

4 Alzheimer's disease

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Alzheimer's disease is a common condition in the elderly. In the past 20 years knowledge about the dementias in general, and Alzheimer's disease in particular, has increased rapidly.

Epidemiology

Dementia

There is no shortage of information on the epidemiology of dementia. Many studies and several reviews have been published. The difficulty is integrating the results because:

- (a) The types of population vary enormously in parameters such as place of residence (e.g. community versus hospital-based samples) and age range (as dementia is much more common in the very elderly, a sample stratified towards the upper age ranges will contain numerically more cases).
- (b) The diagnostic procedures vary, some involve personal examination by trained staff, others rely on second-hand information.
- (c) The use of ancillary investigations and diagnostic categories vary.
- (d) Many reports simply talk of cognitive impairment, some diagnose dementia, but relatively few attempt accurate subtyping of cases into Alzheimer's disease or vascular dementia.

In view of these problems, it has been claimed that the simple question "what is the prevalence of dementia?" is not answerable (Jorm, 1990). However, it is important to know the available evidence, as well as the methodological problems.

Prevalence

Ineichen (1987) uses the rule of thumb, dementia affects 1% of those aged 65 to 74, and 10% of those 75 and above. While the actual number

of affected cases varies from study to study, Jorm (1990) has shown that the prevalence rate increases with age with remarkable uniformity across studies – prevalence doubles every 5.1 years. The EURODEM project (Hofman *et al*, 1991; Rocca *et al*, 1991) pooled data from a number of studies around Europe which employed standardised diagnostic criteria and epidemiological methods (Table 4.1).

Incidence

The suggested incidence of dementia is about 0.5% up to the age of 75, increasing to about 1–3% aged 90. There is debate as to whether it levels off in the very old.

Gender

There is no gender difference in prevalence rates, but racial and community differences have been found, possibly due to the confounding effect of poorer education. Incidence studies have suggested that there is a higher incidence in women, and a higher incidence in New York compared with London.

Alzheimer's disease

The EURODEM prevalence rates for Alzheimer's disease are given in Table 4.2 (Rocca *et al*, 1991). Neuropathological studies have suggested that plaques and tangles affect 5% of all subjects aged 65 to 74 coming to post-mortem, 20% of those 75 to 84 and 45% of those over 85. There is a suggestion that Alzheimer's disease is more common in women than in men, while the reverse is true for vascular dementia. Alzheimer's disease is the most common dementing illness in clinical studies from Europe and North America, while vascular dementia is more common in reports from Russia, Japan and China. Neuropathologically,

Table 4.1 EURODEM prevalence rates for dementia (adapted from Rocca *et al*, 1991)

Age band	%
65–69	1
70–74	4
75–79	6
80–84	13
85–89	22
90–94	32
95–99	35

Table 4.2 EURODEM prevalence rates for Alzheimer's disease
(adapted from Rocca *et al*, 1991)

Age band	%
60-69	0.3
70-79	3
0-89	20

however, Alzheimer's disease appears to be the most common throughout the world.

Clinical features

Symptoms usually start insidiously and relatives are characteristically unable to pin down their origin with any accuracy. Often, presentation is related to an identifiable life event (e.g. bereavement or retirement). The features may be observed by others. The patient misses an appointment or forgets an arrangement had ever been made. Sometimes the first manifestation is a lack of self-care and the family notice the home becoming dirtier, personal care deteriorating and eating habits neglected. Wandering can be an early sign and is particularly dangerous if the patient gets lost, especially during winter. By the time the patient comes to the psychiatric services (with the exception of a selected group of subjects who tend to refer themselves and make use of memory clinics) the degree of dementia is apparent and obvious cognitive deficits will be seen (see Box 4.1).

Amnesia

Amnesia is universal and characteristically said to be for recent memory. Not unusually, relatives say that the patient is able to remember events happening many years ago but not earlier that day. Disorientation is the rule, with disorientation for time usually being more obvious than for place.

Aphasia

Aphasia usually supervenes later, and is often a mixture of a receptive and expressive problem. Occasionally, an expressive aphasia is obvious during normal conversation, but usually it is apparent only on close questioning.

Apraxia

Apraxia is often tested for by asking the patient to copy a design, or demonstrate a simple task. From the history there may be evidence of an inability to put on clothes in the correct sequence or there may be a suggestion of an inability to eat correctly with a knife and fork.

Agnosia

Agnosia may be demonstrated as an inability to recognise parts of the body (not to be confused with an inability to name them). A particular form is finger agnosia, which in conjunction with right-left disorientation, acalculia and dysgraphia indicates the Gerstmann syndrome. Failure to recognise faces (prosopagnosia) may lead to the belief that a relative is not real, and occasionally this misidentification is combined with a duplication or replacement phenomenon (Capgras syndrome).

