

# The aetiology and pathology of dementia

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In the first article of this special feature on dementia, the authors discuss the commonest forms of dementia seen in clinical practice

*“Without memory you can merely look, and the world glides through you without leaving a trace.”*  
J. Bernlef “Out of mind”<sup>1</sup>

**S**enile dementia is a term rarely used in clinical practice. It was originally used to distinguish between cognitive decline in persons aged over 65 years and presenile dementia occurring in persons below 65 years of age. However, with increasing knowledge of the epidemiology and aetiology of the dementias, it has become clear that there are clinicopathological features common to both age groups, and clinical distinction on the basis of age alone is not useful.

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Dementia is now defined as “a syndrome consisting of progressive impairment in two or more areas of cognition (that is, memory, language, visuospatial and perceptual ability, thinking and problem-solving, personality) sufficient to interfere with work, social function, or relationships, in the absence of delirium or major non-organic psychiatric disorders (for example, depression, schizophrenia).”<sup>2</sup>

Included within most diagnostic criteria are evidence of gradual progression, the presence of functional limitations and exclusion of other primary psychiatric disorders. Some authors have proposed a clear distinction between the presence and absence of dementia, dividing the latter into distinct subtypes. Others have proposed the theory of a continuum between normal ageing and dementia, with a smooth unimodal distribution of cognitive performance scores in the population.<sup>3</sup> In keeping with this theory,

they proposed a distinction between dementing and demented subjects, which is reflected in the newly introduced International Classification of Diseases (ICD)-10 category of mild cognitive impairment.<sup>4</sup>

The commonest forms of dementia seen in clinical practice are Alzheimer’s disease (AD), vascular dementia (VD) and dementia with Lewy bodies ([DLB], which has clinical, pathological and prognostic features that distinguishes it from AD). Another less common group of dementias are the frontotemporal dementias (FTD). Functional changes within the frontal lobes can arise directly from the effect of neurodegenerative disease within this region of the brain, or result from secondary failure to engage the otherwise normal frontal lobes by damaged stimulatory pathways to this area. Hence, FTD can include atypical presentations of cortical disorders like AD or the subcortical disorders of Parkinson’s dis-

ease, progressive supranuclear palsy, corticobasal (ganglionic) degeneration and vascular dementia. However, the distinct form of FTD is due to frontal lobe degeneration, a neurodegenerative disorder with neuropathology that is distinct from AD. This disorder occurs chiefly in the presenile period, with most common onset between 45 and 60 years of age. FTD is not considered further in this article.

#### ■ EPIDEMIOLOGY

The presence of dementia increases exponentially with age and, after age 65, roughly doubles every five years: the prevalence is 2 per cent in those aged 65 to 69, rising to 20 per cent in the 85 to 89 age group.

In the UK, there are presently well over half a million people suffering from dementia. With the increase in older people as a proportion of the population in developing and developed countries,<sup>5</sup> the absolute number of persons suffering from Alzheimer's disease and other types of dementia will also increase.<sup>6</sup> Many of these people will be looked after by carers who are themselves over 65 years, and a substantial number will be cared for in residential and nursing homes. This represents not only a large economic burden for the individual and society, but a major challenge to all individuals responsible for their care. Recognition of this large public health problem has generated much scientific interest in elucidating the pathogenesis of dementia in the hope of developing new therapeutic agents that may control not only the symptoms, but hopefully halt and ideally reverse the disease process.

#### ■ ALZHEIMER'S DISEASE

Allois Alzheimer described the first case of Alzheimer's disease, Auguste D, in 1907,<sup>7</sup> and in 1910, Perusini described the pathology in four cases of AD.<sup>8</sup>

As a condition, it presents insidiously and deterioration is gradual. In the early stages, long term memory is preserved and deficits are mainly in short term memory and language, especially nominal dysphasia. As the disease progresses, complex psychomotor tasks become increasingly difficult to perform, and in the end stages there may be failure to recognise spouses and close family members (agnosia).

