Elderly Medicine

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The dementias

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Clin Med 2003;**3**:404–8

The terms 'pre-senile' (onset before the age of 65) and 'senile' dementia, in common use in the past, should now be avoided. Previously, Alzheimer's disease (AD) was thought to be a relatively rare cause of a dementia that occurred in middle life, whereas senile dementia was considered to result from cerebral arteriosclerosis. Post-mortem studies then identified the typical neuropathological changes of AD in most patients with so-called senile dementia. In fact, AD is the commonest cause of dementia in adults whatever their age.

The relative frequencies of different dementias vary according to the age of onset. This article will concentrate on AD and the vascular dementias, the commonest causes of dementia in people over the age of 65. A previous CME article considered other dementias.[1]

Table 1. Reversible or partially reversible causes of dementia.

Cause	Treatment
Deficiency states:	Specific corrective therapy
• vitamin B12	
• folic acid	
• vitamin B1	
Endocrine disease:	Replacement therapy for underactivity; control of excess production for overactivity
• hyper/hypothyroidism	
• hyper/hypoparathyroidism	
• Cushing's syndrome	
• Addison's disease	
Infections:	
• AIDS dementia complex	Antivirals
• syphilis	Antibiotics
Toxins:	
• alcohol	Removal and/or withdrawal of toxin
• drugs	Supportive therapy
• heavy metals	Specific antidote where available
• carbon monoxide poisoning	
Other:	
• tumours, especially meningioma	Surgical evacuation Steroids for associated oedema
• subdural haematoma	Surgical evacuation
• normal pressure hydrocephalus	Surgical shunt
• depression ('depressive pseudodementia')	Antidepressants, especially SSRIs Psychotherapy ECT

ECT = electroconvulsive therapy; SSRI = selective serotonin reuptake inhibitor.

What is dementia?

Dementia is an acquired impairment of intellectual function and other cognitive skills that leads to a decline in the ability to perform daily activities as well as to behavioural changes. A decline in memory, especially in the learning of new information, is almost always a feature. In addition, there is a decline in other cognitive abilities, characterised by deterioration in judgement and thinking, such as planning and organising, and in the general processing of information.[2] For a confident clinical diagnosis, the symptoms should have been present for at least six months.

Patients and their families often mistake early symptoms for normal ageing changes and physicians may fail to recognise the early signs of dementia. Dementia and ageing are not synonymous. Expected cognitive changes of ageing – for example, a slowing of information processing – are benign, while dementia is usually progressive and disabling and not an inherent part of growing old.[3]

Assessment and diagnosis

A specific diagnosis is essential wherever possible. Dementia is not always irreversible; it is therefore important to exclude and treat conditions that are fully or partly reversible (Table 1).

With the advent of effective drug treatments, patients are increasingly presenting for assessment and diagnosis earlier in the disease process. This can be a challenge diagnostically. The reliability of diagnosis is improved by using criteria such as those provided for dementia in ICD-10[2] and for AD in DSM-IV[4] and the NINCDS-ADRDA.[5]

Up to 20% of people over 80 have some form of dementia, and prevalence figures nearly double with every five years increase in age from 60 to 94 years,[6] so a low threshold for considering the diagnosis is important even in the absence of complaints.[3] Evidence of decline in previous abilities is a cardinal feature for making the diagnosis, so personal knowledge of the patient by a family member or friend is often more

valuable than any laboratory test or imaging technique.

A focused history and examination should be undertaken together with appropriate investigations (Table 2). It is particularly important to assess problems with everyday activities (Table 3). Measurement of daily function is one of the major outcomes used to assess interventions in dementia such as drug treatment.

Cognitive assessment is central to diagnosis and management of dementia. The Mini-Mental State Examination (MMSE)[7] is the most widely used brief measure of cognitive function and is appropriate for intermittent routine use. Despite limitations, it is the standard screening instrument for detecting cognitive impairment in older people and can also be used as a brief assessment for following response to antidementia drugs.[8] For subjects with more than eight years of education, a score of 23 or less out of 30 usually indicates cognitive impairment (Table 4). No cognitive test should be used by itself to diagnose dementia. Asking the patient to draw a clock face and set the hands at 11.10 is a useful addition to the MMSE. More detailed neuropsychological testing is useful especially in borderline or difficult cases (these are beyond the scope of this article).

Table 2. Investigations for suspected dementia.

Routine	Blood count (particularly Hb & MCV) ESR/viscosity Urea or creatinine and electrolytes Liver function Calcium and bone biochemistry Glucose Vitamin B12 & red cell folate Thyroid function Syphilis serology Urinalysis
Common	CT scan of brain* or MRI
Occasional	Gamma-glutamyl transferase HIV Serum lipids CSF examination EEG SPECT Carotid ultrasound Cardiac ultrasound

* A further view through the temporal lobe is of special help in Alzheimer's disease.
CSF = cerebrospinal fluid; CT = computed tomography; EEG = electroencephalogram; ESR = erythrocyte sedimentation rate; Hb = haemoglobin; MCV = mean corpuscular volume; MRI = magnetic resonance imaging; SPECT = single-photon emission CT.

