THE BARE ESSENTIALS

Dementia

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Dementia is a syndrome characterised by progressive deterioration of cognitive function, most commonly of memory, but other domains such as language, praxis, visual perception and most notably executive function are also often affected. Most of the causes of this syndrome are progressive, but not invariably so. As cognitive function worsens, there is increasing interference with the patients' daily activities leading to loss of independence and eventually for some the need for nursing home care. The patients usually survive 5–10 years.

Dementia is common and already places a tremendous burden, not only on patients and their carers, but also on society, a burden that will increase as life expectancy increases. Because of these worrying facts and the development of the first symptomatic treatments, dementia is of growing interest to medical professionals and the public. Furthermore, because disease modifying treatments may be on the horizon, it is ever more important to understand the pathophysiology of the different causes and types of dementia, and to make the diagnosis early—it will probably be easier to stop the damage than to undo it.

EPIDEMIOLOGY

- Dementia is rare in young and middle age but after the age of 50 years it becomes more and more common. At age 60–65 years, approximately 1% of the population is affected, rising to 10–35% in those over 85 years of age. It is more common in men than in women over the age of 80 years (fig 1).
- Of the patients with late onset dementia (≥65 years), about half have Alzheimer's disease, 16% vascular dementia, 30% other forms of dementia such as dementia with Lewy bodies and frontotemporal lobar degeneration (fig 2).
- In younger patients, Alzheimer's disease is relatively less common but it is still the most prevalent cause, while frontotemporal dementia, alcohol related dementia and dementia secondary to other diseases such as multiple sclerosis are relatively more common (fig 3).

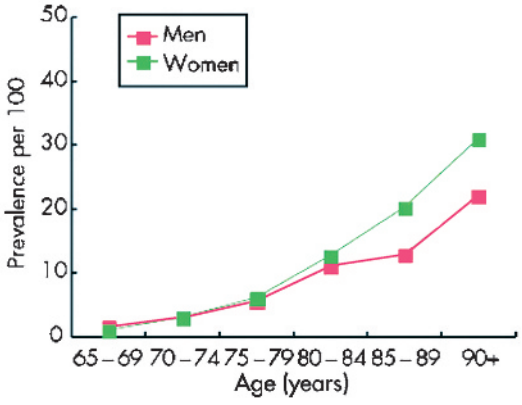

Figure 1 Pooled prevalence (%) of dementia by age and sex (based on Lobo *et al*, see further reading).

Risk factors

- *Age* is the most consistent risk factor, presumably because during life the brain is exposed to various forms of damage, such as minor vascular events, white matter disease and inflammation. Furthermore, the increasing risk of Alzheimer's disease is probably a reflection of increasing amyloid plaque formation with age.
- *Level of education* More years of education appear to offer some protection against Alzheimer's disease.
- *Family history* of a first degree relative with Alzheimer's disease increases the risk of developing Alzheimer's disease by about four times, two first degree relatives by about eight times.
- *Genetic factors* Mutations in three genes cause familial Alzheimer's disease: amyloid precursor protein, presenilin 1 (PS-1) and presenilin 2 (PS-2). Patients with these genes usually have young onset (<65 years). Besides these gene mutations, polymorphism of apolipoprotein E is a risk factor for Alzheimer's disease. Apolipoprotein E exists in three common polymorphisms (ε2, ε3 and ε 4); ε4 heterozygotes have a 2–3 times and ε4 homozygotes a 6–8 times higher risk of developing Alzheimer's disease than non ε4 carriers.
- *Vascular risk factors* Hypertension, hypercholesterolaemia and diabetes mellitus have all been associated with an increased risk of Alzheimer's disease, as well as with vascular dementia.

DIFFERENT TYPES OF DEMENTIA

Our perspective on dementia evolved tremendously in the 20th century. Before 1900 there where no specific diagnoses but with much effort by clinicians to recognise various types of dementia, with help from pathology, genetics and neuroimaging, it is now possible to classify "the dementias". Deteriorating memory, known to be

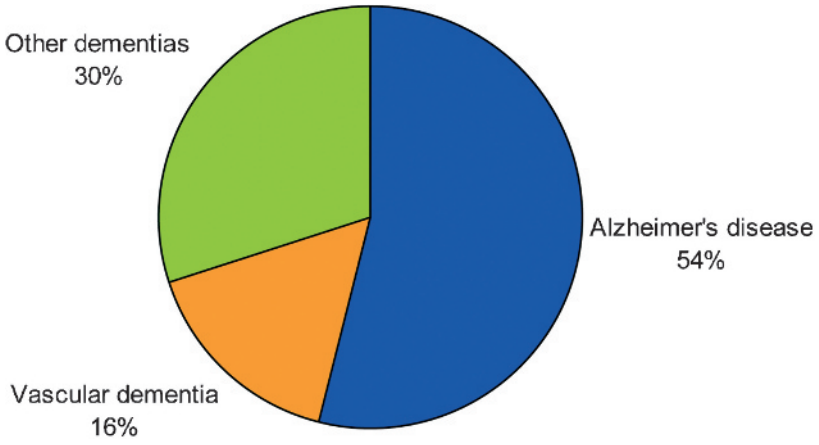

Figure 2 Causes of dementia with late onset (≥65 years) (based on Lobo *et al*, see further reading).

the key feature in dementia, is no longer essential for the diagnosis. For example, the criteria for dementia with Lewy bodies emphasise the early deficits in attention and visuospatial function. Similarly, in frontotemporal lobar degeneration, memory disturbance is absent or occurs late, thereby causing us to think rather differently about the notion of dementia—it is not just decline in memory. Cognitive problems in domains other than memory, such as language, visuoperception and character changes, are now possible features—and criteria—for a diagnosis of dementia (table 1).

A recent development has been the recognition of a state which may precede dementia, so-called mild cognitive impairment. The most common form is amnestic, defined by memory complaints by the patient, preferably supported by an informant, in combination with an objective memory deficit, but without interference with activities of daily living. The relevance of recognising this state is that 15–20% progress to dementia (mostly Alzheimer's disease) per year compared with 1–2% of the elderly population.