Unfortunately, there is no simple diagnostic test for AD, and as the definition of dementia implies, it is partly a diagnosis of exclusion. A comprehensive clinical interview including personal and family history with both the person and their main carer is crucial to establishing a diagnosis. Clinical examination is necessary to detect any signs indicative of other neuropathology or vascular disease. Assessment is not complete without chest X-ray, electrocardiogram and

blood tests, for example, serum vitamin B<sub>12</sub>, folate and thyroid function tests, to exclude other causes of cognitive decline which could be treated. Erythrocyte sedimentation rate (ESR) can also be estimated to exclude vasculitis. Other tests include syphilis serology and, more relevantly in the future, HIV testing. In addition, all individuals should have a computerised tomography (CT) scan, as shown in figure 1, and in some cases, magnetic resonance imaging (MRI).

Various tests of cognitive function are used in clinical assessment. The most commonly used and easily applied test is the mini-mental state examination (MMSE). MMSE has high inter-rater reliability, sensitivity of 92 per cent and specificity of 96 per cent in identifying cases of organic disorder and depressive states and in their differential diagnosis. There is international consensus on the use of MMSE as the first stage instrument for assessing cognitive function, followed by either the CAMDEX (Cambridge mental disorders of the elderly examination) or CAMCOG (Cambridge cognitive examination).

With the development of standardised assessment instruments and operational diagnostic criteria, it has been possible to carry out prevalence studies. One such study by Hofman *et al* revealed a prevalence of 1.2 per cent in the 60 to 64 age group and 32.2 per cent in the 89 to 94 age group.<sup>9</sup>

#### ■ RISK FACTORS

Studies designed to assess factors predisposing to AD have been largely retrospective case control studies. Large prospective studies currently being undertaken, for example, the EURODEM (European studies of dementia) and MRC-CFAS (Medical Research Council cognitive function and aging study) projects, may yield more accurate information.

Most of the current information is from a meta-analysis by the EURODEM group on 12 case control studies. All 12 studies showed that increasing age is a robust risk factor for AD, but uncertainty exists about what happens to this risk in the very old.<sup>10</sup> Age reflects the passage of time. Hence, increasing age can affect disease incidence in several ways: more time for genes to express themselves, increasing inability to repair cell damage and more time to be exposed to environmental agents, any of which may be relevant for the onset of AD.

Some other identified risk factors for AD are: hypothyroidism, head trauma, depression, older maternal age and a family history of dementia, Down's syndrome, or Parkinson's disease. Other possible risk factors include epilepsy, herpes zoster or herpes simplex, alcohol, smoking<sup>10</sup> and increased exposure to aluminium.

#### ■ GENETIC FACTORS

A genetic contribution to the aetiology of AD has long been recognised. It is likely that it is a polygenic multifactorial disorder in which some major gene effects may be found but where environmental influences and other modulatory effects may be of central importance.

A considerable amount of interest has been shown in apolipoprotein E which may represent a genetically determined risk factor in the development of AD. Apolipoprotein E is one of a number of protein constituents of the plasma involved in lipid transport and metabolism. It mediates the binding of lipoproteins to low density lipoprotein receptors, which initiates their uptake and degradation, leading to the use of lipoprotein cholesterol in the regulation of cholesterol metabolism.

Apolipoprotein E is polymorphic, with three major isoforms: apo-E2, apo-E3 and apo-E4. These are the products of the alleles  $\epsilon 2$ ,  $\epsilon 3$  and  $\epsilon 4$  at a single gene locus on chromosome 19. (An allele is any one of a series of two or more different genes that may occupy the same position or locus on a specified chromosome.) Apo-E3 is considered the parent form and E2 and E4 differ by a single amino acid substitution. Three homozygous (apo-E2/2, E3/3 and E4/4) and three heterozygous (E2/3, E3/4 and E2/4) phenotypes arise from expression of any two of the three alleles. Apo-E3/3 is the most common (60 per cent of all phenotypes) followed by E3/4 (23 per cent) and E3/2 (12 per cent). Apo-E2 has relatively low binding capacity while apo-E4 has high binding activity. These differences result in hypercholesterolaemia in individuals homozygous for the apo-E  $\epsilon 4$  allele and