Psychiatric symptoms

Psychiatric symptoms are of three main types (Burns *et al*, 1990a):

Disorders of thought content

These occur in about 15% of patients and include delusions and paranoid ideation (persecutory beliefs not held with delusional intensity). Delusional ideas may take many forms. Simple uncomplicated beliefs may occur (e.g. that a handbag or other personal possession has been stolen, while in reality it has been misplaced). Generally, delusional ideas require relative preservation of cerebral structures.

Disorders of perception

These include visual and auditory hallucinations (affecting about 10–15% of patients over the course of their disease). Various forms of misidentification have been described, including misidentification of mirror image, of other people, of events on the television and also the belief that another person is living in the house (the ‘phantom boarder’ syndrome which may also be classified as a delusion). Hallucinations have been associated with a rapid cognitive decline. Misidentifications appear to be present in younger patients.

Disorders of affect

These are relatively common, depression occurring in up to half of patients but usually of a mild nature. Depressive symptomatology

requiring treatment can occur in up to 20% of patients. By contrast, mania is rare.

There have been a number of instruments published for the assessment and quantification of neuropsychiatric features of dementia. The Manchester and Oxford University Scale Psychopathological Assessment of Dementia (MOUSEPAD; Allen *et al*, 1996), based on the work of Burns *et al* (1990a) is a structured interview with carers, and tracks the development and severity of neuropsychiatric features over the evolution of the dementia. Other published instruments include the BEHAVE-AD (Reisberg *et al*, 1987), the Present Behavioural Examination (Hope & Fairbairn, 1992) on which the MOUSEPAD is based, the Columbia University Scale for Psychopathology in Alzheimer's Disease (CUSPAD; Devanand *et al*, 1992b) and the Neuropsychiatric Inventory (NPI; Cummings *et al*, 1994). Each has advantages and disadvantages, and the choice of instrument depends on the nature of the question being asked.

Behavioural disturbances

Behavioural disturbances are particularly important as they can affect a patient's ability to live in the community. Behavioural disturbances include: aggression, wandering, excessive eating, sexual disinhibition, explosive temper, incontinence and searching behaviour.

Personality changes

Personality changes are said to occur early in the course of dementia and changes often involve coarsening of affect and egocentricity. They are probably non-specific and so do not offer much in terms of diagnosis (see Chapter 11).

Subtypes

Subtypes of Alzheimer's disease have been described by a number of authors. Mayeux *et al* (1985) described four groups: (a) a benign group

Box 4.1 Clinical features of Alzheimer's disease

Insidious onset
Amnesia, aphasia, apraxia and agnosia
Disorders of thought content
Disorders of perception
Disorders of affect
Behavioural disturbances
Personality changes

which had little or no progression over a four-year follow-up; (b) a group with myoclonus, severe intellectual decline and a younger onset; (c) a group with extrapyramidal signs, severe intellectual and functional impairment and associated psychotic symptoms; and (d) a 'typical' group which had a gradually progressive decline without distinguishing features.

The early- and late-onset dichotomy has also received widespread attention. It is said that cases with an early onset (defined as 65 years or less) have more aphasia and apraxia, a more rapid course and a poor survival rate. It has also been suggested that more early-onset cases are left handed, perhaps indicating left hemisphere damage and a genetic component. The presence of agraphia may be associated with autosomal dominant transmission of disease. Certainly, apraxia and parietal lobe involvement have been associated with a poorer survival, even in groups of patients over the age of 65.

Differential diagnosis

When presented with a patient in whom dementia is suspected, two fundamental questions need to be answered:

- (a) Does the patient has a confusional state (alone or in conjunction with an underlying dementia)?
- (b) What is the cause of the dementia syndrome?

There are many causes of dementia, the most common being Alzheimer's disease and vascular dementia (see Chapter 5). For reviews of rare and potentially treatable dementias see Reichman & Cummings (1990) and Byrne (1987). There are a number of pointers in the history and investigations which are suggestive of one or other types of dementias. These are mentioned briefly, emphasising their importance in the differential diagnosis of Alzheimer's disease (Box 4.2).

Diagnostic criteria

ICD-10

Until recently, a diagnosis of Alzheimer's disease was essentially one of exclusion. A summary of the ICD-10 (World Health Organization, 1992) criteria for Alzheimer's disease is: presence of a dementia; insidious onset with slow deterioration; absence of evidence that the cause may be due to another condition such as hypothyroidism; and absence of sudden onset or focal neurological signs.

