tures of depression include sleep disturbance, and loss of appetite and libido. Other common symptoms are low energy, lack of interest in hobbies and activities, and nihilism about the future. There may be a past personal or familial history of depression. The cognitive picture is typically of impaired attention and patchy performance on memory and frontal tasks. There may be some inconsistency in test perform- ance and often patients easily give up on testing. Language output may be sparse but individual words are usually pronounced normally. Even after detailed testing, it may on occasions be difficult to distinguish de- pression from dementia, noting that depression may coexist with, and is not an uncommon consequence of a diagnosis of dementia; and in some cases, late onset depression may be an early sign of a developing neurodegenerative disease. If doubt remains, a therapeutic trial of an antidepressant and or psychiatric assessment may be warranted, and the patient should be monitored to ensure there is no progression. A related group of patients who make up a significant proportion of referrals particularly to young onset dementia clinics are those anx- ious about their cognition in the absence of objective evidence for significant impairments—sometimes referred to as the

‘worried well’, or as having subjective cognitive impairment. In contrast to patients with dementia, these individuals are often much more concerned about their symptoms than their friends or family members; appro- priate investigation and explanation is the mainstay of management. Patients with major psychiatric disorders, including schizophrenia, may have significant psychomotor retardation sufficient to mimic dementia. Long-term use of antipsychotic drugs can produce par- kinsonian features resembling Lewy body disease; in these cases, a negative dopamine transporter scan may be helpful to exclude the latter. Finally, rarely patients may present with a rapid onset of memory and/or intellectual impairment likely representing a form of conversion disorder. There is loss of personal identity and salient personal and life events, which is unlike most organic disorders of memory. There may be an obvious precipitant (such as marital 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, for example, when asked ‘How many legs does a horse have?’, they reply three or five. Even with such functional states, the examiner must be aware that some organic (e.g. autoimmune) conditions can present rap- idly and with unusual symptoms, and that concomitant organic dis- orders can exaggerate the psychiatric condition. Delirium This clinical syndrome may be caused by a range of disorders af- fecting the brain including intracranial infections, head trauma, epi- lepsy (postictal states and nonconvulsive status), raised intracranial pressure, or subarachnoid haemorrhage, or secondary to many sys- temic illnesses or insults—including infections, metabolic derange- ments, 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 hal- lucinations, 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 be- haviour. The most consistent abnormality is inattention, with a re- duced ability to maintain attention to external stimuli, leading to distractibility and difficulty answering questions, and to appropri- ately 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 a proportion of older people no cause is found. Importantly, dementia and delirium commonly coexist, and unexplained rapid decline in cognition in a patient with an es- tablished dementia should prompt investigation to rule out causes of delirium. Although the course and prognosis depend on the underlying diagnosis, if there is resolution of the precipitant there is potential for cognitive improvement to the baseline state. Neurodegenerative causes of dementia Neurodegenerative diseases make up most causes of dementia. These disorders have several features in common. Most cases are sporadic, although for many diseases a proportion of cases occur on an autosomal dominant basis. Deposition of abnormally conformed proteins within the brain is thought to be a key initiating event, with subsequent propagation of abnormal proteins through neural net- works, neuroinflammation, synaptic and neurotransmitter loss and neuronal death, all of which precede the develop of symptoms, in the case of some diseases by many years. Each of the neurodegenerative diseases is associated with a specific abnormal protein species or combination of abnormal proteins, and it is the specific protein(s) that define the disorders pathologically. For reasons that are as yet unknown, different protein species have particular tropism for dif- ferent brains networks, which goes some way to explaining the fairly consistent clinical phenotypes associated with each of the disorders. However, in some cases the same protein abnormalities, and indeed the same genetic mutation, can cause a range of different symptoms; different neurodegenerative diseases can occur in combination; and particularly in elderly populations cerebrovascular disease is very common and is likely to influence phenotype. Alzheimer’s disease

Overview Alzheimer’s disease is the most common cause of dementia. Of the 5–10% of the population aged over 65 years who have some kind of cognitive decline, over 60% of cases will be due to Alzheimer’s dis- ease; and, although accounting for a smaller percentage of younger onset cases, Alzheimer’s disease is still the single largest cause. The initial disease description by Alois Alzheimer (1864–1915) in 1907 was of a woman in her fifties with a progressive dementia and be- havioural disturbance, who was found to have neurofibrillary tan- gles and amyloid plaques throughout her cerebral cortex, latterly determined to be due to a mutation in the Presenilin 1 gene. The term ‘Alzheimer’s disease’ was then applied to similar cases with a presenile dementia, before it was determined that identical patho- logical changes were seen in most elderly demented patients. Histological diagnosis remains the ‘gold standard’, and aside from those patients with rare autosomal dominant mutations, there is no definitive diagnostic test available during life. While for many years Alzheimer’s disease was essentially a diagnosis of exclusion as reflected by the widely used NINCDS–ADRDA criteria, these and

SECTION 24 Neurological disorders 5836 other criteria have recently been updated to incorporate advances in biomarkers, allowing for the diagnosis to be made with increased confidence. 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. Updated biomarker-supported clinical and research criteria from both the National Institute of Aging and International Working Group allow not only for patients with dementia due to Alzheimer’s disease to be diagnosed, but also for Alzheimer’s disease to be diagnosed in pa- tients with mild cognitive impairment (Table 24.4.2.3). While only currently of relevance for research, the finding that a substantial pro- portion of apparently healthy individuals have positive Alzheimer biomarkers has led to the concept of prodromal or presymptomatic forms of the disease with associated research criteria/frameworks, paving the way for trials aiming to prevent or delay symptom onset. Epidemiology and risk factors Familial Alzheimer’s disease While most cases of Alzheimer’s disease occur on an apparently sporadic basis, a very small proportion (<0.5%) arise due to muta- tions in the Presenilin 1 gene on chromosome 14, the amyloid pre- cursor protein (APP) gene on chromosome 21, or very rarely the Presenilin 2 gene on chromosome 1. In these families, disease onset is typically but not exclusively at an early age (35–55 years), and is fairly consistent within families; as with Huntington’s disease, pene- trance is complete for Presenilin 1 and APP, but more variable for Presenilin 2. Individuals with Down’s syndrome (trisomy 21) de- velop Alzheimer’s disease during their third and fourth decades, likely due to having an extra copy of the APP gene. Sporadic Alzheimer’s disease For patients with sporadic Alzheimer’s disease, age is the most im- portant overall risk factor, with the prevalence approximately doubling every five years from 0.5% at the age of 60–65, to more than 40% in those living beyond 90. From a genetic perspective, Apolipoprotein E (ApoE) has long been established as a risk factor for Alzheimer’s dis- ease and remains the single most common genetic determinant of sus- ceptibility to late onset 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: ε2, ε3, and ε4. One or two ε4 alleles confer an increased risk of Alzheimer’s disease and lower the age of onset in a ‘dose-dependent’ fashion. Recent advances in genetic technology have led to the identification of more than 20 other risk loci for Alzheimer’s disease. While each locus individually confers only a very small increased risk, their identification has provided evidence implicated cholesterol processing, inflammation, and endosomal traf- ficking in Alzheimer pathogenesis; and taken

together, genetic factors are estimated to account for c.2/3 of the risk for Alzheimer's disease. Many epidemiological studies have investigated medication, life- style, and related risk factors. Factors reported to reduce risk for Alzheimer's disease include prior treatment with oestrogens, statins, antihypertensivs, and nonsteroidal anti-inflammatory drugs; exposure to folate, vitamins E and C, and coffee; cognitive activity, and moderate alcohol intake. Conversely, elevated homocysteine, depression, midlife cardiovascular risks, and low education may increase risk. Pathology The pathological hallmarks of Alzheimer's disease are: (1) Deposition of amyloid-β peptide (Aβ) in the cerebral cortex in the form of se- nile or neuritic plaques. Plaques range in size from 50 to 200 nm and consist of an amyloid core containing 40–43 amino acid con- taining Aβ fragments, with a corona of argyrophilic axonal and dendritic processes, amyloid fibrils, and microglia. Aβ is also de- posited in small blood vessels in over 80% of cases, so-called cere- bral amyloid angiopathy. (2) Neurofibrillary tangles, formed from bundles of paired helical filaments, replace the normal neuronal cytoskeleton. The central core of the paired helical filaments is the microtubule-associated protein tau. Abnormal phosphorylation of the tau protein causes the microtubular abnormalities and the sub- sequent collapse of the cytoskeleton. The neurofibrillary tangles are seen as intensely staining intraneuronal inclusions with silver stains or specific anti-tau immunochemistry. (3) Macroscopically, patients with Alzheimer's disease have reduced brain weight, although there may be overlap with age-matched controls. Focal neuronal loss, or atrophy, is particularly focused on medial temporal lobe structures including the entorhinal cortex, hippocampus, and parietotemporal association areas, with relative sparing of the primary sensory motor and visual cortices (Fig. 24.4.2.2). As well as protein deposition, loss of neurons, and synapses, neuroinflammation is increasingly recognized as a feature of Alzheimer pathology. Alzheimer's disease is associated with re- duction in a range of neurotransmitters, including a marked cho- linergic deficit. One of the two classes of medications licensed for Alzheimer's disease, the acetylcholinesterase inhibitors, acts by reducing enzymic breakdown of acetylcholine with the aim of improving cognitive function. The pathological diagnosis of Alzheimer's disease requires the presence of both neuritic plaques and neurofibrillary tangles in the brain of an individual with dementia. The distribution of these pathologies each follows its own broadly consistent trajectory as the disease advances. Thal staging of amyloid plaque pathology fol- lows five distinct stages, starting in the neocortex (Stage 1) before spreading sequentially to allocortex (Stage 2), striatum, dienceph- alon, and basal forebrain (Stage 3), brainstem nuclei (Stage 4) and finally the cerebellum (Stage 5). Braak and Braak staging of neuro- fibrillary tangle distribution and severity follows a six-stage pro- cess starting with deposition in the transentorhinal and entorhinal cortices (Stages 1 and 2), followed by involvement of hippocampus and other limbic structures (Stages 3 and 4), before the isocortex becomes involved (Stage 5 and 6). Contemporary pathological cri- teria combine these two criteria with the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) neuritic plaque-score (none, sparse, moderate, or frequent), to produce an 'ABC' score from which an Alzheimer's neuropathology likelihood level—none, low, intermediate, or high—is determined. Pathophysiology The dominant hypothesis to explain the mechanisms leading to Alzheimer's disease is the amyloid cascade model, which proposes that the Aβ fragment of the APP gene plays an essential and up- stream role in the pathogenesis. APP may be processed to pro- duce nontoxic species, but when cleaved sequentially by β- and γ-secretases, leads to the accumulation of toxic, short, forms