Table 3. Activities of daily living.

Basic physical activities	More complex (instrumental) activities
Eating	Shopping
Toileting	Using the telephone
Washing/grooming	Cooking
Walking	Housekeeping
Dressing/undressing	Self-medication
	Handling finances
	Use of transport

Table 4. An example of the Mini-Mental State Examination (MMSE).

1	**Orientation**	
	What day of the week is it today?	0/1
	What month are we in?	0/1
	What is today's date?	0/1
	What year are we in?	0/1
	What season of the year is it?	0/1
	What town are we in?	0/1
	What county (or state/province) are we in?	0/1
	What country are we in?	0/1
	Can you tell me the name of this place?	0/1
	What floor of the building are we on?	0/1
2	**Registration**	
	Repeat until the person remembers three unrelated objects, eg ball, flag, tree (score after 1 trial, but repeat if necessary up to 5 trials)	0/3
3	**Attention and Calculation**	
	Subtract 7 from 100 and keep subtracting until told to stop. Score after 5 subtractions.	
	Spell the word 'WORLD' forwards and ask the subject to spell it backwards 'DLROW'. Score letters in correct position. Enter higher of the two scores	0/5
4	**Recall**	
	What were the three words that you were asked to remember?	0/3
5	**Naming**	
	What is this called? (show a watch)	0/1
	What is this called? (show a pencil)	0/1
6	**Repetition**	
	Repeat after me: 'No ifs, ands or buts'	0/1
7	**Three-stage command**	
	Take this paper in your left hand (or right, if left-handed), fold it in half with both hands and put it on the floor	0/3
8	**Written command**	
	Do what is written on this paper: 'CLOSE YOUR EYES'	0/1
9	**Writing**	
	Write a short sentence	0/1
10	**Copying**	
	Copy this drawing (two intersecting pentagons). All ten angles must be present and the intersection should form a quadrangle	0/1
Total Score		**maximum 30**

Behavioural problems are common and troublesome to carers; they should also be carefully assessed (Table 5).

Mild cognitive impairment

There has been considerable interest in recent years in mild cognitive impairment (MCI), a grey area that appears to lie between normality and dementia.[9] Patients with MCI present with some impairment of memory and cognition that does not significantly affect social or occupational functioning. They therefore do not qualify for a formal diagnosis of dementia. Such patients commonly present to memory clinics and many, but not all, will go on to develop dementia (usually AD) in the following 5–10 years. There is still controversy over the diagnostic criteria. Trials are in progress to see whether drugs approved for AD may delay the change from MCI to dementia.

Key Points

- **Alzheimer's disease (AD) is the commonest cause of dementia in adults whatever their age**
- **In patients over 65, vascular dementia is the second commonest cause of dementia, followed by dementia with Lewy bodies (DLB)**
- **There should be a low threshold for considering the diagnosis of dementia in older people, especially people over 80**
- **It is important to exclude potentially reversible causes of dementia**
- **Cognitive assessment is central to diagnosis and management of dementia; a standardised test such as the Mini-Mental State Examination should be used**
- **People with DLB often react badly to neuroleptic drugs**
- **Three acetylcholinesterase inhibitors, donepezil, rivastigmine and galantamine, are available for treating people with mild and moderate AD**
- **A fourth drug, memantine, that acts on N-methyl-D-aspartate glutamatergic receptors has recently become available for people with moderate and severe dementia**

KEY WORDS: Alzheimer's disease, assessment, cholinesterase inhibitors, dementia with Lewy bodies, diagnosis, memantine, treatment, vascular dementia

Alzheimer's disease

AD accounts for 50–60% of dementias presenting in the over-65s. Using DSM-IV[4] criteria, the diagnosis of AD depends on the features shown in Table 6. AD should not be considered merely as a diagnosis of exclusion. In practice, AD is usually considered as the most likely cause of the dementia, based on the clinical history; this is then confirmed once other causes have been excluded as far as possible.

Routine neuroimaging is not always helpful. Atrophy is first seen in the hippocampal formation and the medial temporal lobe. Computed tomography (CT) scans angled to view the temporal lobe may help differentiate AD from normal ageing and other dementias.[10] Serial CT or magnetic resonance imaging (MRI) may help to confirm progression,[11] but this is unlikely to be a routine procedure. A confused patient with AD may not tolerate an MRI scan.

Table 5. The mean prevalence of problem behaviours in dementia.