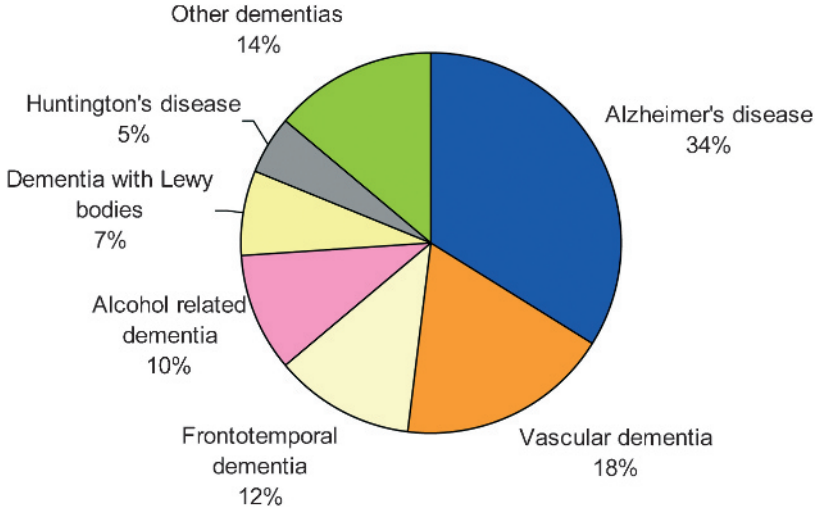

Figure 3 Causes of dementia with young onset (<65 years) (based on Harvey *et al*, see further reading).

Alzheimer's disease

- The most common form of dementia.
- Definite diagnosis of sporadic disease is only possible at post mortem, based on the accumulation of extracellular amyloid and intraneuronal neurofibrillary tangles.
- The clinical diagnosis should be made according to the criteria of the National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) or Diagnostic and Statistical Manual of Mental Disorders IV (DSM-IV); impairment in two or more cognitive domains that interfere with activities of daily living, with progressive decline from a previous level of functioning. Investigations such as brain MRI and CSF are gaining more prominence (see below).
- In the most typical form, impairment in episodic memory is the first complaint. Neurologists often refer to short term memory problems but in neuropsychology this term refers specifically to working memory with a very short duration that can be tested with digit span (which is usually normal in early Alzheimer's disease). As the disease progresses, memory problems are accompanied by a combination of disturbances of language ability, praxis, visuospatial and executive functions. This characteristic type is most commonly seen in younger patients, labelled early onset Alzheimer's disease.
- Later in life, additional cerebrovascular damage is common, usually resulting in a slightly different clinical presentation. These late onset patients present more commonly with confusion, depression, delusions and visual hallucinations.
- A third type is the biparietal Alzheimer variant which presents with deficits in praxis and visuospatial and visuoperceptual skills; deficits in language and memory are usually mild early on. This overlaps with posterior cortical atrophy where the pathology is more posterior; patients present with visual agnosia, features of Ballint's syndrome (visual disorientation, optic apraxia and simultagnosia) and apraxia.
- Alzheimer's disease can also present as a progressive aphasia of the non-fluent type with other cognitive problems developing later.

It is important to realise that Alzheimer's disease can sometimes be associated with several other neurological features: extrapyramidal signs and myoclonus are not uncommon, and dementia in general as well as Alzheimer's disease is one of the main risk factors for late onset epilepsy.

Frontotemporal lobar degeneration

- A heterogeneous group of syndromes with various clinical characteristics and different neuropathological substrates at post mortem.
- Approximately 20–30% of cases are familial and may be associated with mutations in the progranulin or MAPT gene.

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Table 1 Red flags in the diagnosis of dementia and alternative diagnostic possibilities (modified from Kawas 2003, further reading)

Red flag	Diagnosis
Abrupt onset	Vascular dementia
Stepwise deterioration	Vascular dementia
Prominent behavioural changes	Frontotemporal dementia, vascular dementia
Profound apathy	Frontotemporal dementia, vascular dementia
Prominent aphasia	Semantic dementia, progressive aphasia, vascular dementia
Progressive gait disorder	Vascular dementia, normal pressure hydrocephalus, Parkinson's disease dementia
Prominent fluctuations	
► Consciousness	
► Cognitive abilities	Delirium due to infection, medications or other causes, dementia with Lewy bodies, temporal lobe epilepsy, obstructive sleep apnoea syndrome, metabolic disturbances
Hallucinations or delusions	Delirium due to infection, medications or other causes, dementia with Lewy bodies
Frequent falls	Progressive supranuclear palsy, dementia with Lewy bodies
Extrapyramidal signs or gait	Parkinsonian syndromes, vascular dementia
Eye movement abnormalities	Progressive supranuclear palsy, Wernicke's encephalopathy

- At post mortem it can be divided into two neuropathological subtypes: with tau inclusions or with inclusions that are positive for ubiquitin.
- About 7% of cases also have motor neuron disease.
- Clinically there are three presentations.

Frontotemporal dementia typically presents with gradual onset of behavioural abnormalities between the ages of 35 and 74 years.

- Social and personal conduct which is inappropriate, characterised by inertia, loss of volition and social disinhibition, and distractibility, with relative preservation of memory function.
- Emotional blunting and loss of insight, and abnormal behaviour may be stereotyped and perseverative.
- Speech is usually economical, sometimes even leading onto mutism.
- Cognitive deficits occur in the domains of attention, abstraction, planning and problem solving, or executive functions.

Progressive non-fluent aphasia presents with:

- Gradual disturbance of expressive language with effortful speech production, phonological and grammatical errors, and word retrieval difficulties. Patients ultimately become mute.
- Reading and writing can also be impaired.
- Other cognitive functions are usually spared and any behavioural change may occur late.

