# 26.5.2 Dementia 6478 Bart Sheehan

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SECTION 26 Psychiatric and drug-related disorders 6478 26.5.2 Dementia Bart Sheehan ESSENTIALS Dementia is a clinical syndrome, not a specific disease. It is character- ized by impairment of mental functions leading to memory loss, be- havioural changes, and impairment in the activities of daily living. It may be caused by several different diseases, the most common being Alzheimer's disease, vascular dementia, and Lewy body dementia. There are other potentially treatable causes, including depression, which must be excluded. Drug treatment with cholinesterase inhibitors may reduce the progression of dementia for a period, especially in Alzheimer's dis- ease. Antipsychotic drugs should be used with great care. The asso- ciated impairment and behavioural problems often requires social care, sometimes in institutions, and will place an increasing burden on medical services and society. Introduction Dementia is a clinical syndrome in which brain disease leads to ac- quired global impairment of higher mental functions despite clear consciousness. It can be thought of as chronic 'brain failure'. It is usually (but not always) progressive and usually (but not always) found among older people. The functions affected include cognitive function, particularly amnesia (memory loss), dyspraxia (difficulty carrying out complex motor actions), dysphasia (difficulty with speech), and agnosia (inability to recognize and interpret sensory inputs). There may also be psychiatric and behavioural symptoms, in descending order of frequency: depression, paranoid ideas, mis- identifications, hallucinations, aggression, and wandering. Finally there are deficits in activities of daily living (ADLs), with progres- sive impairment in ability to manage both instrumental ADLs (e.g. cooking, using telephone, managing bills) and basic ADLs (washing/ dressing/elimination). Aetiology Dementia is caused by many different diseases. Alzheimer's disease is responsible for about half of cases, and in post-mortem series the other common causes are vascular dementia (20–30% of cases), de- mentia with Lewy bodies (10% of cases), and frontotemporal de- mentia (2–5% of cases). Table 26.5.2.1 shows likely causes, grouped by neuropathological mechanisms. Epidemiology The prevalence of dementia is similar in most countries and most races. Men and women are about equally affected. The incidence in younger and middle-aged people is low and increases with age. Five to seven per cent of people aged 65 and over are affected, and 40% of people aged 95 and over. Worldwide this means that in 2014 about 45 million people had dementia, a figure that is projected to triple by

2050. Already, over half of people with dementia are in low- and middle-income countries, which will also see the greatest rises in coming decades. Clinical features General The clinical features vary according to the cause. Distinguishing be- tween causes may be difficult clinically, especially in the early stages of disease. Patients with dementia usually have histories of acquired progressive memory loss (e.g. forgetting to take tablets or repeating things), with associated deficits in other cognitive areas, especially speech (expressive or receptive dysphasia), dyspraxia (e.g. difficulty carrying out complex motor sequences like cooking or dressing), and agnosia (e.g. not recognizing oneself in the mirror). There is frequently difficulty in coping with the basic activities of daily living; for example, relatives may have to take over managing finances or shopping, or the patient may become repeatedly lost in a previously familiar place. The patient or relative may also describe failure to cope with a situation they would previously have easily mastered, for example, a holiday abroad. As the dementia progresses, the patient shows worsening failure in multiple areas of life, with increasing dependency on others to accomplish even the basic activities of daily living. Other changes in behaviour such as apathy or irritability are commonly noted at some point of the illness, as well as behavioural changes like wandering, insomnia, and aggression. Alzheimer's disease (AD) Alzheimer's disease, the commonest cause of dementia, is a neurodegenerative condition in which there is progressive loss of cortical tissue associated with two hallmark neuropathological findings; extracellular accumulation of amyloid in plaque-like for- mations, and intracellular neurofibrillary tangles:  paired helical fragments of hyper-phosphorylated Tau (a microtubule-associated protein). These pathological findings are the only absolute diag- nostic criteria for diagnosis of AD. To date, aetiological theories have centred on the likelihood that a primary malfunction in metabolism of amyloid is central to AD, though lack of therapeutic progress has led to questioning of this hypothesis. Progression is often relentless, Table 26.5.2.1 Causes of dementia Neurodegenerative causes Alzheimer's disease Vascular dementia Dementia with Lewy bodies Frontotemporal dementias Dementia in Parkinson's disease Hydrocephalus Infective causes Dementia in HIV Syphilis Creutzfeld–Jacob disease Intoxications and metabolic causes Alcoholic dementia Heavy metal poisoning Vitamin deficiencies, especially B12 Miscellaneous causes Head injury Anoxic brain injury