type III hyperlipoproteinaemia in apo-E  $\epsilon$ 2 homozygotes. Strittmatter *et al* reported an increased frequency of the apo-E  $\epsilon$ 4 allele in late onset familial AD.<sup>11</sup> They also hypothesised that apo-E4 has higher binding activity to  $\beta$ -amyloid (A $\beta$ ) compared with other allelic forms. Several studies have since replicated these studies. A Finnish study showed that 2.9 per cent of individuals with no apo-E  $\epsilon$ 4 alleles have AD whereas 21.4 per cent of those homozygous for apo-E  $\epsilon$ 4 alleles developed AD.<sup>12</sup>

Studies in different racial groups have suggested that there may be important ethnic differences in the increased risk of AD associated with apo-E  $\epsilon$ 4 allele. These differences may have their basis in genetic or environmental factors. A number of studies have also shown that the apo-E  $\epsilon$ 4 allele is associated with an earlier age of onset of AD.<sup>13,14</sup> One study of sporadic AD showed a six-year earlier age of onset for individuals homozygous for the  $\epsilon$ 4 allele<sup>15</sup> and suggested that the increased risk of developing AD is through having the  $\epsilon$ 4 allele.<sup>16</sup> Others have looked at the association between the  $\epsilon$ 4 allele and the rate of cognitive decline, but found little association.<sup>14,17-19</sup> There are some studies that suggest an association between increased risk of AD, female gender and apo-E  $\epsilon$ 4 allele.<sup>20</sup> (Figure 2.) Other possible associated factors, which may interact with the presence of the apo-E  $\epsilon$ 4 allele, include head injury, smoking history and other genetic factors.

Most studies looking at the association between AD and apo-E  $\epsilon$ 4 allele have been

based on prevalence studies. Incidence studies may reveal that possession of the apo-E  $\epsilon$ 4 allele increases survival time in individuals with AD. Similarly, is it the presence of the  $\epsilon$ 4 allele that increases an individual's risk or the relative lack of apo-E  $\epsilon$ 2 allele, which some suggest has a protective effect?<sup>21,22</sup> The association between apo-E  $\epsilon$ 4 and other diseases, such as heart disease, also needs to be considered as this too could clearly affect any prevalence or incidence study of AD.

Interestingly, the apo-E  $\epsilon$ 4 allele also appears to be increased in other neurodegenerative disorders such as Lewy body type dementia,<sup>23-25</sup> Creutzfeldt-Jakob disease,<sup>26</sup> motor neurone disease<sup>27</sup> and possibly vascular dementia.<sup>28,29</sup> However, it is not a good discriminating factor for different types of dementia.

Finally, possession of the apo-E  $\epsilon$ 4 allele appears to have little significance for the clinical course of the disease. At present, the use of apo-E genotyping is of limited clinical value. However, most clinical drug trials of potential therapies for dementia include apo-E genotyping, as it is possible that treatment response may be partially genetically determined.<sup>30</sup> Response to the anticholinesterase, tacrine, may be more pronounced in individuals who do not possess apo-E  $\epsilon$ 4 allele.

## PATHOGENESIS

Neurofibrillary tangles and amyloid plaques are the hallmark pathological lesions of AD (see Figure 3). However, the relationship between the two and an understanding of how neurones are lost and dementia ensues is still poorly understood. In addition to these classic features, a chronic inflammatory response to the presence of these insoluble abnormal materials in the brain as well as degenerating neurones probably have a role in AD pathology.