Semantic dementia presents with:

- Progressive impairment of comprehension of words and naming in the context of fluent, effortless and grammatically correct speech output but relative preservation of repetition and in the ability to read aloud.
- Often there is also visual agnosia; patients are not able to recognise the meaning of visual percepts.
- Memory functions usually remain intact.

Vascular dementia (or vascular cognitive impairment)

A very heterogeneous group of patients with cognitive deficits and proof of vascular damage (in the history, clinical examination or brain imaging), with a likely causal relationship. The clinical features depend on the location and size of the vascular lesions (eg, a dysexecutive disorder with inertia in patients with mostly subcortical lesions, and predominant memory impairment in those with temporal cortical lesions). Other non-cognitive problems such as gait disorders, urinary incontinence, and pyramidal and focal neurological deficits are common. Obvious risk factors are hypertension, smoking, diabetes mellitus and atrial fibrillation. There are cerebrovascular lesion patterns on brain MRI or CT (see imaging below). Vascular dementia is a likely cause for cognitive deficits if there is:

- Abrupt deterioration in intellectual ability after a stroke, or a fluctuant or stepwise course.
- A history of gait disorder or frequent falls.
- Urinary incontinence in the early phase.
- At neurological examination focal deficits such as hemiparesis, sensory loss, including visual field defects, a pseudobulbar or an extrapyramidal syndrome.

An important subtype of vascular dementia is CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukencephalopathy). This tends to affect young patients without vascular risk factors. The core symptoms are recurrent strokes, migraine and a family history. It is associated with a mutation in the Notch 3 gene on chromosome 19.

Dementia with Lewy bodies and Parkinson's disease dementia

Apart from cognitive disturbances, these disorders are recognised by features such as visual hallucinations, parkinsonism, cognitive fluctuation, dysautonomia, sleep disorder and neuroleptic sensitivity.

- It is difficult and rather arbitrary to distinguish dementia with Lewy bodies from dementia in Parkinson's disease as about 40% of patients with Parkinson's disease also develop cognitive problems. The diagnosis of Parkinson's disease with dementia is made when the onset of the cognitive deficits is more than 1 year after the onset of parkinsonism. Parkinsonism in dementia with Lewy bodies is in general less severe than in Parkinson's disease.
- Visual hallucinations appear in approximately two-thirds of dementia with Lewy body patients, usually early. They are vivid and usually consist of animals or humans but can be more abstract or are extracampine (''somebody is looking over my shoulder'').
- Cognitive fluctuations, such as daytime drowsiness lasting more than 2 h, prolonged staring

spells and episodes of disorganised speech, occur in most patients.
- Common is the sleep disorder with vivid dreaming in REM sleep without the usual muscle atonia, resulting in dream-enacting, known as REM sleep behaviour disorder.
- Parkinsonian signs of bradykinesia, rigidity or gait disorders in 70–90% patients.
- Dysautonomia; orthostatic hypotension, urinary incontinence or retention and constipation, and impotence are often early problems.
- Approximately 30–50% of patients have severe sensitivity to dopamine agonists—acute reactions include (irreversible) parkinsonism and impaired consciousness, sometimes in combination with other symptoms of the neuroleptic malignant syndrome. Be very careful prescribing neuroleptics in any patient with dementia.

Creutzfeldt–Jakob disease (CJD)

- CJD is associated with an abnormal isoform of the prion protein which misfolds into insoluble fibrils and causes neuronal damage.
- About 5–15% of cases are familial.
- The new variant form, the human equivalent of bovine spongiform encephalopathy, received much attention in the 1990s but so far only 205 cases (167 in the UK) have been reported.
- In most patients there is no obvious cause (sporadic CJD).
- It is recognised as a rapidly progressive cognitive deterioration over months with behavioural abnormalities and deficits in attention, memory, judgment and perception. Mood changes such as apathy and depression are common but euphoria, emotional lability and anxiety can also occur. Myoclonus, especially provoked by startle, is eventually present in 90% of patients but not always at first presentation. Extrapyramidal signs such as hypokinesia and cerebellar manifestations such as nystagmus and ataxia occur in two-thirds of patients. Pyramidal signs are seen in 40–80% of patients.
- The prognosis is very poor, there is no treatment and death usually occurs within a year.

Huntington's disease

- The symptoms usually start between the ages of 25 and 45 years but onset during childhood or in old age also occurs.
- It is an autosomal dominant disease presenting with a combination of progressive chorea, dystonia, incoordination, cognitive and behavioural disturbances.
- The cognitive syndrome usually starts with slowness of thinking and dysexecutive deficits.
- Depression and suicidal ideation are common in the more advanced stages.
- The mutant protein (huntingtin) in Huntington's disease results from an abnormally high number of CAG repeats in the huntingtin gene on the short arm of chromosome 4. Over generations, the number of repeats usually increases, particularly with paternal inheritance, which is associated with higher penetrance, younger onset and a more severe illness.
- There is no treatment.

Corticobasal degeneration

- This syndrome is characterised by gradual onset of a combination of dementia and asymmetrical motor and/or sensory deficits, including dystonia or the alien hand syndrome.
- Various forms of apraxia affecting limb function are common, especially ideomotor and limb kinetic apraxia, but buccofacial and eye movement apraxia can also be present.
- Patients usually have a dysexecutive syndrome and decreased mental flexibility.
- Asymmetrical atrophy of the paracentral and frontal cortex on brain imaging.

Progressive supranuclear palsy

- Typically this presents between the ages of 50 and 70 years with cognitive problems in combination with frequent falls and (vertical) gaze paresis, often with axial rigidity, gait disorders and retropulsion.
- Cognitive dysfunction usually includes bradyphrenia, personality change and executive dysfunction.
- More atypical presentations start with cognitive problems and character changes (as seen in frontotemporal dementia), later followed by gaze disorders and parkinsonism.
- Sometimes the disease starts with parkinsonism, followed by cognitive problems, making it important to carefully follow-up patients with an atypical presentation of parkinsonism.
- Generally sporadic but some families have a mutation in the MAPT gene on chromosome 1q31.

