ALZHEIMER DISEASE

Anti-amyloid vaccination reduces neurite abnormalities

Anti-amyloid-β (Aβ) active immunization of patients with Alzheimer disease (AD) has been found to have beneficial effects on both neurite morphology and tau pathology, Serrano-Pozo *et al.* report. Their findings indicate that vaccines targeting Aβ can attenuate neuronal alterations associated with AD, in addition to reducing Aβ load in the brain.

AD is the most common form of dementia. Amyloid plaques and neurofibrillary tangles, which are predominantly comprised of Aβ and hyperphosphorylated tau protein, respectively, are considered to be hallmarks of this disease.

Preclinical studies indicate that active immunization with Aβ peptide can remove Aβ deposits in the brain, and that this clearance of Aβ is associated with improvements in cognitive functions. In fact, anti-Aβ immunization of a triple transgenic mouse that develops both amyloid plaques and intraneuronal aggregates of hyperphosphorylated tau—resembling human neurofibrillary tangles—not only successfully cleared plaques, but also improved the neuronal tau pathology.

To establish the effect of vaccination on the neuronal pathology associated with AD, Alberto Serrano-Pozo and colleagues quantified the neuropathology within the hippocampus of five patients with AD who had previously received anti-Aβ active immunization. Immunohistological studies revealed that the hippocampal amyloid burden was substantially reduced in immunized patients compared with non-immunized patients. Moreover, by calculating the neurite curvature ratio—a measure of neurite abnormality—the researchers showed that hippocampal neurites were more abnormal in the non-immunized AD group than in the immunized group. "Remarkably, this parameter was significantly improved in the immunized AD group compared to the non-immunized group; indeed, the values obtained from the immunized group were not significantly different from those obtained in the non-demented group," says Serrano-Pozo.

The beneficial effects of vaccination on hippocampal neurites were also associated with a marked reduction in tau phosphorylation, indicating that immunotherapies that target the removal of amyloid plaques might also attenuate the hyperphosphorylation of tau.

Vaccination was not associated with a robust reduction in cognitive decline in the immunized patients—all of whom had mild to moderate AD at enrollment in the trial—indicating that the morphological changes were not sufficient to improve their clinical symptoms. "It is conceivable that immunization at an earlier stage of the disease would have had a larger effect on these neuropathological measures within the hippocampus and, perhaps, even on the rate of memory decline," suggests Serrano-Pozo.

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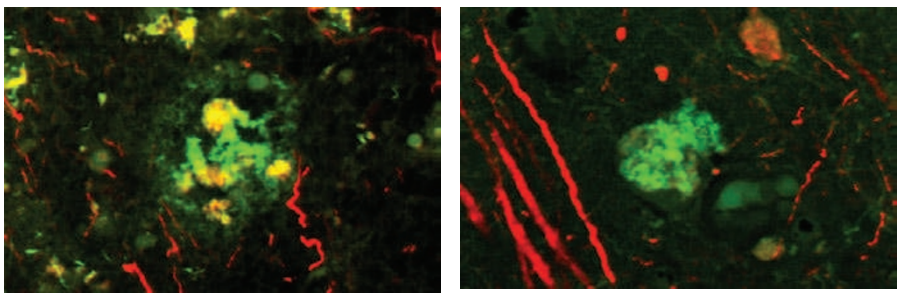

The tortuosity of neurites (red) surrounding amyloid plaques (green) is greater in non-immunized patients with AD (left) than in immunized patients (right). Image provided by Dr Alberto Serrano-Pozo.

Original article Serrano-Pozo, A. *et al*. Beneficial effect of human anti-amyloid-β active immunization on neurite morphology and tau pathology. *Brain* **133**, 1312–1327 (2010)