**Neurofibrillary degeneration** Neurofibrillary degeneration occurs when the neuronal cytoskeleton is progressively disrupted and replaced by bundles of paired helical filaments (PHFs), the neurofibrillary tangles. These occur in the neuronal perikaryon and also accumulate in the neuropil as neuropil threads and dystrophic neurites. The major protein subunit of the PHF neurofibrillary tangles is the microtubule-associated protein, tau, which in AD is abnormally phosphorylated. Tau protein is an essential component of the neuronal cytoskeleton. Microtubules in neurones have a special role in maintaining neuronal morphology and function; their long rigid structure is conferred by the neuronal specific proteins, one of which is tau. The contribution of tau to the microtubule structure is dependent on its phosphorylation.<sup>31</sup> Tau is phosphorylated at multiple sites and the binding of tau to microtubules is

regulated largely by the degree of phosphorylation. When the structure of neurones needs to be relatively plastic, for example, in foetal development, tau is heavily phosphorylated and less likely to bind to microtubules.<sup>32,33</sup> In AD, tau is heavily phosphorylated and this leads to impaired binding of guanine triphosphate to  $\beta$ -tubulin, depressed microtubule assembly, microtubule collapse, loss of microtubule function and subsequent death of the neurone.<sup>34,35</sup>

The heavy phosphorylation of tau and loss of microtubules in AD led to the search for the factors that regulate the phosphorylation of tau. Several enzymes have been shown to be involved in this process, but one in particular, glycogen synthase kinase-3 (GSK-3), has been shown to do this in intact cells.<sup>36</sup> GSK-3 phosphorylation of tau in intact cells results in binding of tau to microtubules and fragile tubules, but what regulates GSK-3 is unknown.

**Amyloid plaques** Amyloid plaques are relatively large extracellular structures, which, in their mature form, contain a central dense core of amyloid protein surrounded by a halo of degenerating neurites. The amyloid of the core is composed of peptides, mainly A $\beta$  derived from the large transmembranous amyloid precursor protein (APP).<sup>37-39</sup> APP is a ubiquitous protein of unknown function. It is thought that it may perform some role in intercellular communication.<sup>40</sup> APP is metabolised through at least two pathways. The processing by  $\alpha$ -secretase leads to secretory APP (sAPP), which is neuroprotective. This is a non-amyloid processing. Processing by  $\beta$ -secretase and  $\gamma$ -secretase is the amyloidogenic pathway and produces A $\beta$ . Both types of metabolism take place normally and A $\beta$  fragments are found in normal cerebrospinal fluid (CSF).<sup>41</sup> Therefore, it would not appear that it is the generation of A $\beta$  itself that results in AD, but decades of relative increase in the production of A $\beta$  might be harmful. Indeed, the relative amount of A $\beta$  has been shown to change with age and disease.<sup>42,43</sup> A $\beta$  peptides have been shown to vary in length by a few amino acids and some may aggregate more readily and hence be more pathogenic.

**Metabolism of APP** Clearly, an understanding of this process may present a possible site for therapeutic intervention.

Mutations in the APP gene have been associated with familial cases of AD. These mutations aggregate on either side of the A $\beta$  peptide gene and perhaps upset the balance between amyloidogenic and non-amyloidogenic metabolism. People with Down's syndrome (trisomy 21) develop the pathological features of AD, and frequently become demented in middle life. The APP gene is located on chromosome 21, and the presence of three copies of the gene may

result in the overproduction of APP and hence increased A $\beta$  peptide deposition.

Increased A $\beta$  deposition is also seen in head injury, and some have suggested that APP itself may be a stress protein which increases as part of the normal cellular response to injury.

Lastly, neurotransmitters share similar intracellular signalling events and APP processing has been shown to be affected by a number of different neurotransmitters. Of particular interest is the demonstration that muscarinic agonists reduce the generation of A $\beta$ -containing metabolic products. Thus, muscarinic agonists may result in some substantial long term benefit on disease progression.

**Effects of A $\beta$  deposition** The A $\beta$  fibrils are toxic to neurones in culture, and this may be dependent upon expression of GSK-3, or on a calcium influx consequent upon A $\beta$  deposition.