Box 4.2 Pointers suggestive of the type of dementia

Vascular dementia has a sudden onset, stepwise deterioration and risk factors for cardiovascular disease

Huntington's disease has prominent non-cognitive symptoms, choreiform movements and often a family history

Pick's disease starts with personality and mood changes, with relative preservation of memory. Age of onset is usually younger and the electroencephalogram is more often normal

Lewy body dementia is recognised by the presence of Lewy bodies in the cortex and is associated with features of parkinsonism, acute confusional episodes and hallucinations. A presentation of intermittent confusion with these other signs is suggestive of the disorder

Dementia of the frontal lobe type is being increasingly recognised, with personality changes and frontal lobe signs. It may be a variant of Pick's disease

Parkinson's disease shows mental slowing and cognitive changes, but an absence of cortical abnormalities. Other features of Parkinson's disease are usually present (up to one-third of patients with Parkinson's disease have a dementia syndrome and not uncommonly they have Alzheimer changes at post-mortem)

Progressive supranuclear palsy is indicated by paralysis of vertical gaze, rigidity and pseudobulbar palsy, and is the paradigm of subcortical dementia

Dementia pugilistica is suggested by a history of repeated head injury

Focal cerebral atrophy is suggested by isolated aphasia, apraxia or agnosia

Motor neurone disease has been described in association with dementia of frontal lobe type

Cerebral lesions are often suspected because of abnormal neurological signs and are usually diagnosed on a brain scan

Normal pressure hydrocephalus has the classical triad of dementia, gait disturbance and incontinence. Occasionally (not invariably) diverting cerebrospinal fluid may improve the dementia

Toxins such as alcohol, drugs and various metals are usually implicated by association, and a careful history is essential in these cases

Thyroid disease, hepatic and renal failure, vitamin deficiencies and endocrine disorders are uncovered on routine screening of blood

Whipple's disease is associated with malabsorption, a trial of antibiotics may be justified

Lymphoma and endocrine disorders are revealed on general medical examination

Further categories include early and late onset. While recognising that associated psychiatric symptoms occur, ICD-10 suggests that additional (functional) diagnoses are made in these cases.

National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association

Research into Alzheimer's disease reached such a pitch in the 1970s and early 1980s that it was considered necessary to supplement existing diagnostic criteria with additional guidelines. In 1984, the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) produced the criteria in Box 4.3 (McKhann *et al.* 1984).

These criteria have been validated neuropathologically and have a high positive predictive value, sensitivity and specificity rate (Tierney *et al.* 1989; Burns *et al.* 1990*b*). While some aspects are unsatisfactory (e.g. whether to place a patient who has hypertension or diabetes in the probable or possible groups), these criteria represent a significant

Box 4.3 NINCDS-ADRDA criteria for Alzheimer's disease

Probable Alzheimer's disease

Criteria include the presence of dementia, deficits in at least two areas of cognition, progressive deterioration, no clouding of consciousness, age between 40 and 90, absence of systemic disorders

Diagnosis is supported by: progressive deterioration of individual cognitive function, impaired activities of daily living, family history of dementia, normal lumbar puncture, electroencephalogram 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 unlikely if: sudden onset, focal neurological signs, seizures or gait disturbance early in the disease

Possible Alzheimer's disease

Diagnosis can be made in the presence of atypical features, in the presence of a systemic disease (not considered to be the cause of dementia), in the presence of a single progressive cognitive deficit

Definite Alzheimer's disease

Criteria are the clinical criteria for probable Alzheimer's disease and histopathological evidence of the disorder

advance in diagnosis. Combined with standardised neuropathological criteria they represent a major step in the categorisation of dementia of the Alzheimer type.

Assessment

History

Any investigative procedure in the elderly begins with a thorough history (also from an informant) and examination. A sudden onset of disturbance of relatively recent origin, with variation in the clinical picture during 24 hours, is strongly suggestive of an acute confusional state.

Mental state examination

The mental state examination should detect clouding of consciousness, which is diagnostic of a confusional state, although its presence can be difficult to ascertain. It also assesses the presence of symptoms such as depression, delusions, paranoid ideations, hallucinations or misidentification phenomena (Burns *et al*, 1990a).

Cognitive testing

Cognitive testing is essential. It is useful (especially if the practitioner is not familiar with such tests) to conceptualise the domains to be assessed by being familiar with one of the standard neuropsychological instruments. Examples are the Abbreviated Mental Test Score (AMTS; Hodkinson, 1972), the Mini-Mental State Examination (MMSE; Folstein *et al*, 1975) and the CAMCOG (part of the CAMDEX, Roth *et al*, 1986) (see Chapter 1).

