

Alzheimer's disease: amyloid *b*-peptide antibody vaccine as plaque remover

Alzheimer's disease (AD) is a major cause of dementia. It is believed to affect 11% of all humans over 65 years of age and 50% over the age of 85 in caucasian populations. It is a chronic brain disorder with a lengthy preclinical phase followed by a malignant stage associated with neuronal degeneration, loss of specific synaptic connections and progressive erosion of cognitive ability. AD begins with a subtle failure of memory, slowly becoming more severe and eventually incapacitating the patient. Neuronal degeneration in AD is highly selective for certain brain regions and types of neurons and can lead to a profound atrophy of the cerebral cortex. The amygdala, hippocampus and parahippocampus show a high degree of neurodegeneration, whereas the striatum and cerebellum are less affected. Subcortical pathways involving catecholaminergic, serotonergic and cholinergic transmissions are affected, whereas neocortical interneurons such as GABAergic and inhibitory are relatively unaffected. A subset of pyramidal cells in layers II, III and V that use excitatory amino acids as transmitters are highly vulnerable in AD. The loss of neurons has a variable time course between individuals and it could take months to years for a neuron to degenerate. Neuronal degeneration in AD starts rapidly from the medial temporal lobe and gradually spreads to other neocortical areas (Vickers *et al* 2000).

Clinical symptoms of AD include confusion, poor judgements, language disturbances, agitation, withdrawal, seizures and hallucinations. Death in AD occurs due to general inanition, malnutrition and pneumonia. The typical clinical duration of AD is 8–10 years, with a range of 1–25 years. Currently AD puts an enormous health, social and economical burden on many countries and this situation is likely to worsen with aging of populations world-wide. Clinical diagnosis of AD is based on the observation of slow progression of dementia and gross cerebral cortical atrophy as demonstrated by CT (computerized tomography) or MRI (magnetic resonance imaging). However, this diagnosis is accurate in 80–90% of AD cases only. A definite diagnosis of AD can be made after the death of a patient by finding *b*-amyloid plaques and intraneuronal NFTs (neurofibrillary tangles) in brain slices. The criterion is that the number of plaques and NFTs in brains of AD patients must be more than that found in age-matched controls without dementia.

Linkage of the *APP* (*b*-amyloid precursor protein) gene to a subset of early-onset familial AD (FAD) and the development of AD early in life in Down's syndrome patients suggested a possible role for the *APP* gene in AD pathology. Subsequently, abnormal processing of *b*-amyloid precursor protein was found to be a central event in the pathogenesis of AD. The gene for *APP* is located on chromosome 21q21.3-q22. The gene has 19 exons and encodes a 695–770 amino acids-long precursor protein whose normal function is not known. Normally *APP* is cleaved into two soluble peptides by α -secretase: a large secreted N-terminal fragment, and a smaller C-terminal component. In an alternate proteolytic pathway, the *APP* could also be cleaved to a soluble form of the entire *b*-amyloid peptide through the action of putative *b*- and α -secretases. In the pathological pathway, *APP* is cleaved by *b*- and γ -secretases into an insoluble (generally 42 amino acids-long) *Ab* (amyloid *b*-peptide) of 4 kDa. *Ab* self-aggregate to form insoluble fibrils and deposit as plaques in the brain.

Approximately 75% of known AD cases are sporadic with no family history of the disease. The risk factors involved in the development of sporadic AD cases include age, genetic predisposition, exposure to head trauma, viruses and toxins. The age of onset of sporadic AD is any time in adulthood. Less than 1% of AD cases are associated with Down's syndrome where the age of onset is 40 years and above. Approximately 25% of AD cases are familial (FAD) with an autosomal dominant mode of inheritance. Familial AD could be late-onset, where the age of onset is after 65 years of age, or early-onset, where

the disease manifests before the 65 years. A gene encoding apolipoprotein E (*ApoE*) and located on chromosome 19q13 was found to be involved in the pathogenesis of late-onset FAD (LOFAD). It codes a protein of 299 amino acids that acts as a cholesterol transport protein. It has been suggested that *ApoE* may also act as a chaperone protein for *b*-amyloid promoting the development of insoluble fibrils. *ApoE* has three isoforms (e2, e3 and e4) that differ by 1–2 amino acids. The *ApoE* e4/e4 genotype increases the risk of developing AD whereas the genotype e2/e2 decreases the risk of AD.

Early-onset familial AD (EOFAD), which accounts for less than 5% of FAD, is caused by mutations in three genes, AD1, AD3 and AD4 located on chromosomes 21q21.3-q22, 14q24 and 1q31-q42, respectively. AD1, AD3 and AD4 genes code for *APP*, presenilin 1 (*PS1*) and presenilin 2 (*PS2*) proteins, respectively. The *PS1* and *PS2* genes are highly homologous and encode for 467 and 488 amino acid-long proteins respectively. Mutations in *PS1* and *PS2* increase plasma *b*-amyloid protein and result in excessive brain deposition of *b*-amyloid. Using transgenic *Caenorhabditis elegans*, Wittenburg *et al* (2000) have recently shown that presenilin is required for the maintenance of proper morphology and function of neurons.

Transgenic mice only partially mimic the human disease; amyloid *b*-peptide accumulates in their brain but they show neither the same loss of nerve cells nor the behavioural abnormalities associated with Alzheimer's patients (Heemels 2000). Just like humans, transgenic mice with a mutant human *APP* also develop plaques as they grow older (Heemels 2000). Bard *et al* (2000) have recently reported that peripheral administration of antibodies against amyloid *b*-peptide to mice transgenic for human mutant *APP* gene was sufficient to reduce the amyloid burden. They observed that the passively administered antibodies were able to enter the central nervous system, decorate plaques and induce clearance of preexisting amyloid. In an *ex vivo* assay with sections of transgenic *APP* or Alzheimer's disease brain tissues, antibodies against amyloid *b*-peptide triggered microglial cells to clear plaques via Fc receptor-mediated phagocytosis and subsequent peptide degradation, suggesting that antibodies against amyloid *b*-peptide can cross the blood-brain barrier and act directly in the central nervous system to clear the plaques (Bard *et al* 2000). This has opened the possibility of using amyloid *b*-peptide antibodies as vaccines in clinical trials. The same group has recently announced its initial results from clinical trials showing that amyloid *b*-peptide antibody vaccine is safe and well tolerated by Alzheimer's patients (see Heemels 2000). However, it has to be seen if the vaccine is really effective, improves behavioural abnormalities and halts neuronal degeneration in Alzheimer's patients.

References

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