 with a typical history of 2–3 years of symptoms at diagnosis, and progression to death after 7–10 years of illness. Vascular dementia In vascular dementia, the accumulation of cortical and subcortical areas of neuronal loss due to infarction (and sometimes haem- orrhage) leads to escalating cognitive and behavioural change. Infarction is much more common than haemorrhage, though per- haps 10% of patients show micro-haemorrhages on MRI, which suggest cerebral amyloid angiopathy. Up to 20% of community pa- tients with dementia are eventually diagnosed with mixed dementia (due to evidence of both Alzheimer's disease and vascular path- ology). Onset may be sudden and associated with clinical evidence of stroke. Progression is typically stepwise, indicating recurrent and accumulative cerebrovascular events. Patients may retain insight if cortical damage is not widespread. A history of stroke, hypertension, and neuroimaging evidence of cerebrovascular disease support this diagnosis. Prognosis is likely to depend on the wider cardiovascular risk status of the patient, but progression to death over 5–7 years, as in AD, is typical. Dementia with Lewy bodies This clinical syndrome is of dementia characterized by severe fluctu- ation (often over hours), evidence of Parkinsonism, and the presence of striking visual hallucinations. Supportive features include the pres- ence of sleep/wake cycle disruption, sensitivity to neuroleptics (often prescribed due to hallucinations), and deficient dopamine transporter uptake in the basal ganglia on SPET or PET imaging. The clinical syn- drome

can therefore be clearly identified with high precision in life. The hallmark of this condition is the deposition of an intracellular body called a Lewy body, which consists primarily of ubiquitin and α-synuclein. The clinical course is not clearly different to that of AD. Frontotemporal dementia These are a group of dementias, among which the best known is Pick's disease. A family history may be prominent, with earlier age of onset (50s/60s) than with other dementias. There may be striking personality change early in the condition, with coarsening, emo- tional lability, and disinhibition. These changes are essentially the frontal variant of frontotemporal dementia. Dysphasia may also be prominent early, often with loss of recognition for words and dif- ficulties with expressive speech. This is essentially the temporal variant of frontotemporal dementia. CT/MRI imaging may show marked frontotemporal atrophy, while functional neuroimaging is likely to show significant frontotemporal hypoactivity. Conditions in which there is abnormal expression of the microtubule-associated protein Tau (known as Tauopathies) are now recognized as leading to the clinical features of frontotemporal dementia. Differential diagnosis Delirium Delirium shares with dementia the finding of cognitive impairment and often significant behaviour problems. Unlike dementia, the onset of delirium is usually rapid, usually transient, and the clin- ical features include inattention, impairment of consciousness, and marked fluctuation during its clinical course. Depression Patients with depression are frequently apathetic with social with- drawal, poor concentration, and retardation leading to poor perform- ance on formal cognitive tests. This sometimes leads to misdiagnosis of depression as dementia; so-called depressive pseudo-dementia. Mild cognitive impairment This term is used for people at high risk of dementia who have cog- nitive deficits (usually defined as a memory performance at least 1.5 standard deviations below expected norms for age and popula- tion) with associated functional impairment, but no clear dementia. It conveys a 10–15% risk of incident dementia each year (about 10 times higher than that of age-matched peers). Clinical investigations History taking is the most important investigation in diagnosing dementia, and must involve a collateral history from someone who knows the patient well. Tests of cognitive functioning can help screen for dementia, increase the precision of diagnostic decisions, and also help to objectively monitor change over time. Blood tests are useful in excluding rare causes of dementia. Neuroimaging is now a routine part of the investigation of dementia. Cognitive tests Many structured cognitive tests are available for use with patients suspected of having dementia. The most commonly used in the last three decades has been the Mini-Mental State Examination (MMSE). Like other common tests, it covers several cognitive areas (memory, recall, orientation, concentration, praxis, receptive and expres- sive speech, and visuo-motor ability) and is short (10–15 minutes for most patients). It is reasonably effective as a screening tool and can crudely monitor progress (e.g. after initiation of drug therapy). False positives (e.g. due to delirium, depression, tiredness, sedation, learning disability, sensory impairment) are, however, common. More detailed cognitive tests can significantly improve the preci- sion of diagnosis and are especially important in early or borderline cases. Administering them often requires specialist resources. Blood tests Routine assessment of suspected dementia should include the fol- lowing tests: thyroid function, full blood count, urea, and electro- lytes, liver function tests, blood sugar, B12/folate. Syphilis serology and HIV testing are recommended in some clinical populations, but may have low yield in routine memory clinic practice. Neuroimaging CT and MRI scanning provide structural images of the brain. Both will identify mass lesions and help to exclude those causes of de- mentia likely to be amenable to surgical intervention (e.g. normal pressure hydrocephalus, subdural haematoma; see Fig.  26.5.2.1). Shrinkage of medial temporal lobe structures and of the hippo- campus may be observed in early AD. Functional imaging may help to identify frontotemporal deficits in frontotemporal dementia (FTD; see Fig. 26.5.2.2). In dementia with Lewy