It is particularly useful to test functions from each of the following areas: (a) orientation; (b) short-term memory (name and address after two minutes); (c) long-term memory (date of first World War); (d) knowledge of current events (e.g. name of the Queen or Prime Minister); (e) aphasia (receptive and expressive); (f) apraxia; (g) concentration (e.g. counting from 20 down to one).

Physical examination

Examination of the central nervous system is important for the presence or absence of focal signs and primitive reflexes, abnormal plantar response, cranial nerve lesions, myoclonus, gait disturbance or signs of Parkinson's disease.

Blood tests

Blood tests should be routinely performed to assess general physical health and exclude other causes of dementia. These include a full blood count, erythrocyte sedimentation rate, urea and electrolytes, liver function tests, blood glucose, thyroid function tests, syphilis serology, serum B12 and folate. A urine culture is also important. In selected cases testing for HIV should be considered.

Electrocardiogram

An electrocardiogram may reveal signs of cardiovascular disease.

Imaging

A chest X-ray may show a malignancy. By far the most useful neuroimaging technique has been computer tomography (CT), which is acceptable to patients, and widely available (see Chapter 12). The main use of CT is to exclude intracranial lesions such as tumours (primary or secondary), brain abscess or subdural hematomas. Shrinkage of the brain (atrophy) (either cortical or subcortical) can be detected by sulcal widening or ventricular enlargement. In individual cases, the changes seen can be striking but are often unhelpful since, generally speaking, the degree of shrinkage corresponds to the degree of dementia (in other words, by the time obvious shrinkage occurs the degree of dementia is apparent). However, subtle changes of cerebral shrinkage support a clinical diagnosis of early Alzheimer's disease. Ventricular enlargement increases with normal ageing, accelerating in subjects over 60. Correlations have been found between ventricular enlargement and cortical atrophy, and the degree of dementia. Other changes such as cerebral infarctions, white matter changes and basal ganglia calcification can be detected and are helpful in the differential diagnosis. Serial changes in CT are also helpful in diagnosis (Burns *et al*, 1991).

Magnetic resonance imaging (MRI) has the advantage of showing cerebral structures in greater detail than CT and does not use radiation. However, the procedure is much more arduous for the individual and not really suitable for many patients with Alzheimer's disease.

Functional imaging is reviewed by Burns *et al* (1989a), Beats *et al* (1991) and Geaney & Abou-Saleh (1990). Single photon emission computed tomography uses gamma cameras, which are available in most nuclear medicine departments, whereas positron emission tomography (PET) requires specialist machinery (a cyclotron) to make radiotracers (see Chapter 12). Patterns of blood flow have

been documented in Alzheimer's disease which appear quantitatively and qualitatively different to normal ageing, and deficits in the temporal, parietal and occipital lobes have been documented which correlate with neuropsychological changes (Burns *et al*, 1989*b*).

Electroencephalogram

The electroencephalogram (EEG) is an important additional investigation. In normal ageing there is a generalised slowing of the alpha rhythm, with an increase in theta, delta and beta activity. In acute confusional states the EEG is the most sensitive diagnostic procedure, and slowing of the tracing occurs. In Alzheimer's disease the tracing is usually normal in the early stages. Thereafter, a slowing in alpha and beta activity occurs, with increased delta and theta waves. As with all investigations there is overlap between the changes in normal ageing and in dementia. Soininen *et al* (1982) found abnormalities in 52% of Alzheimer's disease patients but in only one of 90 age-matched controls. The EEG is more often normal in Pick's disease than Alzheimer's disease (an observation of little practical benefit when dealing with an individual). In Creutzfeldt–Jakob disease, there are characteristic paroxysmal sharp waves with a slow background rhythm. The EEG can be used to make 'maps' of cerebral activity which can be of diagnostic use (Loeches *et al*, 1991).

