The spectrum of dementia and its treatment

Clare J Galton MB BChir MRCP(UK), University of Neurology Unit, Addenbrooke's Hospital, Cambridge

John R Hodges MD FRCP, University Neurology Unit, Addenbrooke's Hospital, and MRC Cognition and Brain Sciences Unit, Cambridge

J R Coll Physicians Lond 1999;33:234-9

The concept of dementia has evolved over the last decade from one of progressive global intellectual deterioration to a syndrome of progressive impairment in memory and at least one other cognitive deficit (aphasia, apraxia, agnosia or disturbance in executive function), in the absence of another explanatory central nervous system disorder, depression or delirium (DSM-IV). However, even this concept is inadequate as researchers and clinicians become more aware of specific cognitive profiles of different dementia syndromes. For instance, in early Alzheimer's disease (AD) there may be isolated memory impairment for several years before progression, and in the frontotemporal dementia (FTDs) memory impairment may appear late in the disease. Accurate diagnosis is essential for patient advice and management. Early detection will become increasingly important with the advent of disease modifying treatments. If a treatment slows progression of dementia, it should be administered at the earliest stage possible.

This review summarises some recent developments, focusing on the common neurodegenerative dementias. The relative frequencies of the different causes of dementia change with the age of onset, are illustrated in Fig 1(a) and (b).

Alzheimer's disease

AD is the commonest cause of dementia. The earliest deficits involve...
episodic memory (day-to-day recall of events and acquisition of new information); this is thought to reflect the earliest site of pathology in the hippocampus and related medial temporal lobe structures. Deficits in attentional processes, and a loss of the knowledge base which underlies language and other cognitive processes (semantic memory), are also found early in the course of the disease. The cognitive characteristics of AD are shown in Table 1.

AD remains a pathological diagnosis, but attempts to improve the accuracy of early diagnosis have focused on two aspects:

- identification of the neuropsychological deficits, particularly the hallmark impairment in recall of verbal material (stories and word lists) after a delay; and
- detection of abnormalities on structural and functional neuroimaging.

Magnetic resonance imaging (MRI) scans show atrophy of the hippocampus and medial temporal lobe early in the disease (Fig 2(a)). Recent research techniques have enabled hippocampal and medial temporal lobe atrophy to be accurately quantified early in the disease process using volumetric and linear measures, but the variability in normal elderly subjects results in poor predictive value. Single photon emission computed tomography (SPECT) scans show reduced blood flow second-
profound loss in conceptual knowledge, causing anamia and impaired comprehension of words, objects or faces.

The characteristic findings are shown in Table 1. It is of note that the Mini Mental State Examination (MMSE) is insensitive at detecting frontal abnormalities, and patients presenting with FTD may perform within the normal range on the MMSE. MRI in these patients demonstrates frontal and/or temporal lobe atrophy. In contrast to AD, the changes involve the lateral temporal structures and spare the hippocampi (Figs 2(b) and 3). About 10% of cases of FTD are familial; in some of these cases, there is a mutation in the microtubule-associated protein tau gene on chromosome 17 (FTDP) (see below). Both sporadic and familial forms of FTD are associated with features of motor neuron disease, particularly bulbar palsy.

Dementia with Lewy bodies

Dementia with Lewy bodies (DLB) is an increasingly recognised cause of dementia in the elderly (Figure 1(b)). The clinical features are shown in Table 2. The neuropsychological profile of DLB is a mixture of subcortical and cortical features, with prominent cognitive slowing plus impairment of both executive (planning and organisational) and visuoperceptual abilities. Compared to AD, these patients tend to have greater deficits in attention and visuospatial processing. The marked cholinergic deficit is postulated to be the cause of the tendency to visual hallucinations.