 Table 24.4.2.3 Prior (NINCDS–ADRDA) and one of the current (IWG-2) criteria for Alzheimer's disease a. 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 neuropyschological tests Decline in memory and at least one nonmemory 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 post-mortem 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 b. International Working Group-2 (IWG2) research criteria for Alzheimer’s disease IWG-2 criteria for typical AD (A plus B at any stage) A—Specific clinical phenotype Presence of an early and significant episodic memory impairment (isolated or associated with other cognitive or behavioural changes that are suggestive of a mild cognitive impairment or of a dementia syndrome) that includes the following features: B—In vivo evidence of Alzheimer's pathology (one of the following) Gradual and progressive change in memory function reported by patient or informant over more than 6 months Objective evidence of an amnestic syndrome of the hippocampal type, based on significantly impaired performance on an episodic memory test with established specificity for AD, such as cued recall with control of encoding test B—In vivo evidence of Alzheimer's pathology (one of the following) Decreased Aβ1–42 together with increased T-tau or P-tau in CSF Increased tracer retention on amyloid PET AD autosomal dominant mutation present (in PSEN1, PSEN2, or APP) Exclusion criteria for typical AD Sudden onset Early occurrence of the following symptoms: gait disturbances, seizures, major and prevalent behavioural changes Focal neurological features Early extrapyramidal signs Early hallucinations Cognitive fluctuations Non-AD dementia Major depression Cerebrovascular disease Toxic, inflammatory, and metabolic disorders, all of which may require specific investigations MRI FLAIR or T2 signal changes in the medial temporal lobe that are consistent with infectious or vascular insults IWG-2 criteria for atypical AD (A plus B at any stage) A—Specific clinical phenotype (one of the following) Posterior variant of AD (including): An occipitotemporal variant defined by the presence of an early, predominant, and progressive impairment of visuoperceptive functions or of visual identification
of objects, symbols, words, or faces A biparietal variant defined by the presence of early, predominant, and progressive difficulty with visuospatial function, features of Gerstmann syndrome, or Balint syndrome, limb apraxia, or neglect (continued)

SECTION 24 Neurological disorders 5838 of Aβ (in particular the Aβ1-42 peptide) in the brain. Acting through mechanisms not fully understood, but likely to involve neuroinflammation and spread of pathology through vulnerable neural networks, this is proposed to initiate a cascade of events that ultimately leads to the accumulation of hyperphosphorylated tau, and neuronal dysfunction and cell death Figs. 24.4.2.3 and 24.4.2.4. 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 Aβ peptides in such a way that the relative proportion of the highly amyloidogenic Aβ1-42 form is increased. Conversely, a very rare APP mutation that reduces production of toxic forms of Aβ may protect against Alzheimer’s disease. In spor- adic Alzheimer’s

disease, there is evidence for impaired clearance of toxic Aβ species. There is evidence that, rather than the highly aggregated Aβ species, soluble oligomeric forms of Aβ may repre- sent the most neurotoxic entity that causes synaptic dysfunction. Logopenic variant of AD defined by the presence of an early, predominant, and progressive impairment of single-word retrieval and in repetition of sentences, in the context of spared semantic, syntactic, and motor speech abilities Frontal variant of AD defined by the presence of early, predominant, and progressive behavioural changes including association of primary apathy or behavioural disinhibition, or predominant executive dysfunction on cognitive testing Down's syndrome variant of AD defined by the occurrence of a dementia characterized by early behavioural changes and executive dysfunction in people with Down's syndrome B—In vivo evidence of Alzheimer's pathology (one of the following) Decreased Aβ1–42 together with increased T-tau or P-tau in CSF Increased tracer retention on amyloid PET Alzheimer's disease autosomal dominant mutation present (in PSEN1, PSEN2, or APP) Exclusion criteria for atypical AD Sudden onset Early and prevalent episodic memory disorders Major depression Cerebrovascular disease Toxic, inflammatory, or metabolic disorders IWG-2 criteria for mixed AD (A plus B) A—Clinical and biomarker evidence of AD (both are required) Amnestic syndrome of the hippocampal type or one of the clinical phenotypes of atypical AD Decreased Aβ1–42 together with increased T-tau or P-tau in CSF, or increased tracer retention on amyloid PET B—Clinical and biomarker evidence of mixed pathology For cerebrovascular disease (both are required) Documented history of stroke, or focal neurological features, or both MRI evidence of one or more of the following: corresponding vascular lesions, small vessel disease, strategic lacunar infarcts, or cerebral haemorrhages For Lewy body disease (both are required) One of the following: extrapyramidal signs, early hallucinations, or cognitive fluctuations Abnormal dopamine transporter PET scan IWG-2 criteria for the preclinical states of AD IWG-2 criteria for asymptomatic at risk for AD (A plus B) A—Absence of specific clinical phenotype (both are required) Absence of amnestic syndrome of the hippocampal type Absence of any clinical phenotype of atypical AD B—In vivo evidence of Alzheimer's pathology (one of the following) Decreased Aβ1–42 together with increased T-tau or P-tau in CSF Increased retention on fibrillar amyloid PET IWG-2 criteria for presymptomatic AD (A plus B) A—Absence of specific clinical phenotype (both are required) Absence of amnestic syndrome of the hippocampal type Absence of any clinical phenotype of atypical AD B—Proven AD autosomal dominant mutation in PSEN1, PSEN2, or APP, or other proven genes (including Down's syndrome trisomy 21) Table 24.4.2.3 Continued

 Importantly, while Aβ is necessary for Alzheimer’s disease to de- velop, it is not sufficient. Biomarker and autopsy studies suggest a significant proportion of older people—perhaps a third of individ- uals in their seventies—harbours significant Aβ pathology, in the absence cognitive symptoms; and it seems likely that the accumula- tion of tau pathology and atrophy are downstream processes both of which correlate more closely with, but still predate the development of, symptoms. Despite promising results in animal models, clinical trials of therapies aiming to clear Aβ pathology from the brain have not been successful in patients with established Alzheimer’s disease, most likely as by this stage the neurodegenerative cascade has al- ready been initiated and is too advanced. There is thus an increasing interest in applying such therapies to asymptomatic individuals with evidence for Aβ pathology, although this currently remains very much in the realm of research. Clinical features Amnestic Alzheimer’s disease As much as it is possible to consider a ‘typical’ form of Alzheimer’s disease, the most common earliest cognitive deficit is impairment of episodic memory (memories for events or episodes, including day- to-day memory and new learning). This is thought to reflect

that the earliest site of pathology is in the medial temporal lobe structures. As discussed earlier, ‘amnestic 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 stages of Alzheimer’s disease. However, MCI can result from deficits in domains other than memory; may be caused by other diseases including depression; and is not always progressive, and when it is can take several years to develop a full- blown dementia syndrome. Recent studies indicate a conversion rate to dementia of around 10–20% per annum. The main clinical fea- tures at this stage are severe forgetfulness, often with repetitive ques- tioning particularly concerning the retention of new information, which over time begins to result in impairments in social functioning or job performance. As the disease progresses to mild Alzheimer’s disease, memory function worsens, particularly affecting recall (e.g. forgetting recent visits or family events), with increasing problems managing complex day-to-day activities such as finances and shop- ping, mental inflexibility, and poor concentration, which reflects in- volvement of attentional and executive function. Insight is variably affected; often patients retain a partial awareness of their difficulties but underestimate the extent of the problem, but on occasions they can be remarkably unaware of their difficulties. Remote memory is typically reported to be relatively well preserved with a temporally graded pattern (i.e. sparing of most distant memories), although this may be difficult to confirm objectively. As the disease con- tinues 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 Fig. 24.4.2.2 Macroscopic and microscopic observations in Alzheimer’s disease (AD). Macroscopic observation of coronal slices shows dilatation of the ventricles (a, *) and reduction in bulk of the deep white matter and size of the hippocampus (a, arrow). Aβ immunohistochemistry shows numerous plaques both cored and diffuse in the frontal cortex (b); shown at higher magnification in (c) (cored plaque arrow; diffuse plaque double arrow). Cerebral amyloid angiopathy can be found in a proportion of AD cases, where Aβ deposits in blood vessels (d). Numerous neurofibrillary tangles and neuropil threads are highlighted with tau immunohistochemistry (e) in the Ca1 hippocampal subregion, shown at higher magnification in F. Bar in (b) represents 100 μm in (b) and (e); 50 μm in (d) and 20 μm in (c) and (f). Courtesy of Dr Tammaryn Lashley, UCL.

SECTION 24 Neurological disorders 5840 impairments and apraxia, which may develop at this stage, are par- ticularly disabling, causing difficulty in dressing, cooking, and per- forming other daily activities. As the cognitive deficits progress there is worsening of language function and semantic memory, and behav- ioural problems can be prominent. Neuropsychiatric symptoms par- ticularly apathy, anxiety, and mood disturbance are common in the earliest stages of Alzheimer’s disease; in the later stages delusions and hallucinations occur in up to 50% and 30% of patients, respectively. Agitation, restlessness, wandering, and disinhibition can 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 can be late features. There is considerable variation in the time from presentation to death: individuals diagnosed in their late 60s to early 70s have a median lifespan of 7–10 years, but this is reduced to three years when diagnosis is made in the 90s. Phase 1 Phase 2 Phase 3 Phase 5 Phase 4 A (a) B stage I transentorhinal region transentorhinal region peristriate region peristriate region parastriate area peristriate region calcarine fissure striate area striate area parastriate area parastriate area peristriate region entorhinal region entorhinal region occipito- temporal gyrus occipito-temporal

gyrus Heschl’s gyrus Heschl’s gyrus occipito- temporal gyrus temporal neocortex transento- rhinal region allo- cortex rhinal sulcus rhinal sulcus superior temporal gyrus superior temporal gyrus superior temporal gyrus lingual gyrus collateral sulcus hippocampus hippocampus stage II stage III stage III stage IV stage V stage V stage VI stage VI (b) (e) (f) (h) (i) (c) (d) (g) Fig. 24.4.2.3 (A) Thal Aβ and (B) Braak and Braak tau staging in Alzheimer’s disease. (A) Phases of β-amyloidosis. Phase 1 is characterized by exclusively neocortical Aβ deposits (Neocortex: black). Phase 2 shows additional allocortical Aβ deposits (red arrows), phase 3 additional Aβ deposits in diencephalic nuclei (red arrows) and the striatum (not shown), phase 4 additional Aβ deposits in distinct brainstem nuclei (red arrows), and phase 5 in the cerebellum and additional brainstem nuclei (red arrows). (B) Stages of cortical neurofibrillary pathology. Involvement starts in the transentorhinal area (Stage 1) before spreading sequentially to the entorhinal cortex and hippcomampus (Stage 2), association areas of the temporal neocortex (Stage 3), insular, neocortical high order sensory association cortex of the temporal lobe (Stage 4), superior temporal gyrus (Satge 5), occipital lobe, and finally sensory association areas and the primary areas of the occipital neocortex (Stage 6). (A) Reproduced with permission from Thal DT et al. (2002). Phases of Aβ-deposition in the human brain and its relevance for the development of AD. Neurology 58(12), 1791−1800. (B) Reprinted from Braak H and Braak E (1995). Staging of Alzheimer’s disease-related neurofibrillary changes. Neurobiology of Aging 16, 271–84. Copyright © 1995, with permission from Elsevier.