HIV dementia

- This is related to the CD4+ T cell count and duration of the immunosuppression.
- There is a combination of cognitive decline (usually deficits in attention/concentration, processing speed, abstraction, memory, speech, visual functioning) and impairment of motor function, along with changes in behavioural or emotional function.

Normal pressure hydrocephalus

- A clinical syndrome characterised by gait apraxia (without pyramidal, extrapyramidal, sensory or cerebellar signs), dysexecutive problems and urinary incontinence, in combination with enlarged lateral ventricles on CT or MRI.

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- Shunting is still widely done but the results are often disappointing and therapeutic success is difficult to predict.
- Of the three cardinal symptoms, the gait problems respond best to shunting.

Alcohol related dementia

- Korsakoff's amnestic syndrome presents with striking anterograde and retrograde amnesia with confabulation and perseveration, mostly (but not exclusively) after an episode of Wernicke's encephalopathy (vitamin B1 deficiency); long term memory and other cognitive skills remain relatively spared.
- Besides Korsakoff's, about 50–70% of alcohol abusers have cognitive deficits on neuropsychological testing; brain imaging usually reveals enlargement of the cerebral ventricles and sulci.

Other (treatable) causes

- Intracranial space occupying lesions such as chronic subdural haematoma, (bifrontal) meningioma, glioma, metastasis.
- Hyper- and hypothyroidism.
- Vitamin B12 deficiency.
- Hyponatraemia, hypercalcaemia, chronic hepatic or renal failure.
- Chronic CNS infections—syphilis, etc.
- Medication induced—sedatives and analgesics.

It is important to note that these causes are rare—<1% of new cases of "dementia".

DIFFERENTIAL DIAGNOSIS OF DEMENTIA

Sometimes a patient who seems "demented" is not in the sense that they do not have a progressive neurodegenerative condition; important alternative diagnoses to consider are the following.

Obstructive sleep apnoea syndrome

- Lack of sleep can result in significant deterioration in cognitive functioning, particularly short term memory and attention.
- Sleep deprivation can also result in poor judgment, irritability, depression or anxiety.
- All of these symptoms often disappear suddenly when normal sleep is restored with appropriate treatment

Depression

- Complaints of cognitive problems are very common, and patients are even more likely to complain about their memory than those with Alzheimer's disease (in these latter patients the memory problem is usually brought up by family members rather than the patient).
- Depressed patients may have signs of psychomotor slowing and produce a poor effort on tests while demented patients try very hard but provide the wrong answers.
- Confusingly, however, depression can be one of the first symptoms of dementia, making the differentiation difficult. Follow-up and psychiatric evaluation are indicated here.

Delirium

- Delirium is characterised by a combination of disturbance of consciousness, or shifting attention and cognitive disturbance, usually with psychomotor behaviour disturbances, altered sleep pattern, visual hallucinations and emotional disturbances (eg, fear or depression).
- The duration is relatively short, hours to days, and the symptoms tend to fluctuate during the course of the day and are usually worse in the evening (so-called sundowning).
- It is a very common cause for cognitive disturbance in older people as a result of underlying infections, electrolyte disturbances and medication; it is important to exclude and treat before diagnosing dementia.
- Late stage dementia is associated with an increased risk of delirium.

Temporal lobe epilepsy

- Cognitive problems can be caused by epilepsy, especially temporal lobe epilepsy, where memory related structures are involved in seizure activity which may or may not be clinically evident.
- Transient epileptic amnesia is a syndrome of recurrent episodes of amnesia which can last from minutes to days. Observers may report staring episodes or periods of confusion. It can be diagnosed by epileptic abnormalities on the EEG although sleep recording is often required, additional typical features of epilepsy (eg, lip smacking), the emergence of more obvious epileptic attacks or a clear response to antiepileptic therapy.
- Long term memory can be impaired in patients with generalised or complex partial epilepsy, perhaps because epileptic activity disturbs the consolidation of memories. Antiepileptic drugs or the underlying cause of the epilepsy also play a role.

DIAGNOSTIC EVALUATION

History

The history must be taken from both the patient and an informant. When a patient comes to the clinic alone without a relative, friend or carer, this is a red flag for the *absence* of dementia. The history from a family member can be crucial because patients tend to downplay their problems. It is essential to understand the patient's degree of dependency in activities of daily living because dependence is a crucial consequence of dementia. Furthermore, the clinician should enquire about cognitive defects in domains other than memory (table 2).

Table 2 Diagnostic evaluation to differentiate between types of dementia

	Alzheimer's disease	Frontotemporal lobar degeneration	Vascular dementia	Dementia with Lewy bodies
History/cognitive problems	Short term memory impairment, aphasia, apraxia visuospatial problems, executive dysfunction, interfering with daily life	Compulsive behaviour, disinhibition, apathy, stereotyped behaviour, (isolated) language problems	Abrupt, fluctuant or stepwise cognitive deterioration Vascular risk factors (eg, diabetes mellitus, hypertension), history of stroke	Cognitive disturbances with fluctuations, visual hallucinations, frequent falls, sleep disorders
Neurological examination		Primitive reflexes	Neurological deficits, gait disturbance	Parkinsonism
Cognitive neurological examination	Episodic memory impairment, executive dysfunction, afasia, apraxia, visual agnosia	Disinhibition, stereotypy, inertia, speech disorders	Apathy, slowness of thinking	Hallucinations, delusions
EEG	Generalised slowing	Relatively normal	Asymmetrical pattern	Generalised slowing
MRI	Medial temporal (hippocampal) atrophy, general atrophy, biparietal atrophy	Bifrontal atrophy, asymmetrical temporal atrophy	Large vessel ischaemic strokes, large boundary zone infarcts, profound white matter disease	Cortical atrophy

Memory

- Does the patient forget names of friends and family, or facts about friends and family?
- Does he or she leave keys in odd places, or forget where the car is parked?
- Does the patient forget recent events?
- Does the patient get lost in familiar surroundings (orientation)?
- Has learning ability deteriorated?