Box 4.4 Investigations of suspected Alzheimer's disease

History: present illness, family history

Mental state examination: psychiatric symptoms, behavioural changes and personality changes

Cognitive function (including Abbreviated Mental Test Score, Mini-Mental State Examination, CAMCOG)

Full physical examination

Blood tests: full blood count, erythrocyte sedimentation rate, urea and electrolytes, liver function tests, glucose, syphilis serology, thyroid function tests, vitamin B12 and folate (red cell and serum), calcium, HIV

Urine culture

Chest X-ray, CT head

Electrocardiogram, electroencephalogram

Further investigations include a lumbar puncture, magnetic resonance imaging, single photon emission computerised tomography, positron emission tomography and brain electrical activity mapping

Prognosis

Survival

There is no doubt that Alzheimer's disease is a progressive condition and survival, compared with the general population, is greatly reduced. It was differential survival patterns which formed the basis for Roth's validation of clinical categories in old age psychiatry (Roth, 1955). Studies suggest elderly patients with Alzheimer's disease survive for about 30% of the normal age related life expectancy. Box 4.5 lists factors associated with a poorer survival. More recent papers have commented on the fact that survival for patients with Alzheimer's disease has improved over the past four decades (Burns & Lewis, 1993). There are probably several reasons for this including general improvement of care and the introduction of better medical treatment to control illnesses such as intercurrent infection. Age at diagnosis has been compared in several studies, and controlling for the degree of cognitive impairment, a young age is predictive of poorer survival. It has been shown that elderly patients, while surviving for at least 70% of their disease duration outside hospital, die more quickly once admitted.

Cognitive decline

It is part of the definition of Alzheimer's disease that progressive impairment in cognitive function occurs. A number of studies have attempted to document cognitive decline and identify features which predict cognitive deterioration. Cognition does not deteriorate significantly over a matter of weeks, and testing at least three months

Box 4.5 Factors associated with diminished survival

Parietal lobe damage (as evidenced by parietal lobe signs or decreased density on CT scan)

Being male

Age of onset of less than 65 years

Prominent behavioural abnormalities (such as irritability and wandering)

More severely impaired cognitive function (in particular evidence of apraxia)

Depression observed by a rater

The absence of misidentification phenomenon (i.e. misidentification appears to be protective despite its association with younger age)

apart is necessary to demonstrate statistically significant differences. There is large variation in the degree and rate of cognitive decline. Several studies have shown a subgroup of patients in whom progression in cognitive impairment is very slow (corresponding to the benign subgroup described by Mayeux *et al*, 1985).

Global ratings of dementia severity (including functional and cognitive measures) are better at demonstrating progressive impairment than either measure alone. Attempts at quantifying cognitive decline have shown remarkable consistency, despite wide variations in numbers of patients involved, diagnostic practices, selection criteria and placement. Deterioration occurs at a rate of about 10% per annum. However, the clinical observation that decline in the succeeding 12 months can be based on the last 12 months is not borne out by some studies (e.g. Salmon *et al*, 1990). It has been suggested that a shorter duration of illness is associated with an increased rate of further decline. There is also evidence that rate of cognitive decline correlates with the rate of ventricular enlargement (Burns *et al*, 1991).

Aetiology

Genetics

The existence of familial cases of Alzheimer's disease was demonstrated over 40 years ago (Sjogren *et al*, 1953). These familial cases, usually of early onset, were considered to be rare causes of Alzheimer's disease. Today, evidence suggests that familial genetic factors account for a considerable proportion of Alzheimer's disease in all age groups. This is difficult to verify in an elderly population with characteristically high drop-out rates, because the onset of Alzheimer's disease can vary over a wide age range. The estimated lifetime risk to develop Alzheimer's disease comes close to 50% for first-degree relatives, independent of their gender. This is consistent with an autosomal dominant inheritance. On the other hand, the observed concordance rate in monozygotic twins is less than 50%, indicating the importance of environmental factors (Nee *et al*, 1987).

At least four different genetic sites have been implicated in Alzheimer's disease, and this holds promise for future treatments of the disorder. Missense mutations have been found on chromosome 21 in the gene encoding for the beta amyloid precursor protein (Goate *et al*, 1991), emphasising the central place that amyloid formation has in the genesis of the disease. This seems to account for approximately a quarter of early-onset Alzheimer's disease cases, the remaining three-quarters being found on chromosome 14, the gene of which has been cloned (Sherrington *et al*, 1995). This has been referred to as

Box 4.6 The genetics of Alzheimer's disease

Presenilin 2 gene (chromosome 1)
Presenilin 1 gene (chromosome 14)
Beta amyloid precursor protein gene (chromosome 21)
Apolipoprotein E gene (chromosome 19)

presenilin 1. More recently, a presenilin 2 gene has been identified on chromosome 1 (Levy-Lahad *et al*, 1995), which also seems to be transmitted as an autosomal dominant condition.