A gene, presenilin-1 (PS-1), on chromosome 14 has been identified, and mutations of PS-1 are associated with early onset, autosomal dominant, familial AD<sup>44</sup>. Mutations of an additional near-identical gene on chromosome 1 (PS-2) also cause early onset familial AD, while polymorphism of PS-1 is associated with late onset AD.<sup>45</sup> The protein product of PS-1 predicts a structure that traverses the membrane seven times, and has a possible role as a receptor, possibly coupled to G protein.<sup>46</sup> It is unclear how presenilins function in AD, but they may alter APP processing directly or alter signal transduction cascades that affect APP processing and tau phosphorylation.

It has been suggested that the susceptibility to AD associated with apo-E4 protein is due to its capacity to bind more readily to A $\beta$  which might therefore promote plaque formation or reduce plaque clearance. Others have suggested that apo-E3 binds more tightly to tau and other microtubule-associated proteins and that apo-E3 or apo-E2 may protect tau from hyperphosphoryla-

tion. It is possible that apo-E has a role in the brain in contributing to the tau-induced stabilisation of microtubules, with apo-E  $\epsilon$ 3 and  $\epsilon$ 2 having a positive effect and apo-E  $\epsilon$ 4 a destabilising effect. Over a lifetime, this may be adequate to explain an individual's risk of developing AD.

Neither neurofibrillary tangles nor amyloid plaques are exclusive to AD. Beta amyloidosis occurs abundantly in the normal, aged human brain, sometimes in similar quantities to that seen in AD brains. Neurofibrillary tangles resulting from the hyperphosphorylation of tau protein are also seen in other tauopathies such as adult Down's syndrome, Pick's disease, frontotemporal dementias, cortical basilar degeneration, progressive supranuclear palsy and pallidopontonigral degeneration. The number of neurones undergoing neurofibrillary degeneration increases with the progression of the disease and correlates with the degree of dementia.

**Inflammatory response** Inflammatory mediators produced in response to the presence of degenerate neurones, neurofibrillary tangles and A $\beta$  plaques include the cytokines interleukin-1 (IL-1), interleukin-6 (IL-6) and tumour necrosis factor- $\alpha$  (TNF- $\alpha$ ). IL-1 is secreted by astrocytes, microglia and brain endothelial cells. Its expression is increased in AD, most markedly by microglia associated with A $\beta$  deposits. It has been shown to stimulate the production of a neurite growth-promoting cytokine, which stimulates neurite sprouting within plaques. IL-1 may also interact with A $\beta$  deposition directly, and has been shown to promote the synthesis and processing of A $\beta$  APP.

IL-6 is barely detectable in the adult central nervous system but is strongly induced in pathological conditions, including AD. Microglia, astrocytes, brain endothelial cells and neurones express IL-6. It possibly modulates APP synthesis by enhancing APP transcription and expression, via a reciprocal regulation loop. IL-6 induces the expression of other inflammatory mediators and recent studies have suggested that polymorphism of the IL-6 gene may protect from AD.

TNF- $\alpha$  is also increased in the serum, CSF and cortex in patients with AD. It is reportedly expressed by microglia and is cytotoxic to human cortical neurones *in vitro*.

Whether these inflammatory cytokines are anti-inflammatory and neuroprotective is debatable. Indeed, they are equally as likely to be destructive to the brain under the chronic inflammatory conditions seen in AD. The cytokine transforming growth factor TGF- $\beta$ , on the other hand, may be protective. It is expressed by neurones, astrocytes and microglia and is regulated in brain injury.

Chemokines may also play a role in attracting astrocytes to their distinct peri-

plaque position. The cyclo-oxygenase, COX-2, is expressed by neurones and is regulated by IL-1, TNF- $\alpha$ , reactive oxygen and nitrogen species. All the components of the classic complement pathway are present in increased quantities in AD brain and are classically associated with A $\beta$  deposits. Hence, a number of studies have clearly demonstrated that a pathophysiologically relevant inflammatory process occurs as a response to A $\beta$  deposition, neurofibrillary tangles and neurodegeneration.<sup>47</sup> The presence of an inflammatory process is supported by epidemiological studies showing that those taking anti-inflammatory drugs are less likely to develop AD.