Activities of daily living

- Is the patient still able to do their domestic tasks?
- Is the patient still able to do his or her work?
- Is the patient able to use (new) household devices?
- Is the patient still able to do simple administrative tasks?
- Can the patient learn to operate a new mobile phone or DVD recorder?
- How does the patient take care of him or herself?
- Can he or she understand complex situations?
- Is the patient able to make sensible decisions?

Personality and mental state

- Has the patient changed in character?
- Are there any features of depression?
- Loss of interest?
- Have their been changes in interpersonal relations?
- Has the patient become impulsive, disinhibited with loss of decorum, what about compulsive behaviour?
- Have there been changes in eating pattern?
- Has the patient lost initiative?
- Has the patient become apathetic?
- Are there delusions or hallucinations?

General

- Is there a history of cardio- or cerebrovascular events, thyroid disease, alcohol abuse?
- Is the patient on possibly relevant medications (eg, sedatives, hypnotics, anticholinergics)?
- Has there been bladder or bowel incontinence?
- Are there any balance disturbances?
- Is there a family history of vascular disease, dementia, Parkinson's disease or motor neuron disease?

Examination

General physical examination should pay special attention to blood pressure and any evidence of vascular disease.

Neurological examination with attention to eye movements, primitive reflexes, visual impairment (eg, field defects indicating vascular damage), balance and gait disturbances, parkinsonism, motor and sensory deficits, and tendon reflex asymmetry (table 2).

Observation of behaviour with attention to personal hygiene, dependence which can be assumed clinically by the so called "head turning sign" (when asked a question the patient first looks towards his/her spouse for an answer), disinhibition, apathy, perseveration, confabulation, insight into the problem, trivialisation of the problem, delusions, hallucinations, stereotypy, mood, attention/concentration and inertness.

Cognitive neurological examination, especially in the early phase, is essential to help identify the specific type of dementia (table 2), in particular noting the various domains of cognitive disturbance:

- For *attention and concentration* first impressions are during history taking, while further testing can be done with serial-7s of the Mini-Mental State Examination (MMSE) (see box), counting backwards or naming the months of the year backwards.
- *Language* is tested by listening to spontaneous speech (history taking), naming (pictures or pen/watch of MMSE), repeating (sentence "No ifs, ands or buts" from MMSE), writing

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Mini-Mental State Examination

Orientation

- What is the (year) (season) (date) (day) (month)? [5 points, 1 per item]
- Where are we (state) (country) (town) (hospital) (floor)? [5 points, 1 per item]

Registration

- Name three objects: pony, quarter, orange (1 s to say each). Then ask the patient to name all three after you have said them. Give 1 point for each correct answer. If needed, repeat them until he/she learns all three. [3 points]

Attention and calculation

- Serial 7s. Subtract 7 from 100 and continue to subtract 7 from each subsequent remainder until I say stop. [5 points, 1 for each subtraction]
- Alternatively, spell "world" backwards.

Recall

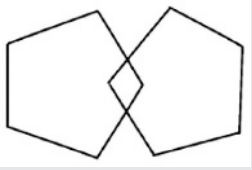
- Ask for the three objects repeated above. [3 points, 1 for each right answer]

Language

- Name a pencil and watch. [2 points, 1 per item]
- Repeat the following "No ifs, ands or buts". [1 point]
- Follow a three stage command: "Take a paper in your hand, fold it in half and put it on the floor." [3 points, 1 per item]
- Read and obey the following: CLOSE YOUR EYES. [1 point for closing eyes]
- Write a sentence. [1 point]

Visuospatial function

- Copy the design shown. [1 point if two pentagons overlap resulting in a square]



(sentence from MMSE), reading, understanding commands (eg, "touch your right ear with your left hand").

- *Memory and learning ability* is assessed by testing orientation, recall (immediate and long term memory), episodic memory (eg, news facts) and semantic memory (meaning of words). Possible options are the recall of three words from the MMSE, recall of several pictures and asking about items in the news.
- *Visuospatial functions* are tested by asking the patient to copy figures, such as the cube or intersecting pentagons from the MMSE. Another option is clock drawing.
- *Praxis* is tested with instructions to mime (pretend to comb your hair, brush your teeth, etc) or by observing the patient while he or she gets dressed.
- *Executive functions* are tested by abilities to plan, organise, abstract and by mental flexibility. One could use the Luria or the Go-NoGo from the Frontal Assessment Battery. Other possibilities are the Trail Making, Stroop and verbal fluency tests.

Screening tests include the MMSE, the 7 min screen and the Clinical Dementia Rating.

INVESTIGATIONS

Laboratory tests

These should be used to explore whether the patient has any comorbidity, risk factors for dementia, reason for delirium or—occasionally—a primary cause for dementia. The following blood tests are mandatory:

- erythrocyte sedimentation rate
- full blood count
- electrolytes
- calcium
- glucose
- renal and liver function
- thyroid stimulating hormone.

Further tests will be required in individual cases—syphilis serology, vitamin B12 levels, HIV and in some cases borrelia titres (only when there is a serious suspicion of Lyme disease).

Any comorbidity that is treatable should be treated and then the evidence for dementia reassessed.

Cerebrospinal fluid

CSF provides a "window to the brain", reflecting biochemical changes such as extracellular aggregation of beta amyloid in plaques and the formation of tau tangles.

