Fortnightly Review

Alzheimer's disease

Martin Rossor

Alzheimer's disease affects 400 000 people in the United Kingdom and as such is the commonest cause of dementia. Although predominantly a disease of old age, it is not confined to the elderly population; about 18 000 of those affected are below retirement age, and some have symptoms as early as their fourth decade.

The term Alzheimer's disease refers to the clinico-pathological entity of the histological changes of neurofibrillary tangles and senile plaques in a patient with dementia. A definite diagnosis therefore relies on confirmation at postmortem examination or by cerebral biopsy. Apart from histology there are, as yet, no specific tests for the disease; this means the diagnosis usually remains a clinical one. Furthermore, the key clinical feature of dementia can be due to many different causes; it is a clinical presentation of grave importance.

Clinical approach to the patient with possible Alzheimer's disease

The first point to establish is whether the patient is cognitively impaired. In most instances this impairment will be synonymous with dementia, although on first presentation the patient may have a relatively circumscribed cognitive impairment; this is typically a memory deficit. As the disease progresses, cognitive impairment becomes generalised—that is, the patient fulfils the criteria of dementia (box 1). Several criteria and definitions of dementia have been developed; all include the central feature of multiple domains of cognitive impairment (for example, dysphasia, memory impairment, visuospatial impairment) sufficient to interfere with social and work function.¹ These definitions specifically exclude patients with disturbances of arousal. To assess the extent of cognitive impairment it is essential that a member of the family (commonly the spouse) or a friend is interviewed since patients with dementia may be unaware of their deficit (they may have an anosognosia). It is important to inquire about difficulties at work and any tendency to mislay items, forget appointments and names, fail to recognise people, or get lost when alone. Changes in

Summary points

- All patients with dementia should be investigated fully
- The commonest cause of dementia is Alzheimer's disease
- Alzheimer's disease can be diagnosed with certainty only on histology
- Deposition of β amyloid protein is a central feature
- Some rare familial cases are associated with mutations in the amyloid precursor protein gene
- Associated neurotransmitter deficits, such as for acetylcholine, are amenable to treatment

family roles are useful clues—for example, a person who normally deals with the family finances may recently have given up because of failing memory. A number of brief cognitive assessment schedules (for example, the mini mental state examination and the abbreviated mental test score) are available, but these cannot be used to provide precise numerical cut offs for the diagnosis of dementia. They are, however, useful as rapid bedside tests and usually take no more than 10 minutes to complete.

The next point to establish is whether the cognitive impairment might relate to depression or anxiety. Again, clues will be available in the history both from the patient and from the accompanying family member. In general, patients with cognitive impairment due to Alzheimer's disease underestimate the severity of their cognitive deficit, in contrast to those with depression or anxiety.

Finally, whether the cognitive impairment occurs in the context of other neurological or systemic abnormalities must be determined. For example, patients with a history of hemiparesis or gait impairment may have vascular disease, and the patient with headache and a rapid progressive dementia may have an intracranial mass lesion demanding urgent referral.

Box 1—Clinical syndrome of dementia

- Acquired deficit of cognition
 - Multiple domains of cognitive impairment
 - Must include memory impairment
 - Cognitive impairment not due to disturbance of arousal
 - Can be reversible
- For criteria of of dementia see text

Clinical features of Alzheimer's disease

The most prominent cognitive deficit in Alzheimer's disease is that of memory, and indeed this is often the presenting feature. Episodic or autobiographical memory is predominantly affected, with early loss of memory for everyday events, which can easily be explored by general discussion. In contrast, short term memory, assessed by the digit span, tends to be preserved early in the illness. Language deficits and visuospatial deficits appear as the disease progresses.

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Early language preservation may allow the patient to maintain a social façade that can mask the cognitive impairment. It is usually clear, however, that although speech may be fluent it is rather empty of meaning or the patient may present with some difficulty finding words. Visuospatial deficits are often manifest by impairment of topographical memory, when patients easily get lost; some may develop problems with dressing. Frontal lobe features appear late. Occasional patients have a more focal onset which can precede the loss of episodic memory, such as aphasia or visual disorientation with a profound breakdown in higher visual processing. Non-cognitive symptoms are common and about 40% have depressive features, usually early in the disease.² Delusions, hallucinations, and aggression are commonly encountered and can present considerable management problems. Anosognosia or unawareness of the cognitive deficit can be troublesome, and patients may resist help and medical referral.