24.4.2 Alzheimer’s disease and other dementias 5841 Neurological examination is unremarkable in the early stages, although increased tone (often frontal resistance, or gegenhalten, in type) and mild extrapyramidal features can occur as the dis- ease progresses. Reflex changes such as extensor plantar responses and—in contrast to frontotemporal dementia—primitive reflexes (e.g. grasping, occur late if at all). In the final stages, there can be greatly increased rigidity and joint contractures. Atypical Alzheimer’s disease Patients with autosomal dominant forms of Alzheimer’s disease typically present with amnestic deficits, but can have a range of other features including prominent myoclonus, early seizures, and a spastic paraparesis. Some patients with sporadic forms of Alzheimer’s—typically, but not exclusively those with younger age at disease onset—present with nonamnestic, ‘atypical’ presen- tations. These patients include those with prominent higher level visual problems, and with other deficits implicating parietal lobe dysfunction, with relative sparing of memory—posterior cortical atrophy, sometimes referred to as the visual variant of Alzheimer’s disease; those with hesitant speech and prominent word finding difficulties—logopaenic aphasia; and individuals with prom- inent early behaviour problems, sometimes sufficient to mimic frontotemporal dementia (see next)—behavioural or frontal variant Alzheimer’s disease. Investigations The aims of neuropsychological, imaging, and laboratory inves- tigations in Alzheimer’s disease are, as discussed earlier, first to exclude other potentially reversible causes of, or contributors to, dementia; and second to provide positive evidence for a diagnosis of Alzheimer’s disease. The extent and nature of investigation obvi- ously need to be tailored to the individual, but European, UK, and US guidelines all recommend that patients should undergo a range of blood investigations and brain imaging. Neuropsychological assessment characteristically shows 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. MRI of patients with Alzheimer’s disease in the earliest stages (including amnestic MCI) typically show evidence of symmetrical medial temporal lobe and in particular hippocampal volume loss (Fig. 24.4.2.5), which is now included in new

diagnostic criteria. Familial Alzheimer’s disease Mutations result in increased production of abnormal forms of Aβ Sporadic Alzheimer’s disease Impaired clearance of abnormal Aβ forms results in accumulation Increase in Aβ oligomers Neurotransmitter deficits Cognitive impairment Tau misfolding propagation; synaptic dysfunction Deposition into Aβ plaques Inflammatory responses (?) Fig. 24.4.2.4 Alzheimer’s disease pathogenesis: the amyloid cascade hypothesis. The central event in AD pathogenesis is proposed to be imbalance between Aβ production and clearance, with increased Aβ production in familial AD and decreased Aβ clearance in sporadic AD. Aβ oligomers may directly impact on hippocampal and synapse function. Aβ deposition, inflammation, and oxidative stress leads to tau pathology with tangle formation and atrophy; these downstream events lead to and correlate with neuronal dysfunction and cognitive symptoms.
Fig. 24.4.2.5 Imaging appearances in Alzheimer’s disease. (a) T1-weighted MRI shows hippocampal atrophy; (b) Amyloid PET shows widespread cortical fibrillar amyloid deposition (hot colours).

SECTION 24 Neurological disorders 5842 Generalized volume loss, and parietal lobe atrophy are also common. In mild cases brain imaging can appear within normal limits; in such cases, repeat scanning after an interval may be helpful as in Alzheimer’s disease, as well as other forms of neurodegeneration, progressive volume loss in excess of that seen in normal ageing is expected. T2 or FLAIR sequences often show a degree of white matter change reflecting cerebrovascular disease, which commonly accompanies Alzheimer’s disease, particularly in older people. Iron-specific MR sequences (T2* or DWI) may reveal the presence of cortical microbleeds, reflecting amyloid angiopathy, in a minority of patients. A variety of other MR sequences (diffusion tensor imaging, spectroscopy) may show other aspects of Alzheimer’s pathology, but are not in use in routine clinical practice. FDG-PET or single- photon emission computed tomography (SPECT) scanning typic- ally shows temporoparietal hypoperfusion. PET scanning using ligands that bind fibrillar amyloid allows for the demonstration of amyloid pathology during life (Fig. 24.4.2.5), and several tracers are now licensed; cost and availability currently limit their widespread use. Very recently, it has become possible to image tau deposition in vivo using PET ligands that bind to certain forms of tau, but this remains a research tool. Use of CSF in the diagnosis of dementia varies very consider- ably between countries; importantly interpretation of the results requires that the samples are taken and processed appropriately. Reduction of Aβ1-42 and elevation of total and phosphorylated tau in the CSF is the typical pattern seen in Alzheimer’s disease. Included in new diagnostic criteria, these CSF markers have posi- tive predictive value in determining which individuals with MCI will develop dementia. Genetic testing for mutations in the causative genes may be appro- priate in patients with young onset disease, particularly where there is a family history. Advances in genetic technology allow for several genes to be screened concurrently. Genetic testing should only be done with specific consent and following appropriate counselling, due to the implications for other family members. In contrast to testing for causative mutations, assessing genetic risk factors (e.g. ApoE status), is not currently recommended in clinical practice.
Management and prognosis The management of a patient with Alzheimer’s disease 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 goals at different stages, ranging from aiding failing cognitive function in the setting of independent living, to managing behavioural problems and ag- gression, and eventually to providing full supportive nursing care. There is great variation in the rate of progression, but depending on the age and stage of disease at diagnosis, 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 assist- ance with day-to-day activities. Issues such as establishing fitness to drive, and financial planning while the patient has capacity to do so, are important and should be discussed early in the course of the disease. Depending on individual circumstances, symptoms, and disease stage, there may be different requirements for the support services listed next: • information and education • diet, exercise, mental activity • carer support groups • community dementia team, including home nursing and per- sonal care • community services (e.g. meals-on-wheels, community trans- port services) • access to dementia charities • sitter service • day centre • respite care • residential/nursing home • palliative care Pharmacological treatment Two classes of drugs, the cholinesterase inhibitors (donepezil, galantamine, and rivastigmine) and the N-methyl–d-aspartate (NMDA) receptor antagonist, memantine, are licensed for use in the symptomatic treatment of Alzheimer's disease. In clinical trials, the cholinesterase inhibitors consistently achieve modest improve- ments in cognitive function compared to placebo. There is no evi- dence that they alter the overall course of the disease, although withdrawal of treatment in moderate-severe disease has been shown to worsen cognition and function and to increase the risk of nursing home placement. Memantine has usually been used in patients not tolerating cholinesterase inhibitors, or those with more advanced disease. There is some evidence that combined treat- ment with a cholinesterase inhibitor and memantine may provide benefit in some patients. There is less good evidence for how best to treat other aspects of the disease including depression, agitation, and psychotic phenomena; in such cases, input from a specialist psychiatrist is recommended. Environmental modification and ap- propriate nursing input should be considered prior to instigation of medication. While individual patients may respond, evidence that conventional antidepressants help in depression in the context of Alzheimer's disease is weak at best. Atypical antipsychotic drugs can be useful for treating severe neuropsychiatric symptoms, and risperidone is licensed for the short-term treatment of aggressive behaviour. However, these drugs are associated with an increased long-term risk of mortality and stroke in demented individuals, and so should be used cautiously and only when the benefits outweigh the risks. As discussed previously, approaches to clearing β-amyloid have so far proven unsuccessful, but are currently been trialled in patients with milder disease, and asymptomatic individuals at risk of Alzheimer's disease. Several other approaches, targeting different aspects of the amyloid cascade, neuro-inflammation, and tau path- ology, are in various stages of development/implementation. Frontotemporal dementia Overview Frontotemporal dementia (FTD) is a clinico-pathological syndrome encompassing a range of different clinical syndromes centred on progressive behavioural and/or speech presentations. FTD is now

 preferred to the older term 'Pick's disease' to describe patients with focal frontal and/or temporal focal atrophy, reflecting that the underlying pathology of these syndromes is heterogeneous. Arnold Pick (1851–1924) 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, describing both argyrophilic intracytoplasmic inclusions (Pick bodies) and diffusely staining bal- looned neurons (Pick cells). More recently it has become clear that the spectrum of pathology that accompanies the clinical syndromes within the frontotemporal dementia spectrum is much broader, with a range of distinct inclusions as described next. There is

additionally very considerable heterogeneity in the clinical features within the FTD spectrum, including overlap between FTD and motor neuron disease (MND, also referred to as amyotrophic lateral sclerosis), and atypical parkinsonism. A significant proportion of cases—and par- ticularly those with behavioural presentations—are familial, with up to c.40% having an affected family member; three major and several minor causative genetic mutations are recognized. While there is no one-to-one match between clinical syndrome, pathology, and gen- etic mutation, some fairly consistent patterns are emerging which can be diagnostically useful (Fig. 24.4.2.6). Epidemiology FTD is increasingly recognized as a common cause of dementia, particularly in the younger age groups (see Fig. 24.4.2.1). The peak incidence of onset is 45–65 years of age, but 10% or more may have onset after the age of 70. Men and women are equally affected. Pathology While FTD is used to describe the clinical syndromes, the term frontotemporal lobar degeneration (FTLD) is used to describe the pathology. The gross pathological appearance in typical cases is of selectively 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 subcor- tical gliosis, loss of large cortical nerve cells, and microvacuolation. At a microstructural level, FTLD is classified on the basis of the spe- cific pathological intracellular protein inclusions (see Fig. 24.4.2.7). Approximately 40% of FTLD is underpinned by tau pathology (FTLD-tau), which can be further subdivided based both on morph- ology and predominance of the number of micro-tubule binding repeats: 4-repeat tauopathies include corticobasal degeneration, pro- gressive supranuclear palsy, argyrophilic grain disease and globular glial tauopathy; 4- and 3-repeat tauopathies include some cases of frontotemporal dementia due to mutations in the microtubule-associated protein tau (MAPT) gene on chromosome 17; classical Pick’s disease is a 3-repeat tauopathy. Approximately 50% of FTLD cases are associated with inclusions containing the 43 kDa TAR DNA-binding protein (TDP-43), that is, FTLD-TDP. FTLD-TDP can be further subdivided into four subtypes (A, B, C, and D). Rarer inclu- sions seen in FTLD include fused-in-sarcoma protein (FTLD-Fus), which comprises three different, very rare, conditions, neurofilament inclusion body disease, atypical FTLD-U (aFTLD-U) and basophilic inclusion body disease; and FTLD-UPS due to CHMP2B mutations. Genetics About 40% of patients with FTD have a positive family history, al- though in not all cases will a causative mutation be detected. In those with a confirmed mutation (familial FTD), three causative gene mutations account for more than 90% of cases. The first mutation, found in the late 1990s, involves the MAPT gene on chromosome 17, and results in tau pathology. In 2006, the second major locus close to MAPT, the progranulin gene, was discovered and shown to result in TDP-43 (type B) pathology. In 2011 a hexanucleotide repeat expansion on chromosome 9 (C9orf72) was identified as a cause of familial MND, familial MND, or combinations of both diseases; and with either TDP-43 type A or B pathology. Very rare other genetic causes include mutations in transactive DNA-binding protein (TARDBP), fused-in-sarcoma, valosin-containing protein, chromatin-modifying protein 2B (CHMP2B), Sequestosome-1 (SQSTM1), and TANK-binding kinase 1 (TBK1). FTD bvFTD PNFA SD CBS/ PSP MND/ ALS Tau Ubi Clinical syndromes Pathology Genetics TDP FUS UPS MAPT GRN C9ORF72 VCP, SQSTM1, TARDBP, TBK1 FUS CHMP2B Fig. 24.4.2.6 Autosomal dominant genetic causes (red), pathology (green) and clinical syndromes (blue) of frontotemporal dementia. bvFTD, behavioural variant frontotemporal dementia; PNFA, progressive nonfluent aphasia; SD, semantic dementia; CBS, corticobasal syndrome; PSP, progressive suprnuclear palsy; MND, motor neuron disease; ALS, amyotrophic lateral sclerosis; Ubi, Ubiquitin; TDP, Tar DNA-binding protein; FUS, fused-in-sarcoma protein; UPS, ubiquitin proteosome system VCP. Courtesy of Dr Jonathan Rohrer, UCL.