Table 2. Clinical features of dementia with Lewy bodies (adapted from Ref 12).

| Feature | Description |
|---------|-------------|
| Dementia in association with: | |
| • fluctuations in cognition (especially attention and alertness) | |
| • visual hallucinations (typically well formed) | |
| • mild spontaneous parkinsonism | |

| Supportive features: | |
| • repeated or unexplained falls | |
| • syncope or transient loss of consciousness | |
| • neuroleptic sensitivity syndrome | |
| • hallucinations in other modalities | |
| • systematised delusions | |
Subcortical dementia syndromes

The typical cognitive pattern in subcortical dementia (SCD) is that of mild changes in memory, cognitive slowing and executive dysfunction (Table 1). The neurodegenerative conditions associated with features of an SCD commonly have neurological signs of a movement disorder. Both the cognitive syndrome and the neurological features are thought to result from damage to the basal ganglia, midbrain and brainstem structures. Typical examples (Table 3) are:

- **Huntington’s disease**, in which the cognitive and behavioural symptoms and motor symptoms of chorea and inco-ordination worsen as the pathology in the caudate nucleus and putamen progresses.

- **Progressive supranuclear palsy (PSP)**. Although PSP is similar to Parkinson’s disease (PD), it does not respond well to levodopa. The differing pathology is reflected by the particular features of supranuclear gaze palsy, rigidity of axial muscles, bulbar symptoms and a marked tendency to falls.

Other causes of SCD include:

- **Parkinson’s disease**. In PD there is a subcortical dementia in one-third to one-half of patients.

- **Corticobasal degeneration** is an increasingly recognised cause of dementia, with an asymmetric akinetic rigid syndrome, marked limb apraxia, and the almost pathognomonic feature of alien limb phenomenon in which the hand(s) act as if ‘with a will of their own'\(^{14}\). Dementia is common in the later stages with a frontal emphasis. The pathology is focused in the frontal and parietal cortices plus the substantia nigra, basal ganglia and thalamus.

**Neuropathology**

Recent research in the molecular neuropathology of the neurodegenerative dementias has provided new insights into these conditions. Neuronal and glial inclusions have been found in a range of neurodegenerative dementias (Table 4). They are composed either of abnormal forms of the microtubule-associated tau protein or of \(\alpha\)-synuclein. The function of \(\alpha\)-synuclein remains unknown, but it may be a lipid-binding protein in the brain. Tau protein has six isoforms, and the proportion of these isoforms forming filamentous inclusions varies in the different diseases. The suggestion that neurons degenerate as a result of these abnormal inclusions is supported by the discovery of mutations in the tau gene (causing FTDP) and in the \(\alpha\)-synuclein gene in some early-onset familial PD cases\(^5\).

**Table 3. Major causes of subcortical dementia.**

| Disease                        | Filamentous inclusion                          | Main component      |
|-------------------------------|-----------------------------------------------|---------------------|
| Degenerative:                 |                                               |                     |
| - progressive supranuclear palsy | Neuromyelin lesions                           | Tau protein         |
| - Huntington’s disease         |                                              |                     |
| - Parkinson’s disease          |                                              |                     |
| - corticobasal degeneration    |                                              |                     |
| Vascular disorders:           |                                               |                     |
| - multi-infarct dementia       | Neuromyelin lesions                           | Tau protein         |
| - subcortical                  |                                              |                     |
| -Binswanger’s disease          | Neuromyelin lesions                           | Tau protein         |
| Metabolic:                    |                                               |                     |
| - Wilson’s disease             |                                              |                     |
| Demyelinating disease:        |                                               |                     |
| - multiple sclerosis           |                                              |                     |
| - leucodystrophies             |                                              |                     |
| - AIDS dementia complex        |                                              |                     |
| Miscellaneous:                |                                               |                     |
| - normal pressure hydrocephalus|                                               |                     |

**Table 4. Intraneuronal inclusions in neurodegenerative diseases** (adapted from Ref 10).

| Disease                        | Filamentous inclusion                          | Main component      |
|-------------------------------|-----------------------------------------------|---------------------|
| Alzheimer’s disease            | Neurofibrillary lesions                       | Tau protein         |
| Pick’s disease                 | Pick bodies                                    | Tau protein         |
| FTDP-17                       | Neurofibrillary lesions and glial fibrillary lesions | Tau protein |
| Progressive supranuclear palsy | Neurofibrillary lesions                       | Tau protein         |
| Parkinson’s disease            | Lewy bodies                                    | \(\alpha\)-Synuclein|
| Dementia with Lewy bodies      | Lewy bodies                                    | \(\alpha\)-Synuclein|
| Multiple system atrophy        | Glial and neuronal inclusions                  | \(\alpha\)-Synuclein|