#### Neurotransmitter and receptor defects

Of the several neurotransmitter system abnormalities identified, the one that is commonly noted is decreased activity of choline acetyltransferase, an enzyme involved in the synthesis of acetylcholine, an important neurotransmitter in learning, memory and attention.

At the receptor level, presynaptic muscarinic (M<sub>2</sub>) acetylcholine receptors are deficient, while cortical postsynaptic muscarinic (M<sub>1</sub>) receptors are normal. In addition, it has been noted that patients with AD have reduction in nicotinic cholinergic receptors both pre- and post-synaptically. Based on these findings, drugs are being developed not only to inhibit acetylcholinesterase, thus increasing the level of acetylcholine, but to potentiate the response of nicotinic receptors to acetylcholine through an activator site on the receptor or through modulation of the receptor activity.

#### SUMMARY

It has been hypothesised that AD is a metabolic disorder of middle to old age which requires either a genetic predisposition, known risk factors such as APP mutations, trisomy 21, head injury, or one or more environmental factors, that affects one or more specific signal transduction pathways, resulting in protein phosphorylation or dephosphorylation, imbalance in the affected neurones and an increased deposition of toxic A $\beta$  in plaques, probably by altering APP metabolism. The product of this is the abnormal hyperphosphorylation of tau that leads to neurofibrillary degeneration, neuronal death and dementia.

Age is the single important predisposing factor for the development of AD. With age, the membrane fluidity is decreased and less resistant to insults that may affect one or more signal transduction pathways.

There is also some evidence that this process may be enhanced by the presence of the pathogenic isoform of apo-E  $\epsilon$ 4, and might be reduced by  $\epsilon$ 2 and possibly  $\epsilon$ 3. The role of the presenilins in this model is uncertain at present.

## DEMENTIA WITH LEWY BODIES

Lewy bodies (LB) are a pathological feature of several neurodegenerative diseases. The major clinical correlate of LB formation in the cerebral cortex is a dementing syndrome which, in the past, has been referred to by various names but the preferred term now in use is dementia with Lewy bodies (DLB).

An outline of the new clinical guidelines for DLB<sup>48</sup> are given below. DLB is characterised by progressive cognitive decline that interferes with normal social or occupational function. Prominent or persistent memory impairment may not occur in the early stages. However, deficits on tests of attention and of frontal-subcortical skills and visuospatial ability may be prominent.

Two of the following core features are essential for a probable diagnosis, one for a possible diagnosis:

- Fluctuating cognition, with variation in attention and alertness
- Recurrent visual hallucinations
- Spontaneous motor features of parkinsonism

Supportive features are:

- Repeated falls
- Syncope
- Transient loss of consciousness
- Neuroleptic sensitivity
- Systemised delusions (restricted to well defined areas of life)
- Hallucinations in other modalities

Diagnosis is less likely if there is:

- Presence of stroke disease
- Evidence of any physical illness or other brain disorder sufficient to account for the clinical presentation

Lewy bodies are neurofilament proteins which have been phosphorylated by protein kinases, as a consequence of which the neurofilaments have become cross-linked, forming insoluble complexes which constitute the dense central core of the classical LB. (See Figure 4.) They also contain ubiquitin, ubiquitin carboxylterminal hydroxylase (PGP9.5), multicatalytic protease (MCP) and alpha  $\beta$ -crystallin, all of which are involved in the elimination of abnormal or damaged proteins within the neurone. Lewy bodies may therefore represent a neuroprotective response.<sup>49,50</sup> They are fundamentally different from neurofibrillary tangles. The latter do not appear to have a cytoprotective potential. Instead, they are probably markers of dysregulation of another major constituent of the cytoskeleton, the microtubules. Lowe has suggested that Lewy body formation represents a cell stress response in neurones which leads to a col-

lapse of the intermediate neurofilament network under the influence of alpha  $\beta$ -crystallin, itself a cell stress protein known to associate with intermediate filaments. Once the neurofilaments have collapsed, they become phosphorylated and truncated by proteolysis. Finally, ubiquitin and enzymes of the ubiquitin system become associated with the LB. This scheme is however speculative and there is no certainty about their precise nature.