Behaviour	%
Verbal aggression/threats	54
Physical aggression/agitation	42
Sleep disturbances	38
Restlessness	38
Wandering	30
Apathy/withdrawal	27

Vascular dementia

Epidemiological studies suggest that vascular dementia (VaD) is the second most common cause of dementia in western countries. It accounts for up to 25% of all dementia; above the age of 85 years it may be commoner than AD.[12] The prevalence increases with age, from 1.5–4.8% of people aged 70–79 years to 2.8–16.0% for those aged 80–89 years. VaD is a rather vague term, and the widely misused term 'multi-infarct dementia' should be avoided except where it is clear that multiple small infarcts are indeed responsible.

There are a number of risk factors for VaD (Table 7). VaD may be caused by large infarcts, numerous lacunar infarcts

Table 6. Diagnostic criteria for dementia (based on DSM-IV criteria).[4]

1. Memory impairment (inability to learn new information and to recall previously learned information)
2. At least one of:
   - aphasia (language disturbance)
   - apraxia (problems with motor activities despite intact motor function)
   - agnosia (problems recognising or identifying objects despite intact sensory function)
   - disturbance in executive functioning (planning, organising, sequencing, abstracting)
3. The deficits in 1 and 2 significantly impair social or occupational functioning and are a significant decline from before
4. The deficits do not occur exclusively during delirium
5. The deficits are not better accounted for by another disorder (eg depression, schizophrenia)

For a diagnosis of Alzheimer's disease:
- the onset of the problems should be gradual with continuing decline
- the cognitive deficits should not be explained by other causes of dementia

and infarcts in strategic regions such as the thalamus.

The classic features of VaD include sudden onset, stepwise deterioration, focal neurological signs and symptoms, and evidence of previous strokes. However, these features are often absent, especially in the ill-defined condition called Binswanger's disease (probably another manifestation of the so-called lacunar state). Such patients show slowing of information processing, poor sustained attention, poor memory and executive dysfunction, all of them typical of subcortical dementia.

Leukoaraiosis

A related area of interest and difficulty concerns leukoaraiosis (rarefaction of the subcortical white matter). Leukoaraiosis occurs in normal older people (though even they may show subtle neuropsychological deficits) as well as those with underlying VaD or AD.

Table 7. Risk factors associated with vascular dementia.[13]

Demographic	Age Sex (male > female) Low education
Genetic	Apolipoprotein E4 CADASIL
Vascular	Poorly controlled hypertension Atrial fibrillation History of MI Diabetes mellitus Cigarette smoking Hypercholesterolaemia Hyperhomocysteinaemia
Stroke factors	Past or recurrent CVA/TIAs Number, volume and location Severity of stroke Early urinary incontinence Aphasia/dysphasia Periventricular WMLs, silent infarcts

CADASIL = cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy, a condition associated with migraine, haemorrhage and dementia; CVA = cerebrovascular accident; MI = myocardial infarction; TIA = transient ischaemic attack; WML = white matter lesion.

Alzheimer's disease with cerebrovascular disease

VaD and AD can occur together as a mixed dementia. Cerebrovascular disease, particularly if subcortical, may play an important role in the presence and severity of AD clinical symptoms (as demonstrated in the Nun study).[14]

Dementia with Lewy bodies

In hospital research series, dementia with Lewy bodies (DLB) may be the commonest dementia after AD, although community-based prevalence rates are lower. Diagnostic criteria are shown in Table 8.

Treatment of dementia

Alzheimer's disease

At present AD is the only dementia for which specific drugs are licensed for prescription use in the UK (Table 9). The three acetylcholinesterase inhibitors (AChEI), donepezil, rivastigmine and galantamine have been approved by the National Institute for Clinical Excellence (NICE)[8] as one component of the management of people with mild and moderate AD. It is suggested that the drugs should be initiated by a specialist and usually limited to patients whose MMSE score is above 12 points. For each drug, the dose must be titrated over a few weeks and an assessment of efficacy made after a

Table 8. Diagnostic criteria for dementia with Lewy bodies (DLB).[15,16]

Dementia associated with one (possible DLB) or two (probable DLB) of:
- fluctuating cognition with pronounced variations in attention and alertness
- recurrent visual hallucinations (often detailed and of people and animals)
- mild parkinsonism (but tremor is uncommon)

Supportive features:
- repeated falls
- syncope or transient loss of consciousness
- neuroleptic sensitivity (with an adverse and extreme reaction to neuroleptics that may affect up to 50% of cases, and inadvertently be supportive of the diagnosis)
- systematised delusions
- other types of hallucinations

Note:
- prominent or persistent memory impairment may not occur in the early stages
- medial temporal lobe atrophy is exceptional in DLB and suggests concomitant AD

AD = Alzheimer's disease.

Table 9. Current treatments in Alzheimer's disease (registered indications).