SECTION 24 Neurological disorders 5844 Clinical features While the presentation of FTD is variable, two broad syndromic groups are recognized, that is, patients presenting with a prom- inent behavioural syndrome (behavioural variant FTD, bvFTD); and those with primary disturbance of language, primary progres- sive aphasia. Primary progressive aphasia in turn can be subdiv- ided into progressive nonfluent aphasia, semantic dementia, and logopenic variants. Fig. 24.4.2.7 Microscopic observations in frontotemporal lobar degeneration. Tau immunohistochemistry highlights the pathological hallmarks in FTLD-tau (a–c). The cytoplasmic inclusion called ‘Pick Bodies’ are a prominent feature in the granule cell layer of the hippocampus in Pick’s disease (a); astrocytic plaques are a diagnostic hallmark in corticobasal degeneration (b) and a tufted astrocyte a hallmark of progressive supranuclear palsy (c). FTLD-TDP is divided into four pathological subtypes (subtypes A, B, C, and D) all with characteristic pathological features. Subtypes A–C show neuronal cytoplasmic inclusions in the granule cell layer of the hippocampus (d, arrows); FTLD-TDPA is characterized by neuronal cytoplasmic inclusions (e, arrow) and short neuropil threads (e, double arrow); FTLD-TDPB by granular cytoplasmic inclusions affecting all cortical layers (f, arrow) and FTLD-TDPC by long twisted neurites (g). FTLD-FUS contains neuronal cytoplasmic (h, arrow) and intranuclear inclusions (h, double arrow) in the granule cells of the hippocampus; neuronal cytoplasmic inclusions in the frontal cortex (i) and large cytoplasmic and intranucelar inclusions in lower motor neurons (j). Bar in (a) represents 50 μm in (a–g); 40 μm in (h) and (i); 20 μm in (j). Courtesy of Dr Tammaryn Lashley, UCL.

24.4.2 Alzheimer’s disease and other dementias 5845 Behavioural variant FTD Patients present with insidious and progressive changes in person- ality and behaviour that reflect the early locus of pathology in orbital and medial parts of the frontal lobes. There is often impaired judge- ment, an indifference to domestic and professional responsibilities, and a lack of initiative and apathy. Social skills deteriorate and there can be socially inappropriate behaviour, fatuousness, jocularity, and abnormal sexual behaviour with disinhibition. Many patients are restless with an obsessive-compulsive and ritualized pattern of behaviour, such as pacing or hoarding. Emotional lability, mood swings, and loss of empathy are common; psychiatric phenomena such as delusions and hallucinations are less common, although may be seen in some of the genetic forms, and in C9orf72 cases in par- ticular. Patients often become rigid and stereotyped in their daily routines and food choices. A change in food preference towards sweet foods is characteristic. Patients may show changes in music preference and altered sensitivity to pain and temperature. Of im- portance 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 word finding difficulties, anomia and sometimes echolalia (repeating the examiner’s last phrase). Memory is rela- tively spared in the early stages, although it deteriorates as the dis- ease advances. Visuospatial function typically remains unaffected. Primary motor and sensory functions remain normal. Primitive re- flexes such as grasping and utilization behaviour develop during the disease process. Fasciculations or wasting, particularly affecting the bulbar musculature, deltoids or tongue are suggestive of an FTD/ MND cross-over syndrome, which has a worse prognosis; such cases should prompt consideration of testing for an expansion in the C9orf72 gene; and if negative, a TBK-1 mutation. Primary progressive aphasia—progressive nonfluent
aphasia, semantic dementia, and logopenic aphasia In progressive nonfluent aphasia there is a gradual loss of expressive language abilities with impairments in motor speech impairment

(apraxia of speech) and/or grammatical aspects of language produc- tion. 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, at least early in the disease, word comprehension and object recognition are well preserved. Orobuccal apraxia (e.g. inability to cough or yawn to command) is common, and some patients develop parkinsonism and limb apraxia. The pathology is most commonly tau, but can be variable. In semantic dementia there is a profound loss of conceptual knowledge (or semantic memory), causing anomia and impaired comprehension of words, objects, or faces. The patient may com- plain of ‘loss of memory for words’, commonly ask what words mean, and has fluent, empty speech with generic substitutions such as ‘thing’ and ‘one of those’; grammatical aspects are pre- served. 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 may be unaware of their meaning. Patients make surface dyslexic or regularization errors when reading, pronouncing irregular words phonetically (‘sew’ pronounce ‘sue’). Unlike patients with Alzheimer’s disease, day-to-day memory (episodic memory) visuospatial skills and nonverbal problem-solving abilities are rela- tively preserved, at least in the early stages. As the disease progresses behavioural changes often emerge, similar to bvFTD. The pathology is almost always TDP type C. Logopenic aphasia is characterized by word finding pauses, and anomia. Semantic knowledge is variably preserved, and while being able to pronounce individual words patients have grave difficulties repeating longer phrases or sentences, and show impaired working memory (e.g. reduced digit span). The underlying pathology is usu- ally that of Alzheimer’s disease. Diagnosis Diagnosis of FTD and its various subtypes is based on the clin- ical, neuropsychological, and imaging assessments. Consensus clinical criteria developed for bvFTD and the various forms of primary progressive aphasia are shown in Table 24.4.2.4. The dif- ferences between the various syndromes described earlier may be clear early in the disease, but there is increasing overlap between the temporal and frontal syndromes as the disease progresses. In contrast to Alzheimer’s disease, superadded neurological signs (par- kinsonism or motor neuron) are relatively common even in mild to moderate stage disease, particularly in bvFTD and progressive nonfluent aphasia. Neuropsychometry can confirm and quantify the deficits observed at the bedside. Imaging provides invaluable information in the diagnosis of FTD (Fig. 24.4.2.8). MRI findings suggestive of FTD instead of Alzheimer’s disease include anterior– posterior atrophy gradient, and asymmetric atrophy. Patients with bvFTD typically have frontal atrophy; semantic dementia is asso- ciated with highly asymmetric left anterior temporal lobe atrophy; patients with logopenic aphasia often have relatively mild asym- metric atrophy involving the dominant hemisphere but otherwise resembling Alzheimer’s disease; and the MRI in progressive non- fluent aphasia is often fairly unremarkable for the degree of symp- toms, bar some widening of the left Sylvian fissure (Fig. 24.4.2.8). Specific atrophy patterns in the correct clinical context may provide clues to a genetic cause: progranulin mutations are associated with often profound atrophy of one hemisphere, whereas mutations in tau are often associated with symmetrical inferior medial temporal atrophy. Functional imaging using FDG-PET typically mirrors the structural imaging results, with reduced frontotemporal perfusion and hypometabolism, and is perhaps most valuable where the struc- tural imaging is normal or equivocal. Amyloid PET where available may be helpful in excluding Alzheimer’s disease; while not clinically available, the advent of tau PET imaging may in due course have utility in refining the molecular diagnosis further. CSF examination is principally performed to exclude infectious or inflammatory pro- cesses and Alzheimer’s disease. Newer CSF

(e.g. neurofilament light chain) and blood markers (e.g. progranulin) may in due course help in distinguishing FTD subtypes and/or guide prognosis, but are not yet used in routine clinical practice. Management and prognosis There is no curative treatment at present, so the general manage- ment of the person with dementia and their family, as discussed earlier, is of prime importance. Management of some of the behav- ioural aspects can be particularly challenging. Particular care should

SECTION 24 Neurological disorders 5846 Table 24.4.2.4 Consensus criteria for behavioural variant frontotemporal dementia and primary progressive aphasia Criteria for behavioural variant frontotemporal dementia I. Neurodegenerative disease The following symptom must be present to meet criteria for bvFTD A. Shows progressive deterioration of behaviour and/or cognition by observation or history (as provided by a knowledgeable informant). II. Possible bvFTD Three of the following behavioural/cognitive symptoms (A–F) must be present to meet criteria. Ascertainment requires that symptoms be persistent or recurrent, rather than single or rare events A. Earlya behavioural disinhibition [one of the following symptoms (A.1–A.3) must be present]: A.1. Socially inappropriate behaviour A.2. Loss of manners or decorum A.3. Impulsive, rash, or careless actions B. Early apathy or inertia [one of the following symptoms (B.1–B.2) must be present]: B.1. Apathy B.2. Inertia C. Early loss of sympathy or empathy [one of the following symptoms (C.1–C.2) must be present]: C.1. Diminished response to other people’s needs and feelings C.2. Diminished social interest, interrelatedness or personal warmth D. Early perseverative, stereotyped or compulsive/ritualistic behaviour [one of the following symptoms (D.1–D.3) must be present]: D.1. Simple repetitive movements D.2. Complex, compulsive, or ritualistic behaviours D.3. Stereotypy of speech E. Hyperorality and dietary changes [one of the following symptoms (E.1–E.3) must be present]: E.1. Altered food preferences E.2. Binge eating, increased consumption of alcohol or cigarettes E.3. Oral exploration or consumption of inedible objects F. Neuropsychological profile: executive/generation deficits with relative sparing of memory and visuospatial functions [all of the following symptoms (F.1–F.3) must be present]: F.1. Deficits in executive tasks F.2. Relative sparing of episodic memory F.3. Relative sparing of visuospatial skills III. Probable bvFTD All of the following symptoms (A–C) must be present to meet criteria A. Meets criteria for possible bvFTD B. Exhibits significant functional decline (by caregiver report or as evidenced by Clinical Dementia Rating Scale or Functional Activities Questionnaire scores) C. Imaging results consistent with bvFTD [one of the following (C.1–C.2) must be present]: C.1. Frontal and/or anterior temporal atrophy on MRI or CT C.2. Frontal and/or anterior temporal hypoperfusion or hypometabolism on PET or SPECT IV. Behavioural variant FTD with definite FTLD Pathology Criterion A and either criterion B or C must be present to meet criteria. A. Meets criteria for possible or probable bvFTD B. Histopathological evidence of FTLD on biopsy or at post-mortem C. Presence of a known pathogenic mutation V. Exclusionary criteria for bvFTD Criteria A and B must be answered negatively for any bvFTD diagnosis. Criterion C can be positive for possible bvFTD but must be negative for probable bvFTD A. Pattern of deficits is better accounted for by other nondegenerative nervous system or medical disorders B. Behavioural disturbance is better accounted for by a psychiatric diagnosis C. Biomarkers strongly indicative of Alzheimer’s disease or other neurodegenerative process Criteria for primary progressive aphasia (PPA) Inclusion and exclusion criteria for the diagnosis of PPA Inclusion: criteria 1–3 must be answered positively

1. Most prominent clinical feature is difficulty with language
2. These deficits are the principal cause of impaired daily living activities

3. Aphasia should be the most prominent deficit at symptom onset and for the initial phases of the disease Exclusion: criteria 1–4 must be answered negatively for a PPA diagnosis
4. Pattern of deficits is better accounted for by other nondegenerative nervous system or medical disorders