Neurological examination confirms the deficits in higher cortical function. Some patients develop extrapyramidal features which may be associated with cortical Lewy bodies at necropsy (see below). There are otherwise few physical signs, although a careful examination is important to exclude other causes.

Alzheimer's disease is predominantly a diagnosis of later life, although it can occur as early as the fourth decade. Up to half of patients may have a family history, but true autosomal dominant Alzheimer's disease affects perhaps 5-10%. The disease is relentlessly progressive, although plateaus may be observed. A small proportion of patients will develop seizures late in the disease. The median duration of the disease is 7-10 years from diagnosis, and death is most commonly due to bronchopneumonia.

The above features and the characteristic progression have been incorporated into clinical criteria (the NINCDS/ADRDA criteria³; box 2), which provide levels of probability of diagnosis similar to those used for the diagnosis of multiple sclerosis. *Definite* Alzheimer's disease is diagnosed when histology is available together with a clinical diagnosis of *probable* Alzheimer's disease; a diagnosis of *probable* Alzheimer's disease is used when typical clinical features are observed, and *possible* Alzheimer's disease when either atypical features or concomitant systemic diseases are present.

Dementia occurs with many neurological and systemic diseases. Additional symptoms and signs usually aid the differential diagnosis—for example, the presence of focal motor signs in multi-infarct vascular dementia. Several primary degenerative dementias mimic Alzheimer's disease, although the pattern of cognitive deficit can usually alert the clinician. Thus, prominent frontal lobe features would make a diagnosis of Pick's disease or frontal lobe degeneration more likely. Similarly, prominent Parkinsonian features would suggest diffuse Lewy body disease, which can be associated with Alzheimer histopathology. Such patients may be very sensitive to neuroleptic drugs, which cause dramatic worsening of their parkinsonism. A fluctuating course similar to vascular disease, with impairment of attention, is also likely to favour diffuse cortical Lewy body disease.

Investigations

Patients with dementia require specialist referral and investigation; this will depend on the age of the patient, the clinical presentation, and the availability of specialist services. Elderly patients tend to be referred to geriatricians or psychogeriatricians and those with behavioural disturbance to a psychiatrist. Younger patients or those with atypical dementias are usually referred to neurologists. Formal neuropsychological

assessment will establish the extent of cognitive impairment and will also provide information on the overall pattern of deficits. Most investigations are directed towards excluding potentially treatable causes and as such include routine haematology, biochemistry, thyroid function, and treponemal serology (box 3). Serum concentration of vitamin B-12 is routinely measured, although there is unlikely to be confusion between the cognitive impairment that may occur as part of the generalised neurological disturbance associated with B-12 deficiency and Alzheimer's disease.

Neuroimaging is needed to exclude potentially treatable causes of dementia such as hydrocephalus and tumours but may in addition provide evidence of characteristic patterns of atrophy in the degenerative dementias. Thus, measures of medial temporal atrophy on computed tomography scanning may be useful,⁴ and magnetic resonance imaging can provide more detailed regional volumetry to quantify specific areas of degeneration such as hippocampal atrophy.⁵ Functional neuroimaging with single photon emission computed tomography or positron emission tomography shows reduced blood flow and metabolism

Box 2—Clinical criteria for Alzheimer's disease

Probable Alzheimer's disease

Criteria of probable Alzheimer's disease include:

- Presence of dementia
- Deficits in at least two areas of cognition
- Progressive deterioration
- No clouding of consciousness
- Age 40-90
- Absence of systemic disorders

Diagnosis supported by:

- Progressive deterioration of individual cognitive function
- Impaired activities of daily living
- Family history of dementia
- Normal lumbar puncture, EEG, and evidence of atrophy (or progression on CT scan)

Features consistent with the diagnosis:

- Plateaus in the course of the disease
- Associated psychiatric symptoms
- Neurological signs
- Seizures
- Normal CT scan

Diagnosis of Alzheimer's disease unlikely if:

- Sudden onset
- Focal neurological signs
- Seizures or gait disturbance early in the disease