- Amyloid beta 1–42 (Aβ42) is reduced by 50% in Alzheimer's disease and mild cognitive impairment but it is also moderately reduced in other dementias such as vascular dementia, dementia with Lewy bodies and frontotemporal lobar degeneration.
- CSF tau level is increased 2–3 times in Alzheimer's disease and mild cognitive impairment in comparison with non-demented controls with a specificity of 90% and sensitivity of 81% for Alzheimer's disease. It is however also raised in CJD and after acute stroke, and sometimes in vascular dementia and frontotemporal dementia.
- Phosphorylated tau reflects the phosphorylated state of tau protein, and thus the formation of tangles. The CSF level in Alzheimer's disease can be increased by one or two orders of magnitude compared with non-demented controls and is generally considered more specific for Alzheimer's disease than Aβ42 and tau although there are contradictory reports.
- 14-3-3 protein has a sensitivity for patients suspected of having sporadic CJD well above 90% but false positives occur with cerebral infarcts and metastases, paraneoplastic syndromes and rapidly progressive Alzheimer's disease, making it likely that it is a marker of brain cell death rather than for just CJD.

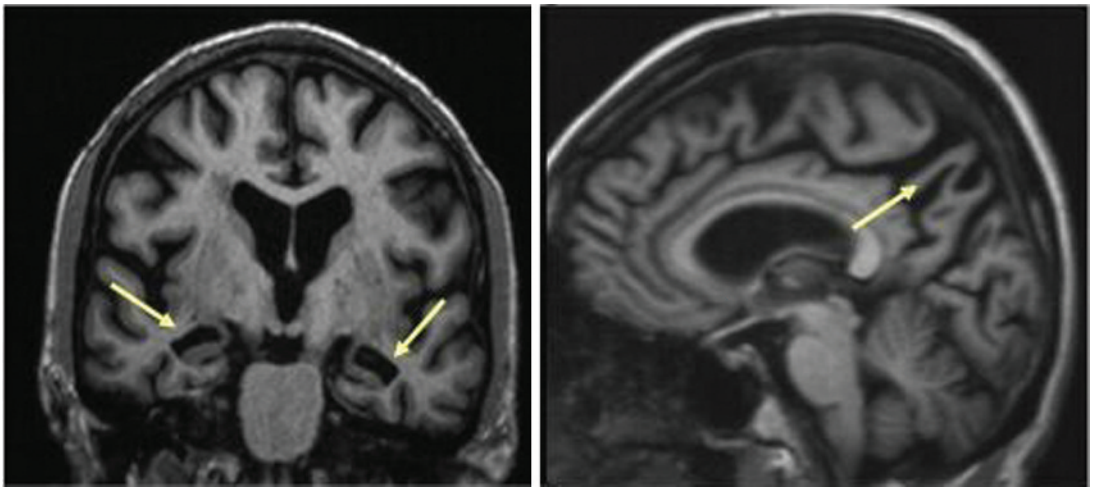


Figure 4 Alzheimer's disease: left image, medial temporal lobe atrophy (arrows) is the most typical abnormality; right image, the less commonly seen posterior cortical atrophy (arrow) on coronal T1 weighted MR image.

Brain imaging (CT or more often MRI with higher sensitivity for brain structure)

Originally, brain imaging was used to exclude various causes of dementia that are potentially treatable (eg, benign brain tumours). In memory clinics, such abnormalities are detected in approximately 4% of patients. Nowadays it is increasingly used to add positive or negative predictive value for the most common types of dementia.

- *Medial temporal lobe atrophy* Hippocampal volume loss is strongly associated with Alzheimer's disease (fig 4). It is a relatively early marker of pathology and has predictive value for progression in mild cognitive impairment patients. But it is not specific as it also occurs in vascular dementia, dementia with Lewy bodies and frontotemporal lobar degeneration.
- *Patterns of atrophy* Some patients with Alzheimer's have prominent posterior cortical or biparietal atrophy (fig 4). Frontal and temporal atrophy are commonly seen in frontotemporal lobar degeneration although their absence does not exclude this diagnosis (fig 5). Progressive non-fluent aphasia typically shows left-sided perisylvian atrophy whereas semantic dementia shows left-sided anterior temporal lobe atrophy. Progressive supranuclear palsy is associated with a "penguin silhouette" or "hummingbird sign" on mid-sagittal MRI due to mesencephalon atrophy (fig 6). Corticobasal degeneration shows hemi-atrophy, or at least asymmetrical atrophy, of the parietal region. Sporadic CJD shows increased diffusion weighted imaging signal in the cortex or deep grey matter, in various patterns (fig 7); later, FLAIR shows high signal abnormalities, generalised atrophy and ventricular dilatation. In variant CJD, high signal in the pulvinar of the thalami is very specific.
- *Vascular pathology* Vascular changes on imaging are regularly seen in all forms of dementia. Lesions that are highly associated with dementia are large vessel ischaemic stroke or boundary zone infarcts in the dominant hemisphere, large or bilateral thalamic infarcts, bilateral anterior infarcts, infarcts of the inferior medial temporal lobe and parietotemporal/temporo-occipital association areas (fig 8). Furthermore, profound white matter disease (more than 25% of white matter) is thought to cause dementia.

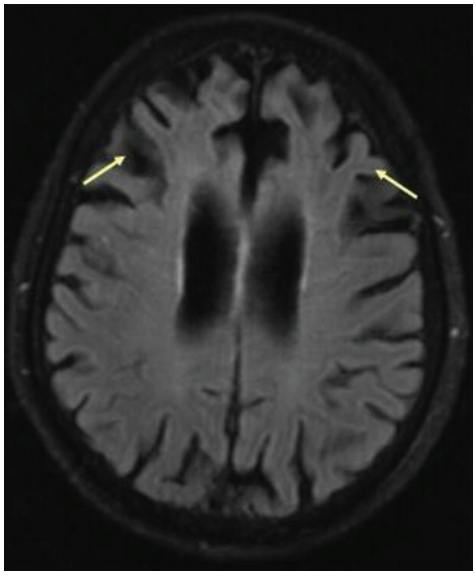


Figure 5 Frontotemporal dementia showing bifrontal atrophy (arrows) on axial FLAIR MR image.

Functional imaging

This is not routinely used. Single photon emission computed tomography and positron emission tomography imaging with a metabolic tracer show hypometabolism and hypoperfusion in the temporal and parietal regions in Alzheimer's disease, and reduction of frontotemporal blood flow even in the absence of atrophy in frontotemporal dementia. An exciting new possibility is imaging amyloid β in the brain.