24.4.2 Alzheimer’s disease and other dementias 5847 2. Cognitive disturbance is better accounted for by a psychiatric diagnosis 3. Prominent initial episodic memory, visual memory, and visuoperceptual impairments 4. Prominent, initial behavioural disturbance Diagnostic features for the nonfluent/agrammatic variant PPA At least one of the following core features must be present:

1. Agrammatism in language production
2. Effortful, halting speech with inconsistent speech sound errors and distortions (apraxia of speech) At least 2 of 3 of the following other features must be present:
3. Impaired comprehension of syntactically complex sentences
4. Spared single-word comprehension
5. Spared object knowledge II. Imaging-supported nonfluent/agrammatic variant diagnosis Both of the following criteria must be present:
6. Clinical diagnosis of nonfluent/agrammatic variant PPA
7. Imaging must show one or more of the following results: a. Predominant left posterior fronto-insular atrophy on MRI or b. Predominant left posterior fronto-insular hypoperfusion or hypometabolism on SPECT or PET III. Nonfluent/agrammatic variant PPA with definite pathology Clinical diagnosis (criterion 1 below) and either criterion 2 or 3 must be present:
8. Clinical diagnosis of nonfluent/agrammatic variant PPA
9. Histopathologic evidence of a specific neurodegenerative pathology (e.g. FTLD-tau, FTLD-TDP, AD, other)
10. Presence of a known pathogenic mutation Diagnostic features for the semantic variant PPA Both of the following core features must be present:
11. Impaired confrontation naming
12. Impaired single-word comprehension At least 3 of the following other diagnostic features must be present:
13. Impaired object knowledge, particularly for low-frequency or low-familiarity items
14. Surface dyslexia or dysgraphia
15. Spared repetition
16. Spared speech production (grammar and motor speech) II. Imaging-supported semantic variant PPA diagnosis Both of the following criteria must be present:
17. Clinical diagnosis of semantic variant PPA
18. Imaging must show one or more of the following results: a. Predominant anterior temporal lobe atrophy b. Predominant anterior temporal hypoperfusion or hypometabolism on SPECT or PET III. Semantic variant PPA with definite pathology Clinical diagnosis (criterion 1 below) and either criterion 2 or 3 must be present:
19. Clinical diagnosis of semantic variant PPA
20. Histopathologic evidence of a specific neurodegenerative pathology (e.g. FTLD-tau, FTLD-TDP, AD, other)
21. Presence of a known pathogenic mutation Diagnostic features for the logopenic variant PPA Both of the following core features must be present:
22. Impaired single-word retrieval in spontaneous speech and naming

23. Impaired repetition of sentences and phrases At least 3 of the following other features must be present:
24. Speech (phonologic) errors in spontaneous speech and naming Table 24.4.2.4 Continued (continued)

SECTION 24 Neurological disorders 5848 2. Spared single-word comprehension and object knowledge 3. Spared motor speech 4. Absence of frank agrammatism II. Imaging-supported logopenic variant diagnosis Both criteria must be present:

1. Clinical diagnosis of logopenic variant PPA
2. Imaging must show at least one of the following results: a. Predominant left posterior perisylvian or parietal atrophy on MRI b. Predominant left posterior perisylvian or parietal hypoperfusion or hypometabolism on SPECT or PET III. Logopenic variant PPA with definite pathology Clinical diagnosis (criterion 1 below) and either criterion 2 or 3 must be present:
3. Clinical diagnosis of logopenic variant PPA
4. Histopathologic evidence of a specific neurodegenerative pathology (e.g. AD, FTLD-tau, FTLD-TDP, other)
5. Presence of a known pathogenic mutation AD, Alzheimer's disease; FTLD, frontotemporal lobar degeneration; PPA, primary progressive aphasia. a As a general guideline 'early' refers to symptom presentation within the first 3 years. Table reprinted from Rascovsky K, et al. (2011). Sensitivity of revised diagnostic criteria for the behavioural variant of frontotemporal dementia. Brain, 134(pt9), 2456−77, by permission of Oxford University Press. Table 24.4.2.4 Continued Fig. 24.4.2.8 MR imaging in frontotemporal dementia. Each T1-weighted MR image is presented with the patient's clinical diagnosis and pathological or genetic diagnosis in brackets, and in radiological convention (left = right). (a) Right–left-sided medial temporal lobe atrophy; (b) left-sided atrophy in the temporal lobe predominantly affecting the posterior perisylvian and temporoparietal areas; (c) left-sided posterior fronto-insular atrophy, which may be limited to a subtle widening of the left Sylvian fissure; (d) left–right-sided anterior temporal atrophy, particularly involving the temporal pole, the amygdala, and the anterior hippocampus, with relative preservation of more posterior structures; (e) focal (and often severe) atrophy affecting the anteromedial temporal lobes with striking loss in the amygdala, parahippocampus, and hippocampal heads bilaterally; (f) gross frontoparietal atrophy extending into the temporal lobe, predominantly affecting a single hemisphere. AD, Alzheimer's disease; bvFTD, behavioural variant frontotemporal dementia; PNFA, progressive nonfluent aphasia; SD, semantic dementia; PPA, primary progressive aphasia; LPA, logopaenic aphasia; TDP, Tar DNA-binding protein; GRN, progranulin mutation; MAPT, tau mutation. Courtesy of Dr Lorna Harper, UCL.

24.4.2 Alzheimer's disease and other dementias 5849 be taken to regularly assess swallowing function, particularly in pa- tients with nonfluent aphasia; and the clinician should be alert to the possibility of developing motor neuron disease or atypical par- kinsonism, which may require specific interventions. Patients with a family history of dementia should be considered for screening for tau, progranulin, or C9orf72 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 five to ten years, but is often much shorted in those

with FTD/MND. Dementia with Lewy bodies and Parkinson’s disease dementia Definition Since the discovery in the 1960s that patients with Lewy bodies 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, with ‘dementia with Lewy bodies’ (DLB), now preferred. There is however increasing recognition of an overlap between DLB and the dementia associated with Parkinson’s disease (Parkinson’s disease dementia or PDD), with most clinicians now considering the two to be on the same spectrum, termed Lewy body disease (Fig. 24.4.2.9). Consensus criteria arbitrarily suggest that DLB is diagnosed when cognitive symptoms predate the emer- gence of motor parkinsonism by a year or more, with PDD preferred when motor parkinsonism occurs prior to, or within one year of, the development of cognitive problems. Epidemiology DLB is a common cause of dementia in the older population, accounting for 15–30% of cases in post-mortem series. The pro- portions of individuals diagnosed during life varies considerably, with a significant proportion diagnosed with Alzheimer’s disease. Onset is usually between the ages of 60 and 80. A significant pro- portion of individuals with Parkinson’s disease (PD) have some degree of cognitive dysfunction, and, as with Alzheimer’s disease, the concept of mild cognitive impairment due to PD has been intro- duced in recent years. The incidence of dementia is c.2–6 times that of age-matched controls, with a prevalence of over 75% 10 years after a diagnosis of PD. The most established risk factors for developing dementia in PD are increasing age, duration of disease, and severity of motor symptoms. Pathology The cardinal pathological features of both DLB and PDD are the presence of cortical Lewy bodies and Lewy neurites. Lewy bodies are intracytoplasmic eosinophilic neural inclusions predomin- antly composed of α-synuclein (Fig. 24.4.2.10). Brainstem-type Lewy bodies are seen on standard (e.g. haematoxylin-eosin) staining, but detection of cortical Lewy bodies and Lewy neurites requires immunohistochemistry with anti-α-synuclein antibodies. Consensus pathological criteria for DLB require the determination of distribution and severity of Lewy type α-synuclein pathology in ten different brain regions, allowing for designation as neocor- tical (diffuse), limbic (transitional), or brainstem predominant. The degree of Alzheimer pathology present is also taken into account in establishing the likelihood that an individual patient’s dementia is due to Lewy body pathology. Alzheimer’s disease pathology also commonly accompanies PDD, with the combination of both Alzheimer’s disease and Lewy body pathology being most robust pathological predictor of dementia. More recently pathology guide- lines from the National Institute on Aging-Alzheimer’s Association recommend the use of the overarching term ‘Lewy body disease’ for both DLB and PDD, and add a further designation of amygdala predominant Lewy bodies, the category most commonly associated with Alzheimer’s disease pathology. Macroscopically, there is typically pallor of the substantia nigra and locus coeruleus, and diffuse cerebral atrophy: prominent at- rophy of medial temporal lobe structures may indicate additional Alzheimer’s disease pathology. In DLB there is loss of cholinergic neurons in the nucleus basalis of Meynert, marked reduction in acetylcholine throughout the cortex, and severe dopamine depletion in the basal ganglia Clinical features In DLB, patients typically present with progressive cognitive de- cline, which can be broadly similar to Alzheimer’s disease, although typically more focused on executive and parietal lobe deficits with relatively less memory involvement. There are, however, three par- ticular characteristic and distinguishing features. First, there is a tendency to marked spontaneous fluctuations in cognitive abilities, particularly alertness and attention. These fluctuations occur in 50–75% of patients, may be profound, and may last anywhere be- tween hours and several days. Second, visual hallucinations, illu- sions, and fleeting

misidentification phenomena occur in at least two-thirds of patients even at an early stage and without drug provo- cation. The hallucinations are typically well-formed, silent, and are usually images of people or animals. In contrast to those seen in major psychiatric disease, these hallucinations are typically not threatening, and indeed may be reported as being comforting. In patients without frank hallucinations, close questioning may reveal a sense of ‘presence’, sometimes extending to the phantom boarder phenomenon (the conviction that there are others living in the house). In some cases, misidentification may lead to the Capgras phenomenon (the belief that someone close to them has been re- placed by an exact double). Many of these phenomena seem at least in part to relate to the marked cholinergic deficit seen in this PD-MCI Bradykinesia Rigidity Tremor Postural instability Dementia Fluctuations Visual hallucinations PD Motor features Cognitive features PDD DLB Fig. 24.4.2.9 The spectrum of Lewy body diseases. PD, Parkinson’s disease, PD-MCI, Parkinson’s disease—mild cognitive impairment, PDD, Parkinson’s disease dementia, DLB, dementia with Lewy bodies.