Interest has also focused on chromosome 19 where the gene for apolipoprotein E is situated. Apo E is a plasma protein involved in the transport and metabolism of cholesterol. A number of studies have confirmed that the proportion of patients with Alzheimer's disease possessing one or more apolipoprotein E4 genes, is raised compared to the normal population (15% in normal people, up to 40% in patients with Alzheimer's disease) (Strittmater & Roses, 1995). Apolipoprotein E is produced by astrocytes in the brain, confirming the special role E4 may have in connection with neurodegeneration (for a summary see National Institute on Ageing, 1996). A recent study (Myers *et al*, 1996), showed that the risk ratio compared with persons without an E4 allele, was four times higher for those with E3/E4, and 30 times for those homozygous for E4. Fifty-five per cent of patients with E4/E3 developed Alzheimer's disease by age 80, compared to 27% who were E3/E4 and 9% for those without an E4 allele. The association between E4 and Alzheimer's disease is one of the most consistent biological findings in late-onset Alzheimer's disease and represents the first real biological risk factor identified for late-onset disease. With regard to studies on aetiology, it is likely that it will be useful in teasing out environmental and biological risk factors (Myers *et al*, 1996).

Other factors

Many other risk factors have been implicated in the genesis of Alzheimer's disease, which suggests no single aetiological factor is responsible. It is important not to confuse the finding of an association between Alzheimer's disease and a particular factor with a causal connection. The following summarises some of the better known associations (see also reviews by Henderson (1988) and Jorm (1990)).

Head injury

Head injury has been examined as a possible precipitating factor and is of particular interest as dementia pugilistica (caused by the

repeated head injuries of boxing) is associated with the presence of neurofibrillary tangles in the neocortex, and the clinical syndrome of dementia. Often the head injury is many years prior to the onset of dementia. Despite some positive findings, several more studies have failed to find an association between dementia and head injury.

Aluminium

Aluminium received attention following a study (Martyn *et al*, 1989) which showed an association between dementia and the level of aluminium in drinking water. It suggested that the poisoning of a water supply in Cornwall was associated with cognitive impairment. Generally, there is no good evidence that excessive intake of aluminium in drinking water (or in antacid preparations) causes an increased risk of dementia. The bioavailability of aluminium, the effect of cooking acidic food in aluminium pans and a possible interaction between aluminium and calcium have all been investigated.

Smoking

Smoking has been found in several studies not to be associated with an increased rate of Alzheimer's disease, although the association has been reviewed.

Organic solvents

Exposure to various organic solvents has been associated with dementia, as has exposure to phenacetin.

Thyroid disease

Thyroid disease was suggested in one study to be associated with Alzheimer's disease. This was of particular interest in view of a previous association between Down's syndrome and thyroid dysfunction. However, this finding has not been confirmed.

Other conditions

Many associated medical conditions such as diabetes, infections and vascular dementia have been reported to have an increased risk of Alzheimer's disease, but the information is too sketchy to be conclusive. One of the earliest findings was an association between lymphomas and Alzheimer's disease, a search prompted by the association between these conditions and Down's syndrome. These

findings have not been replicated, and the few positive results which were found, represented mainly an association with early-onset cases. The association of advanced paternal age and Down's syndrome has led to the search for a similar association in Alzheimer's disease. Both maternal and paternal age have been implicated in Alzheimer's disease, but the body of evidence is generally against such an association.

Neuropathology

Macroscopic changes

Brain atrophy is a frequent, but inconsistent, finding in Alzheimer's disease. Normal ageing is accompanied by minimal loss of brain weight and volume after the age of 50. The volume normally decreases by no more than 2% per decade. However, severe atrophy can occur in the absence of Alzheimer's disease, whereas severe Alzheimer pathology is not necessarily accompanied by corresponding macroscopic changes. The most severe cerebral atrophy (with weight loss of up to 300 g) is usually observed in early-onset Alzheimer's disease.

Sulcal widening in Alzheimer's disease is initially most pronounced over the temporal and parietal lobes, and in the later stages over the frontal lobes. These changes are mostly bilateral and symmetrical; in rare cases they can be unilateral or circumscribed. The most likely nature of this cortical atrophy is not a decrease of cortical thickness, but a reduction in length of the cortical ribbon due to a loss of perpendicularly organised columns of neurons and fibres. Ventricular enlargement has already been mentioned in the section on neuroimaging. Neuropathology studies are generally in agreement with CT findings (see Chapter 12).

Histological changes

Neurofibrillary tangles

Alzheimer (1907), described "the very peculiar neurofibrillary changes" of his famous first case, as the hallmark of this disease. Silver impregnation shows neurofibrillary tangles as flame-shaped or globose, intracellular inclusions in neural perikarya and dendritic processes. Sometimes, the neurofibrillary tangles can occur extracellularly in the neuropil of the dentate gyrus, or as resistant remnants of destroyed nerve cells in other areas of the brain (ghost tangles). Insolubility makes it difficult to isolate the neurofibrillary tangles and has precluded protein sequencing.