bodies, deficient dopamine basal ganglia uptake on single-photon emission computed tomography (SPET) or PET

SECTION 26 Psychiatric and drug-related disorders 6480 imaging strongly supports the diagnosis. In recent years, amyloid ligand imaging on PET scanning has raised the possibility of the very early detection of AD, even before the clinical syndrome can be detected, but the high rate of false positives means that this test cannot be recommended in routine practice. Treatment Drug therapy The treatment of dementia depends on the underlying cause. Great effort has been directed at finding effective biological treatments for the common causes of dementia. In AD, cholinergic neuronal loss is extensive from the early stages, hence the use of cholinesterase inhibitors which prevent the breakdown of the neurotransmitter acetylcholine is rational. These are the current mainstay of AD treat- ment, with available drugs shown in Table 26.5.2.2. Cholinesterase inhibitors have clear benefit in AD, delaying pro- gression of the disease for one to two years on average, rather than reversing established deficits. Withdrawal of these agents is then as- sociated with a worsened prognosis long term, hence they should be continued as long as side effects allow. While most patients tolerate them well, cholinergic side effects, especially gastrointestinal prob- lems and in some patients brady-arrhythmias, can be problematic. Cholinesterase inhibitors are sometimes also used in vascular de- mentia, though the risk/benefit balance in the condition is unproven. (a) (b) (c) (d) Fig. 26.5.2.1 Hydrocephalus. (a) and (b): Two preoperative computed tomography (CT) scans in an elderly adult who presented with cognitive decline and other neurological features. (c) and (d): Following ventriculoperitoneal shunting (arrow in d), the communicating hydrocephalus resolved with complete recovery of the patient. Reproduced from Ian Whittle. Raised intracranial pressure, cerebral oedema, and hydrocephalus, from Dementia: Comprehensive Principles and Practices by permission of Oxford University Press. RH (a) (b) LH RH - Lateral Fig. 26.5.2.2 (a) Magnetic resonance imaging (MRI) demonstrating bilateral (right [RH] greater than left [LH]) frontal, temporal, and parietal atrophy. (b) Fludeoxyglucose positron emission tomography (FDG-PET) showing prominent bilateral (right greater than left) frontal and temporal hypometabolism (indicated by blue colour). Reproduced from Bradford C. Dickerson, Frontotemporal Dementia, from Dementia: Comprehensive Principles and Practices by permission of Oxford University Press.