In dementia with LB, there is loss of subcortical and cortical neurones which results in specific motor and mental impairments, the most clearly established being a correlation between substantia nigra neurone loss and the severity of extrapyramidal symptoms. Some groups have found a correlation between LB counts in the cerebral cortex and global severity of dementia.<sup>51,52</sup> One problem may be that tests such as the mental test score (MTS) developed for the assessment of mental function in AD may not be appropriate tools for assessing dementia with LB. In DLB there is a predominance of attentional over purely memory deficits, particularly episodic memory.

Secondly, the fluctuating nature of DLB may be related to fluctuations in neurochemical parameters rather than fixed structural changes. Activity of the cholinergic enzyme, choline acetyltransferase, was found to be lower in the neocortex (particularly in the temporal and parietal areas) in DLB compared with AD patients,<sup>53</sup> particularly in hallucinating cases. Nucleus basalis of Meynart neurone numbers were also significantly reduced in hallucinating compared to non-hallucinating DLB cases. An index of 5-hydroxytryptamine turnover (5HIAA:5HT ratio, where 5HIAA is 5 hydroxyindoleacetic acid, a serotonin metabolite) was higher in non-hallucinating cases, and 5-HT<sub>2</sub> receptor binding, which diminishes in AD, was normal in hallucinating DLB cases, suggesting that hallucinations may be related to a neocortical transmitter imbalance based on hypocholinergic and relative hypermonoaminergic function. Clouding of consciousness, confusion and visual hallucinations are recognised side effects of anticholinergic drugs and it is likely that the summative effects of subcortical and cortical

cholinergic dysfunction play a major role in the spontaneous generation of similar symptoms in DLB.

Severe adverse reactions to standard neuroleptic medication are well recognised in this group of people.<sup>54,55</sup> It is probably mediated by a subclinical reduction in substantia nigra neurones, coupled with failure of striatal (putamen) dopaminergic D<sub>2</sub> receptors to upregulate, either in response to substrate depletion or receptor blockade.<sup>56</sup>

## VASCULAR DEMENTIA

Vascular causes of dementia represent 15 to 20 per cent of all causes of dementia.<sup>57</sup> The prevalence of vascular dementia increases linearly with age and varies between countries.<sup>58</sup> Vascular diseases in general are potentially treatable and preventable. This has stimulated interest into the primary pathology of vascular dementia and its possible prevention and treatment.

Epidemiological studies of vascular dementia have been marred by the lack of consensus over definition, diagnostic criteria and assessment procedure. The term "vascular" is a generic one, while "dementia" identifies a person once the pathology has become quite advanced. There is a recognised need to view vascular dementia as a spectrum of disease from the "brain at risk" stage to full blown dementia.<sup>59</sup> It is widely assumed that the risk factors for vascular dementia are the same as for cerebrovascular disease.<sup>60</sup>

Age and race are of considerable importance in the aetiology, possibly through association with other risk factors. The significance of other risk factors such as gender, hypertension, diabetes, cholesterol, smoking, heart disease and atrial fibrillation are less well established.<sup>61</sup> Up to 25 per cent of patients with stroke will develop vascular dementia<sup>62</sup> and this risk seems to be greatest in those with lacunar infarcts. Similarly, a substantial portion of non-degenerative dementia in old age may well represent cerebrovascular disease, and may eventually manifest itself as ischaemic and haemorrhagic stroke. There are a few distinct vascular syndromes, for example, lupus anticoagulant/antiphospholipid antibody syndrome,

which may occur in isolation or as part of an autoimmune condition such as lupus or as a paraneoplastic phenomenon. This condition occurs primarily in younger people and anticoagulation has been proven to be effective. However, little is known of the significance of similar antibodies in the elderly. There is some evidence to suggest that autoantibodies are associated with other vascular pathologies, such as temporal arteritis and polymyalgia rheumatica which are significantly increased in the elderly.

