

Neuropathology of Dementias

Introduction

Dementia is a problem worldwide, not only for patients but also for carers; it affects some 5% of the elderly population over the age of 65 years¹ and the incidence increases with age. *Clinically*, dementia is defined as a syndrome of progressive cognitive decline to a degree that interferes with work, personal relationships and social functioning in the absence of delirium or major psychiatric disorder. Impairment of memory, language, perception, problem solving ability and personality are all features of dementia.¹ There are different clinical syndromes of dementia that correlate with the pathological features in the brain, although there is often some overlap between syndromes and with normal ageing.² In this account, we outline the general pathology of dementias and then concentrate on Alzheimer's disease to review the pathology, some of its possible causes and how immunotherapy is developing as a new treatment for Alzheimer's disease.

General pathology of dementias

The pathological features of dementias are diffuse and affect multiple areas of the brain, thus cerebral atrophy may be the only change seen macroscopically in the post mortem brain and on MRI. A common feature seen microscopically is the accumulation of insoluble proteins and peptides,³ firstly in the extracellular spaces and in blood vessel walls and secondly within cells. The presence of vascular lesions,⁴ infarcts due to cerebrovascular disease, is a further remarkably common finding. These features are summarised in the table.

Extracellular proteins accumulate in the cerebral cortex and other areas of grey matter, as plaques and in artery and capillary walls as Cerebral Amyloid Angiopathy (CAA). Chief among these proteins is Amyloid- β ($A\beta$) in Alzheimer's disease. $A\beta$ is formed in the brain throughout life by cleavage of a 700 amino acid transmembrane amyloid precursor protein (APP) encoded by a gene on chro-

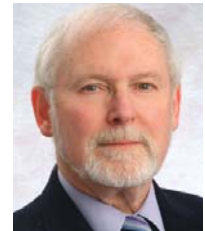
mosome 21.⁵ APP is cleaved by a series of secretases, resulting mainly in the production of a 42 amino acid $A\beta$ ($A\beta$ 1-42) and a more soluble $A\beta$ 1-40. In Alzheimer's disease insoluble $A\beta$ 1-42 is predominantly found in plaques in the cerebral cortex (Figure 1a) and $A\beta$ 1-40 within blood vessel walls (CAA). $A\beta$ and other proteins, such as Cystatin and ABri (in the British type of dementia), accumulate in the brain and in blood vessel walls as CAA⁶ in a range of familial dementias that are associated with genetic mutations. In Creutzfeldt-Jacob disease, insoluble deposits of protease resistance prion protein (PrP) (Figure 1b) accumulate in cerebral and cerebellar grey matter and are associated with spongiform change in neuronal dendrites and with substantial loss of neurons and gliotic scarring.²

The *intracellular proteins* are mainly tau and synuclein; they accumulate as insoluble deposits in neurons (Figure 1c & d) and in their processes (forming dystrophic neurites), and in some cases in glial cells. Both tau and synuclein are associated with ubiquitin which suggests that there is failure of disposal of tau and synuclein through the proteasome system.⁷ Tau has a role in axoplasmic transport and is normally associated with axonal microtubules. The hyperphosphorylated form accumulates with ubiquitin in neurons in dementia, forming the neurofibrillary tangles (NFTs), typical of Alzheimer's disease (Figure 1c). Synuclein is a protein associated with synapses in the brain and accumulates with ubiquitin in spherical Lewy bodies in neurons (Figure 1d), usually in the substantia nigra and in temporal cortex in Dementia with Lewy Bodies.² In Huntington's disease, deposits of the protein huntingtin accumulate within nuclei of neurons and there is selective loss of neurons from the basal ganglia.²

Dementias mostly occur in elderly patients over the age of 65 years, although early-onset familial dementias with mutations in genes encoding tau, APP, synuclein and the presenilins affect people in their 50's.² Age is a major risk



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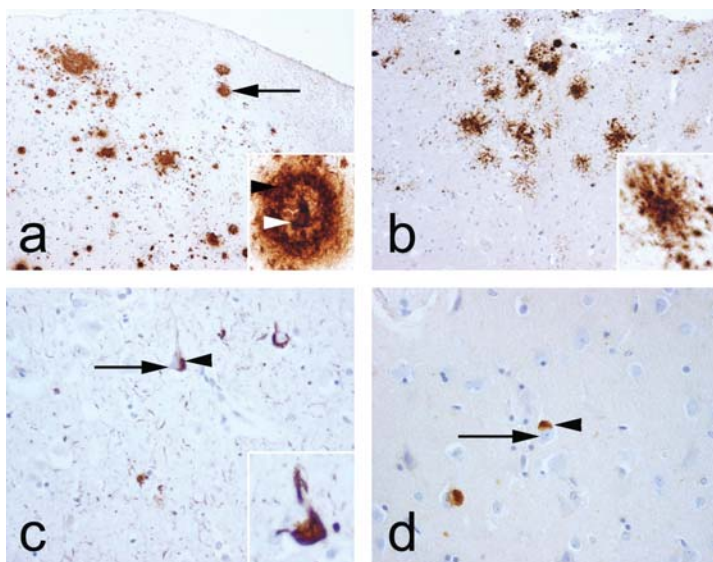