26.5.2 Dementia 6481 In Lewy body dementia, trials of these agents have shown promise and they are usually recommended. More recent efforts to treat AD have focused on active, and lat- terly passive, vaccination strategies designed to elicit an immune re- sponse to amyloid in the earliest states of disease, but thus far these have not proven effective. Social care Despite progress with drug therapy the mainstay of treatment for dementia remains social; family members still provide the vast ma- jority of care for people with dementia. Up to half of people with dementia in Western countries will eventually spend some period of time in institutional care, though most remain outside such settings. The associated costs of care are clearly enormous and increasing. From the societal perspective, the greatest costs accumulate in the later stages of illness, in particular due to hospitalization and the costs of nursing home care, though the direct healthcare costs are always outweighed by those of social care. At all stages, the greatest costs are probably the indirect costs borne by family carers. Treating the psychological and behavioural problems of dementia Most patients with dementia will develop some behavioural or psychological symptoms during the course of their illness. These include low mood, obsessionality, or psychotic symptoms, and behavioural problems like apathy, agitation, insomnia, aggression, and wandering. These symptoms are unsurprisingly the strongest predictors of carer strain and institutionalization of the patient. Many are dealt with simply by the patience and skill of family or paid carers. In some cases

medication is requested, but few medi- cations have high-quality controlled trial evidence to support their use for this purpose. Risperidone has been shown to improve ag- gression in patients with AD and is licensed for this indication in the United Kingdom. All other prescribing is off licence. Medications with a high risk of worsening cognitive impairment, sedation, and falls (e.g. benzodiazepines) are still often used. Antipsychotics are known to increase risk of stroke and mortality in dementia and should only be used for short periods after evaluation of risk/ benefit.
Future developments: Can dementia
be prevented? In the absence of an effective treatment for most causes of de- mentia, and the vast socioeconomic costs, preventive strategies have been widely promoted. Dementia is especially difficult to prevent as the earliest pathological changes in the disease may occur decades before the clinical features become obvious. Delays of even six months in the onset of clinical symptoms would re- duce the population prevalence appreciably (5–10%), while a delay of five years could reduce the population prevalence by up to 50%. Recent epidemiological evidence raises the possibility that the prevalence of dementia in Western countries may be al- ready falling, possibly due to lifestyle changes aimed at improving cardiovascular health. Risk factors that may contribute to risk of dementia and which may be amenable to intervention are listed in Table 26.5.2.3.
FURTHER READING Folstein MF, Folstein SE, McHugh PR (1975). ‘Mini-mental state’: a practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res, 12, 189–98. Kales HC, Gitilin LN, Lyketos CG (2015). Assessment and manage- ment of behavioral and psychological symptoms of dementia. BMJ, 350, h369. Rabins PV, Blass DM (2014). In the clinic: dementia. Ann Intern Med, 161, ITC1; quiz ITC16. Robinson L, Tang E, Taylor JP (2015). Dementia: timely diagnosis and early intervention. BMJ, 350, h3029. Table 26.5.2.2 Antidementia drug treatments (licensed in United Kingdom, July 2018) Drug class Starting dose Target dose Common side effects Cholinesterase inhibitors Donepezil 5 mg OD 10 mg OD Nausea, diarrhoea, frequency, dizziness, psychiatric effects Rivastigmine 1.5 mg BD 3–6 mg BD Galantamine 8 mg /24 hours 24 mg/24 hours Glutamate antagonist Memantine 5 mg OD 20 mg OD Constipation, headache Table 26.5.2.3 Potential mediators of dementia risk (known risk factors) Evidence is Risk factor Notes Supportive Intelligence No feasible intervention Hypertension Treatable Depression Treatable Diabetes Treatable Contradictory Exercise Inactivity increases risk Obesity Recent evidence suggests low weight increases risk Diet Mediterranean diet most commonly recommended Vitamins B vitamins, E vitamins show promise in early research Not supportive Mental activity Best evidence suggests brain training interventions ineffective Social engagement Social benefits unlikely to be accompanied by lower dementia risk

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