FTDP = frontotemporal dementia and Parkinsonism

The first priority is to exclude treatable causes of dementia (Table 5). Our recommended investigations in most cases should include...
Table 5. Treatable causes of dementia.

| Category                  | Examples                                                                 |
|---------------------------|--------------------------------------------------------------------------|
| Depressive pseudodementia | Infections: • AIDS dementia complex • syphilis                             |
| Benign tumours, especially subfrontal meningiomas | Vasculitides: • systemic lupus erythematosus • giant cell arthritis • polyarteritis nodosa |
| Normal pressure hydrocephalus | Alcoholic dementia                                                     |
| Subdural haematoma         | Chronic intoxications: • heavy metals • drugs • carbon monoxide poisoning|
| Deficiency states:         | Wilson’s disease                                                        |
| • B1, B12, B6              |                                                                          |
| Endocrine disease:         |                                                                          |
| • hypothyroidism           |                                                                          |
| • Cushing’s disease        |                                                                          |
| • Addison’s disease        |                                                                          |

Table 6. Recommended investigations in dementia.

| Routine:                                                                 |
|------------------------------------------------------------------------|
| • full blood count and ESR                                            |
| • biochemical profile: urea or creatinine, electrolytes, calcium, liver function serum B12 and RBC folate |
| • thyroid function                                                     |
| • chest X-ray                                                          |
| • CT scan of brain (to exclude structural pathology)                   |

Other tests which may be indicated in certain cases:

| • MRI (especially in presenile cases to look at pattern of disease)   |
| • SPECT                                                                |
| • EEG (e.g., Creutzfeldt-Jakob disease, SSPE)                          |
| • CSF examination                                                     |
| • immunological tests for vasculitides                                |
| • screening for cardiac sources of emboli                             |
| • slit lamp examination for Kayser-Fleischer rings and caeruloplasmin estimation (Wilson’s disease) |
| • specific blood and/or urine tests for inherited metabolic disorders  |
| (e.g., leucodystrophies, young-onset cases)                            |
| • screening for HIV infection                                          |
| • genetic screening for HD mutation/specific AD mutations if familial dementia |
| • cerebral biopsy                                                     |

AD = Alzheimer’s disease; CSF = cerebrospinal fluid; CT = computed tomography; ESR = erythrocyte sedimentation rate; HD = Huntington’s disease; MRI = magnetic resonance imaging; RBC= red blood cell; SPECT = single-photon emission computed tomography; SSPE = subacute sclerosing panencephalitis.

**Table 5.** Treatable causes of dementia.

**Table 6.** Recommended investigations in dementia.

Cases of progressive cognitive impairment are listed in Table 6. In dementia syndromes for which there is no specific treatment, carer support and general common sense strategies can help in day-to-day management (see Box 1 for support groups). The cholinesterase inhibitors, donepezil hydrochloride (Aricept®) and rivastigmine (Exelon®) are licensed for symptomatic treatment in AD. Although these treatments improve cognitive performance in AD, their long-term impact on the course of the disease remains to be established. Vitamin E and selegiline, both less expensive than cholinesterase inhibitors, have shown some benefit in delaying functional deterioration in moderately severe AD patients.

**Conclusions**

Dementia syndromes are complicated by clinical and neuroimaging factors. However, in AD, treatment with donepezil (Aricept®) or rivastigmine (Exelon®) is associated with some improvement in cognitive performance. Although symptomatic treatment cannot improve cognitive function in AD, clinicians may find these treatments rewarding for their patients and their families.