Figure 1. Accumulation of proteins in dementias
a. $A\beta$ immunohistochemistry in the cerebral cortex in a case of AD, magnification x 10. Arrow, a non-neuritic plaque. Insert, a neuritic plaque x 40. White arrow head central core of amyloid, black arrow head surrounding dystrophic neurites.
b. PrP immunohistochemistry in the cerebral cortex in a case of new variant CJD, magnification x 10. Insert, a PrP plaque x 40.
c. Tau immunohistochemistry showing neurofibrillary tangles in the cerebral cortex in a case of AD, magnification x 40. Arrowhead, tangle. Arrow, nucleus of cortical neuron. Insert, an intracytoplasmic neurofibrillary tangle x 80.
d. Synuclein immunohistochemistry showing intracytoplasmic Lewy bodies in the cerebral cortex in a case of DLB, magnification x 40. Arrowhead, Lewy body. Arrow, nucleus of cortical neuron.

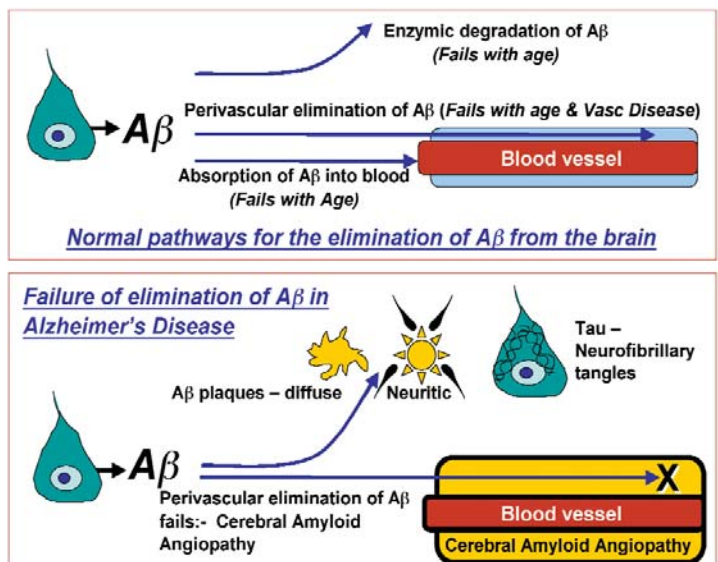


Figure 2. Elimination of $A\beta$ in Normal brains and in Alzheimer's Disease. In normal brain (upper panel), $A\beta$ produced by neurons is eliminated enzymatically, perivascularly and into the blood. All three pathways fail with ageing. In Alzheimer's Disease (lower panel), $A\beta$ accumulates as diffuse plaques (shown by arrow in figure 1a) and neuritic plaques, with a central core of amyloid surrounded by structurally abnormal (dystrophic) neurites (as shown in the insert of figure 1a). Tau also accumulates intracellularly in neurofibrillary tangles (see figure 1c). Cerebral Amyloid Angiopathy develops with accumulation of amyloid around blood vessels.

Table: Pathology of Dementias as characterised by depositions of insoluble peptides and proteins within cells, in the extracellular spaces and blood vessel walls of the brain.

Dementia	Intracellular Deposits in Neurons	Extracellular Deposits	Cerebral Amyloid Angiopathy	Vascular disease - Infarcts
<i>Normal ageing</i>	<i>Tau</i> ↑	<i>Aβ</i> ↑	<i>Aβ</i> ↑	↑
<i>Alzheimer's Disease</i>	<i>Tau</i> ↑↑↑	<i>Aβ</i> ↑↑↑	<i>Aβ</i> ↑↑↑	↑↑
<i>Vascular Dementia</i>				↑↑↑
<i>Dementia with Lewy Bodies</i>	<i>Synuclein</i> ↑↑↑	<i>Aβ</i> ↑↑	<i>Aβ</i> ↑↑	↑
<i>Frontotemporal Dementias</i>	<i>Tau</i> ↑↑↑			↑
<i>Corticobasal Degeneration</i>	<i>Tau</i> ↑↑↑			↑
<i>Multi System Atrophy</i>	<i>Synuclein in glial cells</i> ↑↑↑			↑
<i>Creutzfeldt-Jacob Disease</i>		<i>PrP</i> ↑↑↑	<i>PrP</i> (rare)	↑
<i>Huntington's Disease</i>	<i>Huntingtin (Intranuclear)</i>			↑
<i>Familial Dementias</i>	<i>Tau</i> ↑↑↑ <i>Synuclein</i> ↑↑↑	<i>Aβ; Cystatin; ABri</i> ↑↑↑	<i>Aβ; Cystatin; ABri</i> ↑↑↑	↑

factor for dementias and is also a major risk factor for cerebrovascular disease. Patients with Vascular Dementia show widespread damage in the brain due to cerebrovascular disease with multiple small areas of infarction that may be recognised during life with MRI or by examination of the brain at post mortem.² Such patients often have cardiovascular risk factors such as diabetes and hypertension and may show step-wise progression of cognitive impairment due to the occurrence of new infarcts in the brain. Most patients with Alzheimer's disease also show evidence of cerebrovascular disease so that there is overlap between vascular dementia and Alzheimer's disease both clinically and pathologically.⁸