The role of other more commonly recognised risk factors for vascular disease in the development of dementia is less clear. A possible link between "silent cerebral embolism" and cognitive decline was suggested in the European Atrial Fibrillation Trial in 1996.<sup>63</sup> The role of similar silent embolic events from asymptomatic or high-grade carotid stenosis has not been established. However, there is increasing evidence to suggest that secondary prevention measures, such as cholesterol lowering and antiplatelet agents, may delay and even reduce cognitive decline.

In order to identify risk factors more precisely, we need to be able to define the disorder more accurately. Hachinski and Bowler<sup>64</sup> have suggested the use of the term "vascular cognitive impairment", avoiding the use of the term dementia which has for the large part been deemed to be a progressive and untreatable condition, while also acknowledging that dementia may represent one end of a spectrum under this broader term. ICD-10 (WHO 1991) criteria for multi-infarct dementia and AD are similar and place an emphasis on the presence of long tract signs (pyramidal tract or upper motor neurone signs) and focal neurological deficits in their distinction. Presentation of vascular dementia tends to be with slowing of information processing, impaired memory, poor sustained attention, executive dysfunction including poor word list generation, lack of verbal fluency, impaired motor programming, with meaningless repetition

of actions and thoughts, and difficulty with set shifting. Set shifting is an important aspect of attention and regulation of behaviour, and is usually examined using sorting tasks.

In the subcortical vascular dementias, memory loss is characterised by poor retrieval and intact recognition.<sup>65</sup> The pathological lesion in subcortical vascular dementias affects the neurones interconnecting the caudate nucleus, globus pallidus, thalamus and the frontal lobes. Clinical symptomatology is similar to other subcortical diseases with gait problems arising due to disruption of the thalamocorticomedio-capsular pathways.

Unfortunately, we do not have neuropsychological examinations that can effectively screen people at high risk. By the time a problem is detected, the process has probably progressed considerably. CT and MRI scanning identify areas of leucoarosis (changes in cerebral white matter produced by local vascular insufficiencies), but tell us little about the underlying pathology which may be multifactorial: cerebral atrophy, amyloid angiopathy and associated hypertensive arteriopathy. Leucoarosis is also seen in AD and in individuals with no detected cognitive decline.

Cerebral perfusion studies in patients with leucoarosis without dementia have revealed that there is an increase in oxygen extraction, with less of a decrease in cortical perfusion as compared with the demented. Hence, leucoarosis may represent the pre-clinical stage of vascular dementia. The cognitive decline of vascular dementias may not be due to subcortical white matter ischaemia. The subcortical grey nuclei, including the basal ganglia and thalamus, may contribute to the tests of intellect. Single-photon emission computed tomography (SPECT) studies have shown that the most hypoperfused areas of the brain in Binswanger's disease are the thalamic and basal ganglia,<sup>66</sup> suggesting a role in the loss of cognitive abilities. Binswanger's disease is an

ill-defined term with no characteristic pathology and may overlap considerably with the lacunar state, both having similar clinical manifestations.

An important neuroanatomical site where changes in white matter do produce profound cognitive deficits is at the level of the third ventricle in the region of the genu of the internal capsule. These lesions could disrupt the important tracts interconnecting the dorsomedial nuclei of the thalamus, cingulate gyrus, the frontal lobes and the medial temporal lobe regions.

We need to develop neuropsychological tests that can detect cognitive problems at an early stage, and demonstrate both the cortical and subcortical cognitive impairments, such as poor executive function, lack of verbal fluency, reduced attention and decreased motor performance, encountered in the vascular dementias. When these developments have been achieved and are used with functional neuroimaging techniques we will hopefully be able to elicit more information about the pathogenesis of these vascular dementias.

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