**References**

1. Diagnostic and Statistical Manual of Mental Disorders (DSM–IV), 4th edn. Washington, DC: American Psychiatric Association, 1994.
2. Hodges JR. The amnestic prodrome of Alzheimer’s disease (editorial). *Brain* 1998;121:1601–2.
3. Garrard P, Perry R, Hodges JR. Disorders of semantic memory (editorial). *J Neurol Neurosurg Psychiatry* 1997;62:431–5.
4. Fox NC, Warrington EK, Freeborough PA, Hartikainen P, et al. Presymptomatic hippocampal atrophy in Alzheimer’s disease: a longitudinal study. *Brain* 1996;119:2001–7.
5. Smith AD, Jobst KA. Use of structural imaging to study the progression of Alzheimer’s disease. *Br Med Bull* 1996;52:575–86.
6. Craddock N. New susceptibility gene for Alzheimer’s disease on chromosome 12? *Lancet* 1998;352:1720–1.
7. Hardy J, Duff K, Hardy G, Perez-Tur J, Hutton M. Genetic dissection of Alzheimer’s disease and related dementia: amyloid and its relationship to tau. *Nat Neurosci* 1998;1:355–8.
8. Harvey RJ, Rossor MN, Skelton-Robinson M, Garralda E. *Young onset dementia:*
Box 1. Patient and carer support group addresses.

- Alzheimer’s Disease Society
  Gordon House
  10 Greencoat Place
  London SW1P 1PH
  Tel: 0171 306 0606

- CANDID (Counselling and Diagnosis in Demential)
  National Hospital for Neurology and Neurosurgery
  Queen Square
  London WC1N 3BG
  Tel: 0171 829 8772

- Huntington’s Disease Association
  108 Battersea High Street
  London SW11 3HP
  Tel: 0171 223 7000

- Parkinson’s Disease Society
  22 Upper Woburn Place
  London WC1H 0RA
  Tel: 0171383 3513

- Pick’s Disease Support Group
  Dementia Research Group
  National Hospital for Neurology and Neurosurgery
  Queen Square
  London WC1N 3BG
  Tel: 0171 829 8772

- Creutzfeldt-Jakob Disease Support
  Network
  Birchwood
  Heath Top
  Ashley Heath
  Market Drayton
  Salop TF9 4QR
  Tel: 01630 673 973

- Frontotemporal Dementia Carer Support Group
  MRC Cognition and Brain Sciences Unit
  15 Chaucer Road
  Cambridge CB2 2EF
  Tel: 01223 355 294 X 123

- The Progressive Supranuclear Palsy Association
  22 Upper Woburn Place
  London WC1H 0RA
  Tel: 0171 383 3513

- Pick’s Disease Support Group
  Dementia Research Group
  National Hospital for Neurology and Neurosurgery
  Queen Square
  London WC1N 3BG
  Tel: 0171 829 8772

---

epidemiology, clinical symptoms, family burden, support and outcome. London: National Hospital of Neurology and Neurosurgery. Dementia Group Publications, 1998.

9 Hodges JR, Patterson K, Oxbury S, Funnell M. Semantic dementia: progressive fluent aphasia with temporal lobe atrophy. Brain 1992; 115:1783–806.

10 Goedert M, Spillantini MG, Davies S. Filamentous nerve cell inclusions in neurodegenerative diseases. Curr Opin Neurobiol 1998; 8:619–32.

11 Rakowicz WP, Hodges JR. Dementia and aphasia in motor neuron disease: an under recognised association? J Neurol Neurosurg Psychiatry 1998; 65:881–9.

12 McKelth IG, Galasko D, Kosaka K, Perry UK, et al. Consensus guidelines for the clinical and pathologic diagnosis of dementia with Lewy bodies (DLB): report of the consortium on DLB International Workshop. Neurology 1996; 47: 1113–24.

13 Hansen L, Salmon D, Galasko D, Masliah E, et al. The Lewy body variant of Alzheimer’s disease: a clinical and pathological entity. Neurology 1990; 40: 1–8.

14 Rinne JO, Lee MS, Thompson PD, Marsden CD. Corticobasal degeneration: a clinical study of 36 cases. Brain 1994; 117: 1183–96.

15 Sano M, Ernesto C, Thomas R, Klauber M, et al, for the members of the Alzheimer’s Disease Cooperative Study. A controlled trial of selegiline, alpha-tocopherol, or both as treatment for Alzheimer’s disease. N Engl J Med 1997; 336: 1216–22.

16 Burns A, Levy R (eds). Dementia. London: Chapman and Hall Medical, 1994.