Are we getting to grips with Alzheimer's disease at last?

Recent statistics from the Alzheimer Research Trust suggest that in the UK alone 820,000 people are affected by dementia with a cost to the economy of £23 billion/year. Similar figures apply to all developed countries and most others are catching up rapidly. With increasing life expectancy, age-related dementia is seen globally as an urgent public health priority.

Histological examination of the brain is still regarded as the gold standard for diagnosis of the specific disease process underlying dementia, the commonest cause of which is Alzheimer’s disease. The main features of Alzheimer’s disease are extracellular accumulation of amyloid β-protein (Aβ) in the form of plaques and in blood vessel walls as cerebral amyloid angiopathy; intraneuronal accumulation of tau protein forming tangles in neuronal cell bodies as well as in neuronal processes situated close to plaques (dystrophic neurites) and elsewhere (neuropil threads); activation of microglia and astrocytes; and neuronal and synaptic loss. However, histological assessment of the disease has several limitations including, almost by definition, observations made at only one time point in the disease, usually the end-stage of a neurodegenerative process that has been developing over many years. This means that using post-mortem neuropathology, we have little or no notion of the dynamics of the pathological processes involved, how they are interrelated in terms of cause and effect, and which feature, if any, best correlates with, or causes, the cognitive dysfunction.

The principal hypothesis for the pathogenesis of Alzheimer’s disease for two decades or more has been built around amyloid, and known as the Aβ cascade hypothesis, which states that Aβ, either in the form of extracellular amyloid plaques or in soluble or oligomeric forms, has the key role in initiation of the disease. A powerful way to test the Aβ hypothesis is to modify this aspect of the pathophysiology and observe any effects on other aspects of the pathology and on brain function.

In this issue of Brain, Serrano-Pozo and colleagues (page 1312) have studied the effects of Aβ immunization on neuronal and tau pathology in Alzheimer’s disease. Active immunization with

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full-length Aβ42 peptide (AN1792, Elan Pharmaceuticals) has been shown to lower Aβ plaque load in the brains of transgenic mouse models (Schenk et al., 1999) and in patients with Alzheimer’s disease (Nicoll et al., 2003; Ferrer et al., 2004; Masliah et al., 2005; Holmes et al., 2008), and also to reduce one aspect of neuronal pathology, specifically, the plaque-associated tau-containing dystrophic neurites (Nicoll et al., 2003, 2006). Here, the authors have performed detailed quantitative studies of neuronal pathology in the hippocampi of five patients with Alzheimer’s disease who were immunized with AN1792 and had evidence of Aβ reduction with fewer and smaller plaques. If there is a direct link between Aβ and neuronal pathology, as predicted by the Aβ hypothesis, then alterations in the neuronal pathology would be expected.

A particularly elegant aspect of this study is quantification of the trajectory, or degree of curvature, of abnormal neuronal processes that were identified by immunostaining for neurofilament. This neurite curvature occurs both in the vicinity of plaques and remote from plaques and is putatively due to a toxic effect of the plaque amyloid and/or soluble/oligomeric Aβ on the local neurons. The results show that neurite curvature is ‘improved’ impressively, both near to and distant from plaques, with curvature ratios in the immunized patients with Alzheimer’s disease close to those seen in non-demented controls. The authors postulate that abnormal neurite curvature in Alzheimer’s disease may disrupt cortical synaptic integration and thereby contribute to the cognitive dysfunction. Interestingly, plaques with dense cores that remained in immunized patients with Alzheimer’s disease had more dystrophic neurites associated with them, possibly because immunotherapy releases more soluble/oligomeric Aβ from the plaques until they are completely ‘dissolved’.

Serrano-Pozo and colleagues also provide evidence that Aβ immunization has some effect on tau in neuronal cell bodies. They identified a lower density of neurons staining with paired helical filament-1 (which labels late stage hyperphosphorylated tau) compared with non-immunized Alzheimer’s disease patients, but no difference in the densities of neurons stained with Alz50 (which identifies early misfolded tau) or thioflavin S (which identifies late stage tangles). The authors interpret this as suggesting that Aβ immunization may have reduced the amount of hyperphosphorylated tau, but not the amount of misfolded tau or β-sheet sheet conformation tau. Prior matching of the immunized and non-immunized Alzheimer’s disease cases for Braak stage, an assessment of the distribution and severity of tangle pathology, could have resulted in an underestimation of these effects. It is also worth noting that by the time the patients were immunized, at the stage of clinically defined mild to moderate Alzheimer’s disease, they are likely to have had fairly advanced hippocampal pathology, reflecting the impairment of memory relatively early in the disease. It follows that whether the differences identified in neuronal pathology are due to ‘improvement’ in the pathology or a slowing of progression of pathology is unclear. The neuronal pathology in the cerebral cortex, the presence of which correlates with global cognitive dysfunction and is required to diagnose Alzheimer’s disease pathologically, was not investigated in this study. Potentially, the benefits of immunization to neurons in the cortex could be even greater if the cortical disease process is less advanced than elsewhere at the time of treatment.