Drug	Main mechanism of action	MMSE score: Mild >20	Moderate 19–15	Moderate 14–10	Severe <10	Dosing
Donepezil (Aricept)	AChEI	+	+	+	–	5–10 mg od
Rivastigmine (Exelon)	AChEI	+	+	+	–	3–6 mg bd
Galantamine (Reminyl)	AChEI	+	+	+	–	8–12 mg bd
Memantine	NMDA receptor antagonist	–	–	+	+	10 mg bd

AChEI = acetylcholinesterase inhibitor; MMSE = Mini-Mental State Examination; NMDA receptor = N-methyl-D-aspartate, a glutamatergic receptor.

few months. A drug should be continued only if there is evidence of efficacy and while it is considered to be having a worthwhile effect. The advice is that these drugs should not normally be continued if the MMSE score falls below 12 points. Adverse effects from these drugs are mainly gastrointestinal and may disappear despite continued treatment.

There are clear improvements in some patients in terms of a delay in decline of cognition and everyday activities as well as benefits in behavioural symptoms. The overall benefits appear to be of value to carers and there may be a reduction in rates of institutionalisation.

A fourth drug, memantine, became available in 2002 for use in patients with more severe dementia. It is better tolerated than the AChEIs, but has not yet been reviewed by NICE; further experience with the drug will be required before its full value can be assessed. Cochrane Reviews can be found for all these drugs, together with reviews of many other putative antidementia compounds.[17]

Other dementias

At present no drugs are specifically licensed for use in either VaD or DLB. Any underlying risk factor for VaD should be treated, and most patients will be given low-dose aspirin as a minimum. Hallucinations may be a particular problem in DLB and respond well to AChEIs, although this is an unlicensed indication.

References

1 Galton CJ, Hodges JR. The spectrum of dementia and its treatment. Review. *J R Coll Physicians Lond* 1999;**33**:234–9.

2 World Health Organization. *The ICD-10 classification of mental and behavioural disorders. Clinical descriptions and diagnostic guidelines*. Geneva: WHO, 1992.

3 Small GW, Rabins PV, Barry PP, Buckholtz NS *et al*. Diagnosis and treatment of Alzheimer disease and related disorders. Consensus statement of the American Association for Geriatric Psychiatry, the Alzheimer's Association, and the American Geriatrics Society. Review. *JAMA* 1997;**278**:1363–71.

4 American Psychiatric Association. *Diagnosis and statistical manual of mental disorders (DSM-IV)*, 4th edn. Washington DC: APA, 1994.

5 McKhann G, Drachman DA, Folstein M, Katzman R *et al*. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. *Neurology* 1984;**34**:39–44.

6 Hofman A, Rocca WA, Brayne C, Breteler MM *et al*. The prevalence of dementia in Europe: a collaborative study of 1980–1990 findings. Eurodem Prevalence Research Group. *Int J Epidemiol* 1991;**20**:736–48.

7 Folstein MF, Folstein SE, McHugh PR. 'Mini-Mental State'. A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res* 1975;**12**:189–98.

8 National Institute for Clinical Excellence. Guidance on the use of donepezil, rivastigmine and galantamine for the treatment of Alzheimer's disease. Technology Appraisal Guidance No 19. London: NICE, 2001. www.nice.org.uk

9 Ritchie K, Touchon J. Mild cognitive impairment: conceptual basis and current nosological status. *Lancet* 2000;**355**:225–8.

10 Jobst K, Smith AD, Szatmari M, Molyneux A *et al*. Detection in life of confirmed Alzheimer's disease using a simple measurement of medial temporal lobe atrophy by computed tomography. *Lancet* 1992;**340**:1179–83.

11 Fox NC, Freeborough PA, Rossor MN. Visualisation and quantification of rates of atrophy in Alzheimer's disease. *Lancet* 1996;**348**:94–7.

12 Amar K, Wilcock G. Vascular dementia. Review. *BMJ* 1996;**312**:227–31.

13 Skoog I. Status of risk factors for vascular dementia. Review. *Neuroepidemiology* 1998;**17**:2–9.

14 Snowdon DA, Greiner LH, Mortimer JA, Riley KP *et al*. Brain infarction and the clinical expression of Alzheimer's disease. The Nun Study. *JAMA* 1997;**277**:813–7.

15 McKeith IG, Galasko D, Kosaka K, Perry EK *et al*. Consensus guidelines for the clinical and pathologic diagnosis of dementia with Lewy bodies (DLB): report of the consortium on DLB international workshop. Review. *Neurology* 1996;**47**:1113–24.

16 Barber R, Gholkar A, Scheltens P, Ballard C *et al*. Medial temporal lobe atrophy on MRI in dementia with Lewy bodies. *Neurology* 1999;**52**:1153–8.

17 www.cochrane.org; www.jr2.ox.ac.uk/edcig/