Possible Alzheimer's disease

Diagnosis of possible Alzheimer's disease can be made:

- In the presence of atypical features
- In the presence of a systemic disease (not considered to be cause of dementia)
- In the presence of a single progressive cognitive deficit

Definite Alzheimer's disease

Criteria for definite Alzheimer's disease are:

- Clinical criteria for probable Alzheimer's disease and
- Histopathological evidence of the disorder

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Box 3—Investigations

Neuropsychometry
Full blood count
Erythrocyte sedimentation rate
Serum concentration of vitamin B-12
Routine biochemistry
Thyroid function
Autoantibody screen
Treponemal serology
Chest radiograph
Electrocardiogram
Computed tomography or magnetic resonance imaging
Electroencephalogram

In selected cases:

Cerebrospinal fluid	HIV
Angiogram	White cell enzymes
Jejunal biopsy (Whipple's)	Heavy metal and drug screen
Cerebral biopsy	

predominantly in a posterior biparietal bitemporal pattern, but these techniques are available only in specialist centres. The electroencephalogram may be useful in that slow wave abnormalities are more common with Alzheimer's disease than in the frontal lobe dementias and Pick's disease.

A peripheral marker or diagnostic test for Alzheimer's disease would be of great value but is not yet available. Early changes in functional and structural neuroimaging are being explored, but the specificity of these changes has not been established and the technology is not widely available. Recently there has been interest in changes in acetylcholinesterase⁶ and markers of neuronal degeneration such as neurofilament protein in the cerebrospinal fluid,⁷ but these have yet to be shown to be of clinical value. Ultimately the diagnosis can be established by cerebral biopsy, but this is not to be undertaken lightly; currently this is performed only if alternative conditions that might be treatable, such as cerebral vasculitis, are being considered. However, the need for a definitive histological diagnosis might change should more specific treatments become available.

Neuropathology

The key neuropathological features are neurofibrillary tangles and senile plaques. The neurofibrillary tangles are found within the cell body adjacent to the nucleus and can be readily visualised with silver stains. They are found particularly in the pyramidal cells of the association neocortex, in the hippocampus, and in the cells of certain subcortical nuclei which have diffuse projections to the cerebral cortex, such as the nucleus basalis of Meynert. It is believed that cells which contain neurofibrillary tangles are those which are degenerating and predict subsequent neuronal death. It is now known that a major component of the neurofibrillary tangle is the microtubule associated protein tau, which has an important function to maintain microtubule assembly and integrity. In Alzheimer's disease, the tau is in an abnormally phosphorylated state, which impairs its ability to bind to microtubules, with consequent collapse of the neuronal cytoskeleton.^{8,9}

Particular interest has recently been focused on the senile plaque, which consists of dystrophic axons and dendrites clustered around a central amyloid core. The amyloid protein is distinct from that found in the

systemic amyloidoses but shares with them the formation of insoluble fibrils due to a predominance of β pleated secondary protein structure. The β amyloid of plaque cores has been isolated, sequenced, and found to be a variable length protein of 39-43 amino acids. It is the same as the amyloid that is deposited in blood vessels in Alzheimer's disease, referred to as the congophilic amyloid angiopathy. The amyloid protein is variably referred to as β amyloid, A4 protein, β A4, or A β amyloid and is part of a much larger amyloid precursor protein molecule.^{10,11} This protein is highly conserved and expressed in many tissues other than brain. It probably has a role in cell interaction and synaptic modelling. The A β component of amyloid precursor protein (figure) can be released as a soluble protein, although alternative pathways form a variety of breakdown products, some of which involve cleavage through the A β component.⁸ What converts normal A β soluble protein into the insoluble fibrils of β amyloid is unclear. Moreover, the link between deposition of fibrillary amyloid and the neurotoxicity in Alzheimer's disease is not established, although several proposals have been made, such as the enhancement of glutamate toxicity (for review see reference¹²). However, the central role of amyloid in at least some cases is now clear from the mutations found in the