SECTION 24 Neurological disorders 5850 condition. Third is the occurrence of parkinsonism seen in 70–100% of cases, which is usually mild in the early stages. Rigidity, gait dis- turbance, and bradykinesia are all common, although in contrast to patients with Parkinson’s disease the tremor may be absent and when present 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. There is often an exquisite sensitivity to neuroleptic medication, which can in extreme cases precipitate the malignant neuroleptic syndrome (delirium, hyperpyrexia, muscle rigidity, massive eleva- tion of creatine phosphokinase, and renal failure). Other symptoms include vivid dreams, rapid eye movement (REM) sleep behaviour disturbance, and prominent daytime som- nolence; falls, syncope, and transient loss of consciousness are likely to reflect autonomic dysfunction. In PDD, the cognitive profile is similar with a dysexecutive syndrome with impairments of atten- tion, executive, and visuospatial function. Memory is often affected, but typically to a lesser extent than in Alzheimer’s disease. PDD is associated with neuropsychiatric symptoms broadly similar to those seen in DLB, including hallucinations, apathy, depression, and anx- iety. Hallucinations may be spontaneous but may be associated with, or exacerbated by, dopaminergic medication. As with DLB, daytime somnolence, REM sleep behaviour disturbance, and autonomic dis- turbances are common. While motor parkinsonism is a sine qua non, PDD is more associated with bradykinesia, rigidity, and pos- tural instability than with tremor-dominant PD. Diagnosis In DLB, neuropsychology shows a mixture of subcortical and cortical features, with prominent cognitive slowing plus impair- ment of executive (planning and organizational) abilities and visuoperceptual abilities. Compared with patients with Alzheimer’s disease, those with DLB tend to have greater deficits in attention and visuospatial processing, and (usually) less prominent memory loss. There is no reliable molecular biomarker for DLB. MRI shows broadly similar changes to Alzheimer’s disease, although medial temporal lobe atrophy is often less pronounced. FDG-PET and SPECT shows occipitoparietal hypoperfusion. Dopamine trans- porter typically shows decreased central dopaminergic availability (Fig. 24.4.2.11). Diagnostic criteria (Table 24.4.2.5) defines several core (fluctations, hallucinations, spontaneous parkinsonism, REM sleep behaviour disorder) and indicative biomarkers which in com- bination can be used to classify patients as having either probable or Fig. 24.4.2.10 Microscopic findings in Lewy body dementia. α-synuclein immunohistochemistry highlights cortical Lewy bodies in the frontal cortex (a, arrows); Lewy neurites are also found in the frontal cortex (b); Lewy bodies are also observed in the dopaminergic neurons of the substantia nigra (c) and the hippocampus

(d). Bar in (a) represents 200 μm; 50 μm in (c) and (d), and 20 μm in (b). Courtesy of Dr Tammaryn Lashley, UCL.

24.4.2 Alzheimer’s disease and other dementias 5851 possible DLB. Clinical criteria have also been proposed for the diag- nosis of PDD, and for mild cognitive impairment in PD (PD-MCI). While there are some very rare genetic causes of Lewy body path- ology which can have cognitive impairment (duplications/triplica- tions of the α-synuclein gene, mutations in the glucocerebrosidase gene), there is not a role for routine genetic testing. Management The treatment of patients with Lewy body disorders requires con- sideration of nonpharmacological approaches; minimizing the use of medications that may worsen the condition; and striking a balance between treating motor symptoms that may worsen cog- nition, and treatment for cognitive symptoms that may impact on mobility. As well as general nonpharmacological management of dementia, attention to any coexistent vision and hearing problems is important; ensuring appropriate lighting, especially at night, may improve hallucinations. It is important to review the need for, and where appropriate minimize or discontinue use of, drugs with anticholinergic actions which may worsen cognitive symptoms and postural hypotension. Antipsychotic drugs should be avoided wherever possible; if absolutely necessary, atypical antipsychotics should be used at the lowest possible dose and for the shortest dur- ation possible. Patients with DLB may be very sensitive to the side effects of dopamine-enhancing medications used for the treatment of their motor symptoms. However, although dramatic motor im- provements are not to be expected, a cautious medication trial is worth attempting if motor symptoms interfere with function. In patients with PDD where cognition, and hallucinations in par- ticular, are problematic, simplifying dopaminergic treatment re- gimes and avoiding dopamine agonists may be helpful. There is now good trial evidence that acetylcholinesterase inhibitors such as donepezil and rivastigmine provide symptomatic bene- fits in both DLB and PDD, in terms of attention, cognition, and behaviour. At least anecdotally, there are often marked improve- ments in hallucinations following treatment. While parkinsonian symptoms can worsen with cholinesterase inhibitors particularly in PDD, the effects are usually small and should not preclude a trial of treatment. There is some weaker evidence that memantine may provide benefits in these conditions. Vascular cognitive impairment Definition and epidemiology Recent years have seen significant changes in how we consider the impact that cerebrovascular disease may have on cognition. As it be- came clear that vascular pathologies other than large vessel disease cause cognitive impairment, the term multi-infarct dementia was superseded by the concept of ‘vascular dementia’. However, as the cognitive deficits produced by cerebrovascular disease may be both mild (e.g. not fulfilling conventional criteria for dementia), and due to several different pathologies, the term ‘vascular cognitive impair- ment’ is now preferred to encompass both the spectrum of cognitive impairments presumed to be due to cerebrovascular disease, and its varying aetiologies (Table 24.4.2.6). In particular, disease of small perforating vessels (including not only lacunes in the basal ganglia and deep white matter, but also more diffuse lesions in the white matter, often termed leukoaraiosis) has emerged as a key mechanism of vascular cognitive impairment. Traditionally regarded as the second most common cause of dementia, it is difficult to estimate the true contribution of vas- cular disease to cognitive decline. This relates in part to changes in definitions earlier, but also to advances in MRI, which now allow for a range of vascular pathologies to be detected with ever increasing sensitivity. Furthermore, Alzheimer’s disease and cere- brovascular disease very commonly coexist—and indeed may share common risk factors, including hypertension, diabetes, and hypercholesterolaemia—and are likely to have synergistic impacts on cognitive function. Common

causes of vascular cognitive impairment The varieties of vascular diseases that affect the brain are legion, but from both a clinical and radiological perspective the common vas- cular lesions can conveniently be divided into large and small vessel disease. Large vessel ischaemia Large vessel ischaemia typically resulting from thrombosis or em- bolism, usually results in acute stroke, and discrete cortical, cere- bellar, brainstem, or subcortical lesions on MRI. The cognitive picture is dependent on the site(s) of the lesions. There may be se- vere language impairment, visuospatial disturbance, amnesia, and dyspraxia related to lesions in the middle and posterior cerebral artery distributions. Specific syndromes can result from focal le- sions, for example, lesions of the left angular gyrus result in a fluent aphasia, agraphia, acalculia, right–left disorientation and finger agnosia, known as Gerstmann’s syndrome. 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 Fig. 24.4.2.11 Abnormal dopamine active transporter (DAT) scan in dementia with Lewy bodies. Dopamine transporter imaging shows symmetrical reduced basal ganglia uptake (dot-like, rather than comma-like, in appearance) in a patient with clinically probable dementia with Lewy bodies.

SECTION 24 Neurological disorders 5852 Table 24.4.2.5 Criteria for dementia with Lewy bodies and Parkinson’s disease dementia Probable Parkinson’s disease dementia (PDD)

1. Diagnosis of Parkinson's disease according to Queen Square Brain Bank criteria AND
2. A dementia syndrome with insidious onset and slow progression, developing within the context of established Parkinson's disease and diagnosed by history, clinical, and mental examination, defined as impairment in more than one cognitive domain; representing a decline from premorbid level. Deficits severe enough to impair daily life (social, occupational, or personal care), independent of the impairment ascribable to motor or autonomic symptoms AND Typical profile of cognitive deficits including impairment in at least two of the four core cognitive domains (impaired attention which may fluctuate, impaired executive functions, impairment in visuo-spatial functions, and impaired free recall memory which usually improves with cueing). The presence of at least one behavioural symptom (apathy, depressed, or anxious mood, hallucinations, delusions, excessive daytime sleepiness) supports the diagnosis of Probable PD-D, lack of behavioural symptoms, however, does not exclude the diagnosis. EXCLUSION CRITERIA: Coexistence of any other abnormality which may by itself cause cognitive impairment, but judged not to be the cause of dementia, e.g. presence of relevant vascular disease in imaging Time interval between the development of motor and cognitive symptoms not known Features suggesting other conditions or diseases as cause of mental impairment, which, when present make it impossible to reliably diagnose PD-D Cognitive and behavioural symptoms appearing solely in the context of other conditions such as acute confusion due to Systemic diseases or abnormalities; Drug intoxication; major depression according to DSM-IV; Features compatible with probable vascular dementia. Dementia with Lewy bodies (DLB) Dementia defined as progressive cognitive decline of sufficient magnitude to interfere with normal social or occupational function or with activities of normal living. A patient must have either developed dementia before, or within one year of the onset of parkinsonian syndromes. If more than a year passes before the onset of dementia following parkinsonism, a diagnosis of PDD is made. A “probable” DLB diagnosis requires at least two core features or one core feature and at leas one indicative

biomarker. A “possible” DLB diagnosis requires one of the seven items from the list of core features or indicative biomarkers. Supportive biomarkers are helpful in making the diagnosis but their specificity for DLB is not clear. Core features:

3. Recurrent visual hallucinations
4. Fluctuating cognition
5. Spontaneous features of parkinsonism
6. Rapid eye movement (REM) sleep behaviour disturbance (RBD). Indicative biomarkers
7. Polysomnography confirming RBD
8. Abnormal dopamine transporter (DAT) imaging
9. Abnormal (low uptake) MIBG myocardial scintigraphy And, on four separate lines: Supportive biomarkers
10. Relative preservation of medial temporal lobe structures on CT/MRI
11. Generalized low uptake on SPECT/ PET perfusion scan with reduced occipital activity with reduced occipital activity +/- posterior congulate island sign on FDG-PET
12. Prrominent posterior slow-wave activity on EEG Mild cognitive impairment—Parkinson’s disease dementia (MCI-PDD)
13. Diagnosis of Parkinson's disease as based on the UK PD Brain Bank Criteria
14. Gradual decline, in the context of established PD, in cognitive ability reported by either the patient or informant, or observed by the clinician
15. Cognitive deficits on either formal neuropsychological testing or a scale of global cognitive abilitiesa
16. Cognitive deficits are not sufficient to interfere significantly with functional independence, although subtle difficulties on complex functional tasks may be present Exclusion criteria
17. Diagnosis of PD dementia based on MDS Task Force proposed criteria
18. Other primary explanations for cognitive impairment (e.g. delirium, stroke, major depression, metabolic abnormalities, adverse effects of medication, or head trauma)
19. Other PD-associated comorbid conditions (e.g. motor impairment or severe anxiety, depression, excessive daytime sleepiness, or psychosis) that, in the opinion of the clinician, significantly influence cognitive testing a Depending on the scales used and how comprehensive the neuropsychological battery, PD-MCI can be classified as Level 1 (lesser diagnostic certainty) or Level 2 (higher diagnostic certainty); and for classifications within Level 2 as single or multiple domain PD-MCI. Adapted from: Emre M, et al. (2007). Clinical diagnostic criteria for dementia associated with Parkinson’s disease. Movement Disorders, 22, 1689–1707 (PMID: 17542011); McKeith IG, et al (2017). Diagnosis and management of dementia with Lewy bodies: Fourth consensus report of the DLB Consortium. Neurology 89(1), 88-100 (PMID 28592453); Litvan I, et al. (2011). MDS Task Force on mild cognitive impairment in Parkinson’s disease: critical review of PD-MCI. Movement Disorders, 26(10), 1814−1824 (PMID: 21661055).

24.4.2 Alzheimer’s disease and other dementias 5853 Table 24.4.2.6 Criteria for vascular cognitive impairment

1. The term VCI characterizes all forms of cognitive deficits from VaD to MCI of vascular origin.
2. These criteria cannot be used for subjects who have an active diagnosis of drug or alcohol abuse/dependence. Subjects must be free of any type of substance for at least 3 months.