Overall, this new evidence of a clear effect of Aβ immunization on the neuronal pathology in Alzheimer’s disease should provide important encouragement in support of immunotherapy for Alzheimer’s disease. Despite the evidence from post-mortem neuropathological studies that Aβ plaques can be removed by Aβ immunotherapy, now confirmed in vivo by Pittsburgh compound B-PET imaging in patients before and after treatment (Rinne et al., 2010) and this new evidence of an effect on neuronal pathology, the effects on cognitive function are somewhat disappointing thus far. The cognitive function of the patients with Alzheimer’s disease in the study by Serrano-Pozo and colleagues is not statistically assessed. However, data from other sources suggest that the effect of Aβ immunotherapy on the progressive decline in cognitive function seems modest at best (Hock et al., 2003; Bayer et al., 2005; Gilman et al., 2005; Holmes et al., 2008; Vellas et al., 2009). Nevertheless, there are currently many different trials of Aβ immunotherapy in progress using a variety of different active and passive immunization protocols, including some in Phase 3 studies involving several thousand patients with Alzheimer’s disease (Lemere and Masliah, 2010) as well as patients at earlier stages of the disease. Within a few years, we will have a much clearer understanding of whether Aβ immunotherapy will be important for the treatment and prevention of Alzheimer’s disease.

A second study in this issue (McDonald et al., page 1328) focuses on the soluble and oligomeric forms of Aβ rather than Aβ aggregated as amyloid plaques. In vitro studies have shown that Aβ oligomers are functionally neurotoxic, interfering with long-term potentiation. It is also known that synaptic loss occurs diffusely throughout the cortex, rather than only in the vicinity of plaques, consistent with damage caused by a soluble and diffusible substance. However, despite what seems to be a prevailing view in the field of experimental models of Alzheimer’s disease that Aβ oligomers are more important than Aβ plaques, there have been few studies of oligomeric Aβ in human Alzheimer’s disease. This may reflect the technical difficulties involved and the methodology used, which appear to have a major influence on the findings. For example, the authors note that different studies report differences in the concentration of soluble Aβ with a variation of up to three orders of magnitude. To a non-biochemist, the Aβ oligomer field can seem to border at times on the mystical.

In this study, the investigators have used brains from the Medical Research Council Cognitive Function and Ageing Study (CFAS) in which community-based participants are prospectively enrolled during life, untreated by dementia status. Previous reports from CFAS have made the important observation that a third of cognitively intact elderly people have levels of plaque and tangle pathology sufficient for a diagnosis of Alzheimer’s disease by current neuropathological protocols. This finding implies that there must be factors other than, or additional to, the conventional neuropathological features to cause dementia. This approach has the strength that it is possible to correlate the biochemical findings separately with the different features of Alzheimer’s disease pathology and the presence or absence of dementia. The authors focus specifically on the identification of which biochemically distinct forms of Aβ best discriminate among
Alzheimer’s disease, non-Alzheimer’s disease dementia and non-demented individuals. They confirm the finding that soluble Aβ monomer concentration is strongly associated with Alzheimer’s disease. A major new finding is that sodium dodecyl sulphate-stable dimers of Aβ are only detected in brain extracts of cases with both high Alzheimer’s disease pathology and dementia, and therefore seem to be highly specific for Alzheimer’s disease.

More precise refinement of these biochemical methodologies is important not only to the Alzheimer’s disease field in general, but also specifically to the Aβ immunotherapy field. For example, it is not yet understood if Aβ immunization in Alzheimer’s disease lowers soluble/oligomeric Aβ as well as plaque Aβ. Indeed, there is some evidence that, as plaques are removed by Aβ immunotherapy, the concentration of soluble Aβ rises (Patton et al., 2006). If it is specifically these soluble forms of Aβ that are toxic to neurons, then immunotherapy would seem unlikely to be beneficial to neuronal function. Indeed, the observation by Serrano-Pozo and colleagues that there is more neuritic dystrophy associated with the dense-cored plaques that remain in Alzheimer’s disease after immunization provides support for this view. This implies that it may be best to intervene with Aβ immunotherapy much earlier in the Alzheimer’s disease process, preferably before plaques have formed. It seems that the key test of the amyloid/Aβ cascade hypothesis is whether Aβ immunization in healthy cognitively intact individuals can prevent the development of Alzheimer’s disease.

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