Ideogram of amyloid precursor protein (APP) showing sites of mutations associated with familial Alzheimer's disease. Shaded area indicates A β domain

amyloid precursor protein gene which are associated with familial Alzheimer's disease (figure).¹³ This has important implications, not only for potential treatment but also in that some families can now undergo predictive testing similar to that for the prion dementias and Huntington's disease. Mutations of the amyloid precursor protein gene are only rarely associated with Alzheimer's disease, and recent linkage studies have found a locus on chromosome 14 that explains most pedigrees of young onset familial Alzheimer.¹⁴ The precise nature of this mutation has not been established. The situation with late onset familial disease is less clear, but genotypic variation in apolipoprotein E, which binds β amyloid, may prove to be an important determinant.¹⁵

Treatment and management

At present there is no specific treatment for the neurodegeneration of Alzheimer's disease. Several drugs that are now in advanced phases of development aim to ameliorate some of the neurotransmitter deficits arising from the neuronal degeneration. The cholinergic deficit is the most consistent and arises from damage to the ascending cholinergic projection from the nucleus basalis of Meynert in the basal forebrain to the cerebral cortex. The most widely studied are the acetylcholinesterase inhibitors such as

tetrahydroaminoacridine or tacrine. This has recently received approval in the United States for the treatment of Alzheimer's disease and applications are being made to European licensing authorities. In general, anticholinesterases show some benefit in trials, but it is modest and limited by cholinergic side effects; the aminoacridines can also cause disturbance of liver function.^{16,17} Nevertheless, the anticholinesterases represent the first recognised treatment for what has hitherto been considered an untreatable degenerative disease.

Explaining the disease and the prognosis to the family is important, and an understanding of where the major cognitive deficits lie can be valuable. Treatment of systemic illness is important, as is avoidance wherever possible of drugs and alcohol, all of which can reduce cognitive function. Occasionally, treatment of troublesome behaviour is necessary, but neuroleptic drugs need to be used with care since patients with cortical Lewy bodies can have dramatic worsening of the extrapyramidal syndrome. Early access to community support is valuable and will usually mean alerting the community psychiatric social worker. Thought should also be given to arranging power of attorney while the patient is still able to understand the legal implications. Driving always presents difficulties, and once the diagnosis has been made the patient should inform the Driver and Vehicle Licensing Agency. The decision of when to stop driving is very much an individual matter, and patients with predominant language impairment may still be able to drive whereas patients with early visuospatial difficulties may not.¹⁸ The Alzheimer's Disease Society provides valuable support and information leaflets.

As the molecular pathology of Alzheimer's disease is understood in terms of abnormal phosphorylation of tau and abnormalities of amyloid precursor protein metabolism and amyloid deposition, animal and cellular models can be developed. Considerable effect is now being directed towards therapeutic strategies that might prevent progression of the disease. Although this is for the distant future, there is now a

real sense of hope that effective and specific treatment of the disease process will be available.

The Alzheimer's Disease Society can be contacted at Gordon House, 10 Greencoat Place, London SW1P 1PH.

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Russian Report

Health care in Moscow

Michael Ryan

In the Russian Federation privatisation is affecting the health care sector as much as it is industry and commerce. That the general public support the transfer of state clinics to the private sector is a mark of their dissatisfaction with the old state run system. Doctors too see better opportunities to practise good medicine and be paid better for doing so. In Moscow the health department has set up a commission to license all clinics providing treatment, which should ensure standards of safety, training, and equipment. The Russian Federation is also trying to establish a medical insurance system to cover its citizens for health care, but in Moscow and elsewhere its implementation has been delayed by arguments and bureaucracy. In the meantime the health of Muscovites remains poor, with a high incidence of birth defects, and illnesses among the young.

"The panacea for all economic ills is privatisation." So runs the slogan which encapsulates the Russian

government's momentous strategy not only for industry and commerce but also for services such as the delivery of health care. The private ownership of hospitals and other medical units is seen as a crucial determining factor in the operation of the new system of "insurance medicine."

While some private units will be brand new, others will be housed in former state owned property made available by the relevant local government authority. Far from arousing widespread hostility, as it would in Britain, this strategy for the transfer of buildings commands substantial support among ordinary Russians. Evidence of this can be found in the responses given to one question in a public opinion survey carried out in Moscow during January 1992.

Support for private medicine

The question asked whether the transfer to private ownership of [public] hospitals, polyclinics, and other medical establishments should be permitted in the

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