3. These criteria cannot be used for subjects with delirium. Dementia
4. The diagnosis of dementia should be based on a decline in cognitive function from a prior baseline and a deficit in performance in ≥2 cognitive domains that are of sufficient severity to affect the subject's activities of daily living.
5. The diagnosis of dementia must be based on cognitive testing, and a minimum of 4 cognitive domains should be assessed: executive/attention, memory, language, and visuospatial functions.
6. The deficits in activities of daily living are independent of the motor/sensory sequelae of the vascular event. Probable VaD
7. There is cognitive impairment and imaging evidence of cerebrovascular disease and a. There is a clear temporal relationship between a vascular event (e.g. clinical stroke) and onset of cognitive deficits, or b. There is a clear relationship in the severity and pattern of cognitive impairment and the presence of diffuse, subcortical cerebrovascular disease pathology (e.g. as in CADASIL).
8. There is no history of gradually progressive cognitive deficits before or after the stroke that suggests the presence of a nonvascular neurodegenerative disorder. Possible VaD There is cognitive impairment and imaging evidence of cerebrovascular disease, but
9. There is no clear relationship (temporal, severity, or cognitive pattern) between the vascular disease (e.g. silent infarcts, subcortical small vessel disease) and the cognitive impairment.
10. There is insufficient information for the diagnosis of VaD (e.g. clinical symptoms suggest the presence of vascular disease, but no CT/MRI studies are available).
11. Severity of aphasia precludes proper cognitive assessment. However, patients with documented evidence of normal cognitive function (e.g. annual cognitive evaluations) before the clinical event that caused aphasia could be classified as having probable VaD.
12. There is evidence of other neurodegenerative diseases or conditions in addition to cerebrovascular disease that may affect cognition, such as a. A history of other neurodegenerative disorders (e.g. Parkinson disease, progressive supranuclear palsy, dementia with Lewy bodies); b. The presence of Alzheimer disease biology is confirmed by biomarkers (e.g. PET, CSF, amyloid ligands) or genetic studies (e.g. PS1 mutation); or c. A history of active cancer or psychiatric or metabolic disorders that may affect cognitive function. VaMCI
13. VaMCI includes the 4 subtypes proposed for the classification of MCI: amnestic, amnestic plus other domains, nonamnestic single domain, and nonamnestic multiple domain.
14. The classification of VaMCI must be based on cognitive testing, and a minimum of 4 cognitive domains should be assessed: executive/attention, memory, language, and visuospatial functions. The classification should be based on an assumption of decline in cognitive function from a prior baseline and impairment in at least 1 cognitive domain.
15. Instrumental activities of daily living could be normal or mildly impaired, independent of the presence of motor/sensory symptoms. Probable VaMCI
16. There is cognitive impairment and imaging evidence of cerebrovascular disease and a. There is a clear temporal relationship between a vascular event (e.g. clinical stroke) and onset of cognitive deficits, or b. There is a clear relationship in the severity and pattern of cognitive impairment and the presence of diffuse, subcortical cerebrovascular disease pathology (e.g. as in CADASIL).

17. There is no history of gradually progressive cognitive deficits before or after the stroke that suggests the presence of a nonvascular neurodegenerative disorder. Possible VaMCI There is cognitive impairment and imaging evidence of cerebrovascular disease, but
18. There is no clear relationship (temporal, severity, or cognitive pattern) between the vascular disease (e.g. silent infarcts, subcortical small vessel disease) and onset of cognitive deficits.
19. There is insufficient information for the diagnosis of VaMCI (e.g. clinical symptoms suggest the presence of vascular disease, but no CT/MRI studies are available).
20. Severity of aphasia precludes proper cognitive assessment. However, patients with documented evidence of normal cognitive function (e.g. annual cognitive evaluations) before the clinical event that caused aphasia could be classified as having probable VaMCI.
21. There is evidence of other neurodegenerative diseases or conditions in addition to cerebrovascular disease that may affect cognition, such as: a. A history of other neurodegenerative disorders (e.g. Parkinson disease, progressive supranuclear palsy, dementia with Lewy bodies); (continued)

SECTION 24 Neurological disorders 5854 examination (e.g. spasticity, hyperreflexia, extensor plantar re- sponses, and a pseudobulbar palsy). There are often asymmetric signs on neurological examination, and gait apraxia and/or bladder dysfunction can be early features. Multiple sequential large vessel vascular events can produce the classical stepwise decline histor- ically associated with multi-infarct dementia; however, such pres- entations are seen only in a small proportion of cases of vascular cognitive impairment, most of whom show insidious progressive decline. Cerebral small vessel disease Diseases of the small vessels and associated parenchymal lesions are collectively referred to as cerebral small vessel disease (SVD), and together are the commonest cause of vascular cognitive im- pairment. The pathology of SVD is diverse, and includes fibrinoid necrosis, microatheroma, lipohyalinosis, and cerebral amyloid angiopathy. On MRI, SVD may manifest as one or more of small subcortical infarcts, white matter hyperintensities, prominent peri- vascular spaces, and cerebral microbleeds, occurring very com- monly in combination. Small subcortical infarcts, often referred to as lacunes (when mature with cavitation on neuroimaging) are caused by occlusion in the deep penetrating arterial branches. The basal ganglia, thalamus, and deep white matter are common sites for these lesions, due to the nature of the arterial supply. Lacunes and larger infarcts may coexist contributing to a mixed picture. The typical presentation of SVD-related vascular cognitive impair- ment is with a more subcortical syndrome causing markedly slow processing, impaired attention, and frontal/executive dysfunction, apathy, and emotional lability. Thalamic lacunes can result in a speech disorder and, if bilateral, in amnesia. Examination features of SVD may include rigidity, gait disturbance, and extrapyramidal and pyramidal signs. White matter hyperintensities best seen on T2- or FLAIR-MRI are a common feature of ageing attributed to SVD-related mechanisms (Fig. 24.4.12). While most commonly due to vascular disease, they are also seen in a range of other condi- tions, and notably multiple sclerosis and other inflammatory condi- tions, certain infections, secondary to toxins, or in leucodystrophies for which there are numerous different causes. On MRI, vas- cular white matter hyperintensities are commonly seen in a peri- ventricular distribution and/or deep/subcortical regions, and can be rated using simple scales, with increasing confluence reflecting increasing disease severity. White matter hyperintensities often coexist with subcortical infarcts, and are also associated with the cognitive and other neurological features of the small vessel disease syndrome outlined earlier. Cerebral

microbleeds are small areas of signal void best seen on MRI sequences sensitive to paramagnetic material (e.g. T2* or susceptibility-weighted sequences), and most often reflect small haemorrhages. Microbleeds in the brainstem, cerebellum or deep white matter structures are commonly seen with other manifestations of SVD, and in the context of hyperten- sion. Strictly lobar microbleeds are most commonly due to cere- bral amyloid angiopathy (i.e. deposition of amyloid within the walls of small vessels). MRI features of cerebral amyloid angiopathy are seen in 10–20% of patients with Alzheimer's disease, and some de- gree of cerebral amyloid angiopathy is an invariable pathological feature of Alzheimer's disease. While the cognitive sequelae of cerebral amyloid angiopathy are often difficult to assess, cerebral amyloid angiopathy is a common cause of lobar haemorrhage in older people. 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 (with anticoagulation), large vessel thromboembolism or small vessel occlusion (with antiplatelet agents), and treating vasculitides and vascular risk factors including hypertension and hyperlipidaemia. Where there is evidence for both ischaemia and microbleeds, the risks/benefits of antiplatelet agents and anticoagu- lants in particular, need to be carefully considered. Symptomatic treatment (e.g. with cholinesterase inhibitors) may have modest benefits, particularly if there is coexisting Alzheimer's disease. Rarer causes of vascular cognitive impairment Genetic causes Cerebral autosomal dominant arteriopathy with subcortical in- farcts and leucoencephalopathy (CADASIL) is a rare autosomal dominant disease due to mutations in the notch3 gene on chromo- some 19. While the phenotype is variable, classical features include migraine-like headaches, stroke-like episodes, and the development of a subcortical dementia syndrome in the fourth or fifth decade. The MRI findings typically show subcortical infarcts, microbleeds on iron-sensitive sequences, and diffuse white matter signal change extending into the anterior temporal lobes. Pathologically there is a distinctive angiopathy of the leptomeningeal and perforating ar- teries of the brain, with eosinophilic granular substance replacing smooth muscle. Although CADASIL is the commonest mono- genic form of small vessel disease, other genetic disorders include cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy; and retinal vasculopathy with cerebral leukodystrophy. Several monogenic diseases may present with intracranial haemorrhage, notably the hereditary cerebral amyloid b. The presence of Alzheimer disease biology is confirmed by biomarkers (e.g. PET, CSF, amyloid ligands) or genetic studies (e.g. PS1 mutation); or c. A history of active cancer or psychiatric or metabolic disorders that may affect cognitive function. Unstable VaMCI Subjects with the diagnosis of probable or possible VaMCI whose symptoms revert to normal should be classified as having 'unstable VaMCI'. VCI, vascular cognitive impairment; VaD, vascular dementia; MCI, mild cognitive impairment; CADASIL, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy; CT/MRI, computed tomography/magnetic resonance imaging; PET, positron emission tomography; CSF, cerebrospinal fluid; and VaMCI, vascular mild cognitive impairment. Reprinted with permission from Gorelick PB, et al. (2011). Vascular contributions to cognitive impairment and dementia: a statement for healthcare professionals from the American Heart Association/American Stroke Association. Stroke, 42, 2672–713. Copyright © 2011, American Heart Association, Inc. Table 24.4.2.6 Continued

 angiopathies most, but not all, of which are due to mutations in the APP gene. Inflammatory vascular causes Cerebral vasculitis refers to inflammation of cerebral blood vessels, and can occur in the absence of systemic involvement—so-called primary cerebral vasculitis—or secondary to one of the causes of systemic vasculitis. Primary

cerebral vasculitis has two major causes. Cerebral amyloid angiopathy-related inflammation occurs spontaneously in a small subset of patients with cerebral amyloid angiopathy, and has been observed in a proportion of patients with Alzheimer's disease taking part in clinical trials of anti-amyloid immunotherapy. Patients present with subacute cognitive decline or behavioural changes, seizures, headache, and with white matter hyperintensities, oedema, and microbleeds on MRI; spontaneous remission or a response to immunosuppression (e.g. corticoster- oids) may be seen. Primary angiitis of the central nervous system is a rare sporadic inflammatory disorder of cerebral blood ves- sels which can present with a variety of clinical features including progressive dementia. The MRI is almost invariably abnormal showing infarction often with enhancement, and CSF examin- ation typically shows elevated protein and cell count. While an- cillary investigations including angiography may give important clues, brain biopsy may be required to obtain a definitive diagnosis. Treatment is with immune suppression, usually with corticoster- oids and cyclophosphamide. Subcortical dementias Despite shortcomings, the differentiation between cortical and sub- cortical dementias can be useful in clinical practice (Table 24.4.2.7). This classification highlights the fact that, although disease of diverse cerebral structures can result in dementia, the resultant patterns of cognitive deficits are typically different. Alzheimer's disease is the prototypical cortical dementia; vascular syndromes can pre- sent with a spectrum of features from cortical to subcortical, as can the Lewy body spectrum of diseases. Purer forms of subcor- tical dementia result from pathology of the basal ganglia and its connections or white matter, the prototypical examples being Huntington's disease and progressive supranuclear palsy. The typical cognitive pattern is that of attentional and executive dys- function with marked cognitive slowing (bradyphrenia), causing problems with mentation and information retrieval. Memory is moderately impaired due to reduced attention and poor regis- tration, but is not as severely impaired as in Alzheimer's disease. Fig. 24.4.2.12 Imaging changes in vascular cognitive impairment. (a) Large vessel ischaemia—FLAIR-MRI shows right middle cerebral artery stroke; (b) Small subcortical infarction—T1 volumetric MRI shows left thalamic infarct (arrow); (c) white matter hyperintenstities—T2-W MRI shows confluent white matter disease; (d) amyloid angiopathy—susceptibility-weighted MRI shows numerous microbleeds (peripheral black dots).