The neurofibrillary tangles consist of paired helical filaments twisted into a coil. High levels of hydroxyproline are probably responsible

for the cross-linkage of the filaments. The presence of various constituents of neurofibrillary tangles has been demonstrated with neuroimmunological methods:

- (a) Tau is a cytoskeletal protein which is abnormally phosphorylated in neurofibrillary tangles.
- (b) Ubiquitin is a small, 'ubiquitous', phylogenetically old protein which is present in any eukaryotic cell. Ubiquitin is thought to label short-lived, or abnormal, proteins undergoing non-lysosomal enzymatic degradation.
- (c) Immunostaining of the amino acid sequence A68 with the antibody Al_zSO is currently considered to have a high specificity for Alzheimer's disease typical neurofibrillary tangles.

Neurofibrillary tangles occur in normal ageing and in a number of diseases (Table 4.3). In Alzheimer's disease, neurofibrillary tangles are usually found in the pyramidal cells of the layers III and IV of the mediotemporal cortex and in the CA1 region of the hippocampus. In more advanced stages of illness, neurofibrillary tangles can occur with increasing density in all cortical lobes, and in the multipolar cells of numerous areas in the brainstem.

Plaques

Alzheimer (1907) recognised miliary plaques (i.e. spherical argyrophilic lesions in the neurophil of the upper cortical layers),

Table 4.3 Histological changes in ageing and disease

	Neurofibrillary tangles	Amyloid deposition	Inclusion bodies
Ageing	+	+	GV, Hirano bodies
Alzheimer's disease	++	++	GV, Hirano bodies
Down's syndrome	++	++	GV
Parkinson's disease	(+)	(+)	Lewy bodies (brainstem), GV
Lewy body dementia	(+)	(+)	Lewy bodies (diffuse), GV
Progressive supranuclear palsy	+	++	GV
Pick's disease	+	++	Pick bodies, Hirano bodies, GV
Amyotrophic lateral sclerosis	+	(+)	Hirano bodies, GV
Dementia pugilistica	++	++	

++, essential component; +, occurs in a large proportion of cases; (+) probably incidental finding. GV, granulovacuolar degeneration.

Box 4.7 Neuropathological criteria for the diagnosis of Alzheimer's disease (adapted from Khachaturian, 1985)

Examination of the frontal, temporal, parietal lobes, amygdala, hippocampus, basal ganglia, substantia nigra, cerebellum and spinal cord to exclude other obvious forms of dementia
Any neocortical field of 1 mm² examined with magnification x200 has to show (in the presence of a positive clinical history these criteria should be revised downwards):

Age (years)	Plaques	Neurofibrillary tangles
<50	> 2	> 2
50-65	> 7	(+)
66-75	> 10	(+)
>75	> 15	(+)

but he did not pay great attention to the finding. Their presence in senile dementia and in old people with other illnesses had been known for a long time. Similarly to neurofibrillary tangles, plaques are found in a large number of diseases (Table 4.3). Therefore diagnostic neuropathological standards have to take account of their numbers, and not only of their presence (Glenner & Wong, 1984) (Box 4.7). To date, the diagnostic significance of plaques is valued higher than neurofibrillary tangles because the number of plaques seems to be linked more closely to the degree of cognitive impairment.

At least three forms of plaques can be distinguished. They may reflect different developmental stages:

- (a) The early immature plaque consists primarily of argyrophilic fibres. Closer scrutiny with more advanced techniques reveals swollen neurites staining for acetylcholinesterase and neuropeptide transmitters, indicating that neurotransmitter alterations can occur early in the course of illness.
- (b) The classical mature plaque consists of an amyloid centre surrounded by neuritic debris, reactive astrocytes and neuroglia.
- (c) Isolated amyloid cores were considered as burnt-out, hypermature plaques. Advances in molecular biology have led to the discovery of a very early preplaque of diffuse amyloid protein. There is increasing evidence that morphologically similar plaques in normal ageing, and in Alzheimer's disease, may be immunologically distinct.

Other microscopic features

Amyloid protein

Amyloid protein can be found around arteries, capillaries and venules of the hippocampus and occipital lobe in most Alzheimer's disease cases (Lantos, 1990). This amyloid angiopathy, and the observation of capillaries in the centre of amyloid plaques raise the question of whether the amyloid protein can be imported from the periphery across the blood-brain barrier. Milder forms of such amyloid changes can also be seen in clinically normal elderly people. Severe isolated forms can cause infarction, or lethal bleeds in hereditary cerebral haemorrhage with amyloidosis Dutch type (see Chapter 5).