Electroencephalography (EEG)

- Generalised slowing of background rhythm is frequent in Alzheimer's disease and dementia with Lewy bodies; this is not specific and can also be found in other diffuse encephalopathies.

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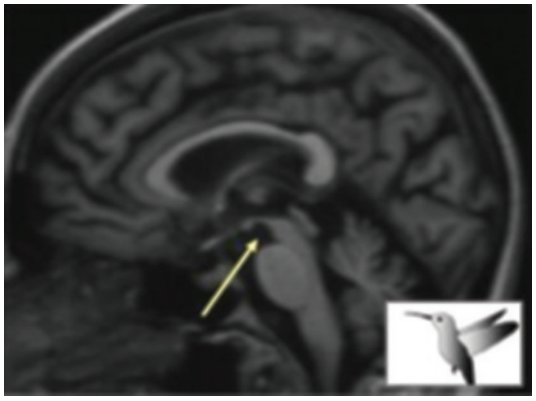

Figure 6 Progressive supranuclear palsy with the "hummingbird sign" (arrow) on a mid sagittal T1 weighted MR image.

- In frontotemporal dementia the EEG is generally normal.
- Typical sharp wave complexes are specific for CJD, particularly the sporadic form.
- Another possible important finding is temporal epileptic activity causing transient epileptic amnesia.

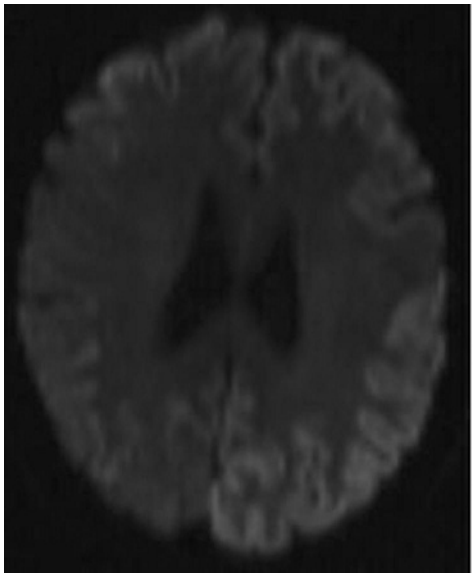

Figure 7 Creutzfeldt–Jakob disease with increased MR diffusion weighted imaging signal in the cortex.

MANAGEMENT

Pharmacotherapy has a role in the symptomatic treatment of different types of dementia. Cognition can be improved (temporarily) by cholinesterase inhibitors or N-methyl-D-aspartic acid (NMDA) receptor antagonists while other common neuropsychiatric symptoms can be treated with a wide range of medications as well with as other strategies.

Cognitive enhancers

- *Cholinesterase inhibitors* (table 3) which increase cholinergic transmission by inhibiting cholinesterase in the synaptic cleft were developed for Alzheimer's disease, based on the notion of reduced cerebral acetylcholine synthesis and thus impaired cortical cholinergic function. They have been approved for the mild to moderate stages of Alzheimer's disease but may also be of some benefit in more advanced stages. According to several international guidelines, including those of the National Institute for Health and Clinical Excellence (NICE) in the UK, these drugs should be offered after the expectations of the patient and carers have been discussed and potential adverse effects reviewed (see table 3); in particular it should be pointed out that these drugs only have a symptomatic effect that may wear off as the disease progresses. There are no good guidelines on when to stop treatment, other than clinical judgement, and there is little evidence that switching from one to another is helpful. These drugs have also been licensed for dementia with Lewy bodies and Parkinson's disease dementia where their main effects are in improving cognition and reducing hallucinations.
- *N-methyl-D-aspartic acid receptor antagonists* (table 3). Another system likely to be involved in Alzheimer's disease is dysfunction of glutamatergic neurotransmission, manifested as neuronal excitotoxicity. Targeting the glutamatergic system, specifically the NMDA receptors, offers a novel approach to treatment in view of the limited efficacy of the drugs targeting the cholinergic system. Memantine is approved in the USA and several countries of the European Union for moderate to severe disease but not by NICE in the UK.

Treatment of behavioural and psychological symptoms

Non-pharmacological interventions are always preferred over medication but there are situations where the burden of symptoms, for patient or carer, justify their use.

- *Psychotic symptoms*. Drug therapy is warranted if the symptoms lead to problematic or dangerous situations. For patients with dementia with Lewy bodies or Parkinson's disease dementia (or parkinsonism in general), neuroleptic medication is contraindicated but it is safe to use rivastigmine 1.5–6 mg twice daily. In Alzheimer's disease, risperidone 0.5–1.5 mg twice daily is preferred.
- *Depression* is common in patients with dementia, and can cause sudden deterioration of the cognitive problems. Treatment with a selective serotonin reuptake inhibitor (citalopram 10–40 mg once daily) is preferred. A tricyclic drug such as nortriptyline 50 mg once daily is second best.
- *Agitation and restlessness* become more of a problem during the course of dementia. Trazodone 50–100 mg three times daily, risperidone 0.25 mg twice daily or oxazepam 10 mg three times daily can be tried, and in severe cases valproate 250–500 mg three times daily is an option.