Pathology of Alzheimer's disease

The classical pathology of Alzheimer's disease was described 100 years ago; intraneuronal neurofibrillary tangles and the extracellular plaques of amyloid were visualised in histological sections stained with silver techniques.² Today, the amyloid plaques of Aβ and the NFT containing tau and ubiquitin are located by immunocytochemistry² (Figures 1a and 1c). The number of extracellular plaques and the distribution of neurofibrillary tangles within neurons of the cerebral cortex and hippocampus are used as criteria to diagnose Alzheimer's disease and to assess its severity.^{9,10} More recently it has been shown that the level of soluble Aβ in the brain and the severity of CAA at post mortem correlate closely with the severity of dementia.^{11,12}

Pathogenesis of Alzheimer's disease

Over 90% of cases of Alzheimer's disease are sporadic with no family history. Three major genes, those encoding APP, presenilin 1 and

presenilin 2, are associated with inherited susceptibility⁵ in the very small number of families with familial Alzheimer's disease. Apart from age, one major risk factor for sporadic Alzheimer's disease is possession of the ε4 isoform of apolipoprotein E (APOE). The 1-2% of the population who are homozygotes for APOE ε4 has an eight to ten fold increased risk of developing Alzheimer's disease and heterozygotes have a two to three fold increased risk.¹³ ApoE co-localises with Aβ in amyloid plaques and in blood vessel walls; it may be involved in the aggregation of Aβ and in its clearance.¹³

The recent use of transgenic mice with mutations for human APP, presenilin and tau genes has illustrated much of the biology of Aβ and tau proteins. Cleavage of APP to form Aβ involves a number of secretases, and the presenilins are also involved in this process. Mutations in these genes result either in the overproduction of the more insoluble Aβ1-42 or in other aberrant forms of Aβ.⁵ Experimental studies using double transgenic mice for mutations in the tau and APP genes¹⁴ suggest that the accumulation of tau in neurofibrillary tangles in neurons may be induced by (and secondary to) the deposition of Aβ in the extracellular spaces of the brain.

Although there may be overproduction of Aβ or aberrant forms of Aβ in familial Alzheimer's disease, there is no clear evidence for this in the much more common sporadic form of Alzheimer's disease. This suggests that failure of elimination of Aβ from the brain may be a major factor in the pathogenesis of Alzheimer's disease rather than its overproduction. One important question, therefore, is "why does the elimination of Aβ fail in the elderly, resulting in Alzheimer's disease?"

Aβ is produced by cells in the brain through-

out life and is eliminated by a number of mechanisms that fail with age. In young animals, and probably in young humans, Aβ is degraded by enzymes such as neprilysin in the brain parenchyma¹⁵ and is absorbed into the blood by binding to a low density lipoprotein receptor related protein-1 (LRP-1);¹⁶ in older individuals these mechanisms for the disposal of Aβ are less efficient and fail.¹⁶ Aβ is also eliminated from the brain with interstitial fluid (ISF) by diffusion through the brain parenchyma and then by bulk flow pathways along the basement membranes of capillary and artery walls, effectively the "lymphatics of the brain"^{17,18} (Figure 2). The motive force for the perivascular drainage of Aβ and ISF appears to be the pulsations in the vessel walls.¹⁹ It is possible that cerebrovascular disease in the elderly interferes with the perivascular elimination of Aβ from the brain (by increased rigidity and hence decreased pulsation), resulting in the accumulation of Aβ in brain tissue and vessel walls that is characteristic of Alzheimer's disease²⁰ (Figure 2).

Therapy for Alzheimer's disease

As failure of elimination of Aβ from the ageing brain appears to be a major factor in the pathogenesis of Alzheimer's disease, therapies that remove Aβ from the brain may be beneficial. Following reports that immunisation against Aβ1-42 eliminated plaques of insoluble Aβ from the brains of transgenic APP mice,²¹ clinical trials were instituted for immunotherapy in Alzheimer's disease. The study of post mortem brains from patients who died following immunisation against Aβ showed not only clearance of insoluble Aβ plaques from cerebral cortex but also showed a reduction in the number of damaged neurites containing tau protein (Figure 2) that sur-

The neuropathology of the majority of dementias is characterised by the accumulation of proteins within cells, within the extracellular spaces and in blood vessel walls indicating failure of elimination of such proteins from the ageing brain