Granulovacuolar degeneration

The pyramidal cells of the hippocampus often contain vacuoles which are filled with argentophilic or eosinophilic granules. This granulovacuolar degeneration can also occur in Pick's disease, Down's syndrome and other illnesses (Table 4.3).

Lewy bodies

Lewy bodies (i.e. globoid, rod- or serpent-shaped eosinophilic inclusions) surrounded by blue halo (haematoxylin-eosin stain), found frequently in the substantia nigra of patients with Parkinson's disease, have been reported with increasing frequency in the cortex of patients with concomitant Alzheimer pathology. It is unclear whether this is a coincidence, or whether it represents a variant of Alzheimer's disease.

Hirano bodies

Hirano bodies, short eosinophilic rod-shaped structures, can be found in the CA1 area of the hippocampus.

Astrocytes

Hypertrophic and proliferating activated astrocytes, intensely staining with glial fibrillary acidic protein, are seen in the upper-cortical layers and in the white matter of patients with Alzheimer's disease.

White matter changes

Cranial CT and MRI have led to increased awareness of white matter changes in the elderly. Such alterations, leuko-araiosis, are a common

finding in Alzheimer's disease. Their nature is currently under debate. These changes could be due to subacute incomplete white matter infarctions or, in the absence of risk factors, to Wallerian 'dying back' neuropathy. They seem to have a weak relationship with more severe cognitive impairment and poor prognosis.

Neurochemistry

Neurotransmitter changes

The widespread nature of the histological changes in Alzheimer's disease suggests that multiple neurotransmitter systems can be involved secondarily (Rossor, 1987). Table 4.4 gives a brief outline of some of the cell groups affected by underlying pathological changes, consecutive neurotransmitter alterations and reported changes of receptor density and sensitivity.

Acetylcholine

It has been suggested that impaired cholinergic function could cause the cognitive impairment in Alzheimer's disease. A number of findings support this hypothesis:

- (a) Ninety per cent of the large multipolar neurons in the basal nucleus of Meynert are cholinergic and responsible for the cholinergic innervation of the cerebral cortex. These neurons are subject to severe changes in the course of Alzheimer's disease: tangle formation, reduction in cell size and eventually cell death (Whitehouse *et al*, 1982).
- (b) The activity of cholineacetyltransferase and consequently acetylcholine, is reduced in cortical and subcortical structures.
- (c) A subclass of muscarinic receptors, the presynaptic M2 receptors, appear to be reduced in density.

All these changes can be explained by the degeneration of cholinergic neurons in the basal nucleus of Meynert. The alterations correlate with clinical measurements of cognitive impairment.

Other neurotransmitters

Aminergic deficits in Alzheimer's disease are caused by the degeneration of noradrenergic cells in the locus coeruleus and by the loss of serotonergic neurons in the raphe nuclei. Dopamine was reported to be normal in the cerebral cortex, but low in amygdala and striatum. Gamma-aminobutyric acid from inhibitory cortical interneurons and glutamate, probably from pyramidal cells of layer

Table 4.4 Neurotransmitter changes in Alzheimer's disease

Origin	Neurotransmitter	Receptor
Basal nucleus of Meynert	D choline-acetyltransferase	N nicotinic
	D acetylcholine	D muscarinic (M2)
Locus coeruleus	D dopamine-beta-hydroxylase	N alpha
	D noradrenaline	N beta
Dorsal raphex nucleus	D serotonin	5-HT ₂
Striatum/amygdala	D dopamine	
Cortical neurones	?D GABA	
	?D glutamate	
	?D somatostatin	D STH
	?D CRF	? supersensitivity

D, decrease; N, no consistent change.

III, was reduced, but this change could be due to post-mortem decay. Neuropeptides, which can coexist in cholinergic, monoaminergic and gamma-aminobutyric acid neurons, are affected by the disease process to a variable extent. Decreases of cortical somatostatin and corticotrophin releasing factor have been observed. Nucleolar volume and cytoplasmatic ribonucleic acid are reduced in the basal nucleus of Meynert, hippocampus and locus coeruleus, indicating impaired intracellular signalling and protein formation.

Conclusion

Alzheimer's disease is a significant cause of morbidity and mortality in the elderly. Its onset is usually insidious, and primarily affects memory, although there are a number of associated clinical features. It is important to differentiate Alzheimer's disease from other causes of dementia. This process is being refined with the development of more precise clinical, imaging, genetic and pathological criteria. The aetiology of Alzheimer's disease is better understood than ever before, and advances in genetic research offer the hope of new treatments.

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