 There is often an associated personality change and mood dis- turbance with prominent apathy. Spontaneous speech is impov- erished and slow. Huntington's disease Huntington's disease is an autosomal dominant inherited disorder with an incidence of about 4–10 per 100 000. The mutation is an expansion of the trinucleotide repeat in the IT-15 gene on chromo- some 4, which encodes the polyglutamine protein, huntingtin. Mean age of onset is 40 years, but is related to the length of the tri- nucleotide repeat. Psychiatric symptoms, such as depression, irrit- ability, and personality changes, often precede the motor disorder, which is typically choreiform. Progressive cognitive changes, which can precede the motor features, are of a subcortical pat- tern, with deficits in attention and concentration, executive func- tion, and memory retrieval. Death is typically 15–20 years after symptom onset. Progressive supranuclear palsy Progressive supranuclear palsy (PSP) is a rare, but increasingly rec- ognized disorder with an incidence of 5–6 per 100 000. The motor deficits are symmetrical in onset, with severe rigidity in the axial muscle groups and bulbar symptoms. A supranuclear gaze palsy al- most invariably develops, but in the early stages may be absent, or the only feature may be slowing of fast vertical eye movement (sac- cadic slowing). Another common early feature is a marked tendency to (backwards) falls. While the cognitive symptoms are usually those of a subcortical dementia, as discussed earlier, it can present as a frontotemporal dementia, either with behavioural problems or

a progressive nonfluent aphasia before the motor and other features become apparent. Pathologically, PSP is characterized by neuro- fibrillary tangles, neuropil threads containing four-repeat tau, and neuronal loss and gliosis in the subthalamic nucleus, red and dentate nuclei, and substantia nigra. 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 seven years. Corticobasal degeneration Corticobasal degeneration (CBD) is a rare cause of a dementia and motor signs. In its classical motor form, patients present with an asymmetrical akinetic rigid syndrome, together with limb apraxia, and the almost pathognomonic feature of alien limb phenom- enon in which the affected limb(s) acts as if 'with a will of its own'. Myoclonus and dystonia also occur. While dementia was origin- ally an exclusion criterion, it is now recognized not only to be a common late feature, but that CBD can present with a large range of cognitive features including those of a frontotemporal dementia (behavioural or usually a progressive nonfluent aphasia) or a pos- terior cortical atrophy syndrome. In practice, where there is an overlap between cognitive symptoms and atypical parkinsonism, the term 'corticobasal syndrome' is preferred, reflecting the range of pathologies—including CBD, PSP, Alzheimer's disease, and other forms of frontotemporal lobar degeneration—which can be difficult to distinguish during life. In common with PSP, CBD is a four-repeat tauopathy, with the pathology focused in the frontal and parietal cortices as well as the substantia nigra, basal ganglia, and thalamus. Other important causes of dementia and
cognitive impairment Hydrocephalus Hydrocephalus can present or be associated with a subcortical de- mentia with frontal features and psychomotor slowing. The gait dis- order is a dyspraxia and when asked to walk patients may appear 'being stuck to the floor', although there is an absence or paucity of signs when the patient is examined in the supine position. The condition may be secondary to a prior disturbance of CSF flow (re- sulting from, for example, head injury, meningitis, or subarachnoid haemorrhage), but often no cause is found in older people. The com- bination of idiopathic hydrocephalus, cognitive impairment, gait disturbance, and incontinence with ventricular enlargement dispro- portionate to the degree of cortical atrophy is often referred to as normal-pressure hydrocephalus. While this remains a controversial entity, carefully selected cases where alternate diagnoses have been excluded may respond to neurosurgical CSF diversion. Chronic subdural haematomas This potentially treatable cause of dementia is usually caused by head trauma. It is common in individuals at risk of recur- rent head injuries from falls, such as older people, those with al- cohol problems, and people with epilepsy. Risk is also increased

Table 24.4.2.7 Subcortical and cortical dementias

Feature	Cortical	Subcortical
Examples	Alzheimer's disease	Parkinson's and Huntington's diseases
Speed of mental processing	Normal	Slowed
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

 by coagulation disorders, either pathological or iatrogenic. The clinical features are of a subacute dementia with fluctuating cog- nitive performance, focal neurological signs, and sometimes symptoms of raised intracranial pressure; diagnosis is confirmed by neuroimaging. The peripheral mass lesions may be of varying signal density on computed tomography (CT), depending on the age of the lesion(s). If the lesions are isodense with the brain tissue, the diagnosis can be easily overlooked. Treatment is by neurosur-

gical evacuation, except in clinically insignificant collections. The outcome is variable, and in some cases 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, apathy, cognitive slowing, and other frontal fea- tures. Besides the neuropsychological abnormalities there may be associated neurological signs, including anosmia, unilateral or bi- lateral visual failure, and optic atrophy. Other relatively benign mid- line 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 typically give rise to acute/subacute-onset cognitive impairments, producing delirium rather than dementia. While rare at least in developed countries, chronic metabolic and endocrine disorders can cause or complicate a dementia syn- drome. Hypocalcaemia and recurrent hypoglycaemia can result in a dementia accompanied by ataxia and involuntary movements. Endocrine disorders including hypothyroidism, Addison's disease, and hypopituitarism can present with dementia, with or without psychiatric features. 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.
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 di- minished vibration sense in the lower limbs and/or sensory ataxia. Although most patients have a macrocytic anaemia, neurological manifestations can occasionally occur in the absence of haemato- logical features. Severe thiamine (vitamin B1) deficiency results in the Wernicke–Korsakoff syndrome, with delirium, ataxia, and oph- thalmoplegia. The most common causes are alcoholism and recur- rent prolonged vomiting, such as hyperemesis gravidarum. Prompt replacement is required as otherwise an irreversible chronic amnesic syndrome can develop. 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 con- firmed with serology and examination of CSF. Treatment with appro- priate antibiotics 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 per se is a common cause of dementia in some parts of the world. HIV encephalopathy is characterized by psychomotor slowing, person- ality change, and other features of a subcortical dementia. However, it is now recognized that cognitive impairment is common even in HIV patients on retroviral therapies, and can have a much wider phenotype, now referred to as HIV-associated neurocognitive syn- drome (HAND). (Fig. 24.4.2.13). Examination of the CSF may show a pleocytosis, increased protein, and oligoclonal bands. White matter changes are visible on neuroimaging. Not least as it is potentially treatable, the diagnosis—which can be established through simple serological testing—should be considered in all patients with young onset or atypical forms of dementia. Cognitive changes in patients with HIV may also be due to opportunistic infections such as cerebral toxoplasmosis and cryptococcal meningitis, and progressive multi- focal leucoencephalopathy, which all require specific treatment.
Transient epileptic amnesia Frequent subclinical seizures affecting temporal lobe structures, so-called transient epileptiform amnesia, can cause memory impair- ments sufficient to be mistaken for a neurodegenerative dementia. Patients often report unusual symptoms including complete loss of memory for salient events such as holidays. Close questioning may HIV-associated neurocognitive disorders Mild cognitive impairment that does not interfere with activities of daily living Asymptomatic neurocognitive impairment Mild cognitive impairment that interferes with

activities of daily living Mild neurocognitive disorder Marked cognitive impairment that produces marked interference with activities of daily living HIV-associated dementia Fig. 24.4.2.13 HIV-associated neurocognitive disorders. Summary of the Frascati criteria for HIV-associated neurocognitive disorder. Reprinted from The Lancet, 13(11), Nightingale S et al., Controversies in HIV-associated neurocognitive disorders, 1139–51. Copyright © 2014, with permission from Elsevier.

SECTION 24 Neurological disorders 5858 elicit a history of prominent déja vu, episodes of abnormal smells or tastes, or staring episodes. The diagnosis may require prolonged electroencephalography recording and, when confirmed, causes of focal epilepsy should be excluded. Treatment with anticonvulsants typically improves symptoms but does not always result in complete recovery. Obstructive sleep apnoea Obstructive sleep apnoea is increasingly recognized as a cause of cognitive impairment, likely as a consequence both of day time somnolence and impaired attention, and impaired memory con- solidation during sleep. The diagnosis should be considered in the context of snoring and somnolence, and can be confirmed with a formal sleep study. Immune mediated disorders As well as the vasculitides discussed earlier, a range of other immune mediated disorders can cause cognitive impairment. Cognitive impairment and dementia are common sequelae of (usually advanced) multiple sclerosis. Other causes include systemic lupus erythythematosis, sarcoidosis, and Behçet's syndrome. Paraneoplastic syndromes can produce often rapid onset cognitive impairment, and in particular a limbic encephalitis—with features including amnesia, behavioural change, and seizures—often with associ- ated limbic signal change and swelling on MRI. A variety of dif- ferent antibodies are associated with testicular, ovarian, and lung tumours; other manifestation may include eye movement abnor- malities, neuropathy, and cerebellar ataxia. Antibodies directed against the NMDA receptor cause an autoimmune encephalitis often accompanied by a hyperkinetic movement disorder. NMDA encephalitis may occur in the context of an ovarian teratoma or without an identifiable tumour, and often respond to tumour re- moval (where present) and/or immune suppression. Antibodies directed against components of the voltage-gated potassium channel (Lgi1 and CASPR2) are an important cause of usually non- paraneoplastic limbic encephalitis in the middle-aged and elderly. Presentation can be with brief jerks of the arm and face (faciobrachial dystonic seizures) that can mimic prion disease. There is typically a subacute onset of memory impairment, seizures, and personality change, sometime accompanied by hyponatraemia. While some cases may be self-limiting or mild, prompt immune suppression can prevent the development of irreversible atrophy and cognitive impairment. FURTHER READING Albert MS, et al. (2011). The diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendations from the National Institute on Aging–Alzheimer's Association workgroups on diag- nostic guidelines for Alzheimer's disease. Alzheimers Dement, 7, 270–9. American Psychiatric Association (1994). Diagnostic and statis- tical manual of mental disorders, 4th edition (DSM-IV). American Psychiatric Association, Washington, DC. Armstrong MJ, et al. (2013). Criteria for the diagnosis of corticobasal degeneration. Neurology, 80, 496–503. Bang J, et al. (2015). Frontotemporal dementia. Lancet, 386, 1672–82. Bettens K, et al. (2013). Genetic insights in Alzheimer's disease. Lancet Neurol, 12, 92–104. Braak H, Braak E (1991). Neuropathological staging of Alzheimer- related changes. Acta Neuropathol 82, 239–59. Brookmeyer R, et al. (2002). Survival following a diagnosis of Alzheimer disease. Arch Neurol, 59, 1764–7. Dementia UK (2014). Update 2014. https://www.alzheimers.org.uk/ dementiauk Dubois B, et al. (2014). Advancing research diagnostic criteria for Alzheimer's disease: the IWG-2 criteria. Lancet Neurol, 13, 614–29. Emre M, et al.

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