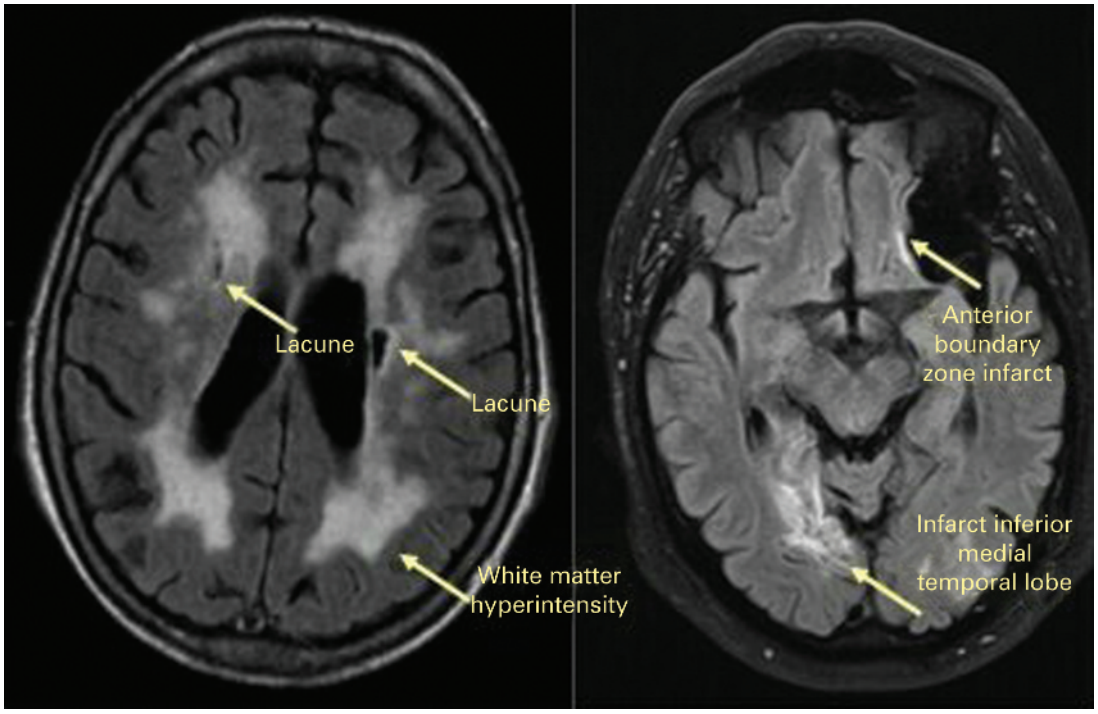

Figure 8 Vascular dementia with (on the left image) extensive periventricular white matter hyperintensities and two small lacunes and (on the right image), an infarct of the inferior medial temporal lobe (arrow) and an anterior boundary zone infarct. Axial FLAIR MR image.

- *Anxiety and panic attacks* Citalopram 10–40 mg once daily, oxazepam 10 mg three times daily or alprazolam 0.25 mg three times daily.
- *Sexual disinhibition* is common in frontotemporal dementia and can be treated with an androgen antagonist such as cimetidine 400 mg 1–2 times daily (an inhibitor of cytochrome P450 system) or spironolactone 50 mg 2–3 times daily.
- *Sleep disorders* It is very important that dementia patients are encouraged to keep to a normal day and night rhythm. If necessary, temazepam 10–20 mg or zoplicone 7.5 mg may be used at bedtime.
- *Delirium* General medical causes for delirium should be excluded and, if necessary, haloperidol 0.5–1.5 mg 2–3 times daily can be tried, or a benzodiazepine.

Non-pharmacological treatment

- *Nutrition* There is no evidence that patients already diagnosed with any type of dementia benefit from various suggested preventive strategies such as supplementary fish oil, ginkgo biloba, fruit polyphenols, red wine or homocysteine.
- *Activity* A physically active and socially integrated lifestyle in late life seems to protect the elderly from the development of dementia. The effect in patients diagnosed with dementia is uncertain.
- *Caring for the carers* Carers are at risk of depression and other psychiatric or physical complaints. Burden relief or support groups can reduce or prevent these problems. Nursing home care is usually inevitable in the advanced stages to relieve the carer.

Table 3 Cognitive enhancers

Drug	Type	Starting dose	Maintenance dose	Comments
Rivastigmine	ChE inhibitor	1.5 mg bd, oral	3–6 mg bd (increase over 2–4 weeks in 1.5 mg twice daily steps)	Give with meals Nausea, vomiting, diarrhoea and loss of appetite are common adverse effects
		4.6 mg/24 h patch	9.5 mg/24 h	Can cause rash; rotate sites
Donezepil	ChE inhibitor	5 mg once daily, oral	10 mg per day (increase after 4–6 weeks)	Nausea, vomiting, diarrhoea and loss of appetite are common adverse effects
Galantamine	ChE inhibitor	4 mg bd, oral	12 mg bd (increase by 4 mg twice daily per month)	Give with meals Nausea, vomiting, diarrhoea and loss of appetite are common adverse effects
Memantine	NMDA antagonist	5 mg once daily, oral	10 mg bd (increase by 5 mg daily per week)	Headache, sleepiness, constipation and dizziness occur

Bd, twice daily; ChE, cholinesterase; NMDA, N-methyl-D-aspartic acid.

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Legal and safety issues

- *Driving* Patients with dementia have an increased risk of being involved in a car accident, increasing every year after the diagnosis. Health professionals should consult national regulations to advise their patients and their relatives properly and to be aware of their duty to report demented patients to the authorities.
- *Cooking* can lead to injuries, burns and fires, due to distractibility and forgetfulness; meal services and early use of a microwave oven are helpful options.
- *Becoming lost* Although the risk of becoming lost is higher when the patient is left unattended, many still become lost even in the presence of a carer. Although wandering is a risk factor for becoming lost, even patients who never wander can still get lost. Continuous supervision is the best preventive strategy; identification bracelets, etc, may help to facilitate return.
- *Falling* Evaluation of dangerous situations in and around the house and advice for or treatment of other causes (eg, orthostatic hypotension, visual impairment, gait disturbance) are important, as are preventive strategies.

CONCLUSIONS

- Dementia is one of the most prevalent neurological disorders.
- The most common type of dementia is Alzheimer's disease.
- Age is the most important risk factor.
- Ancillary investigations are of great help in the diagnosis but in the end most types of dementia are diagnosed by their clinical syndrome, thus attention to the history of the patient and caregivers as well as careful clinical work-up are crucial.
- Medication can have modest beneficial effects but care of the patients and their caregivers is just as important.

This article was reviewed by Martin Rossor, London, UK.

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