Is Chlamydia associated with Alzheimer's?

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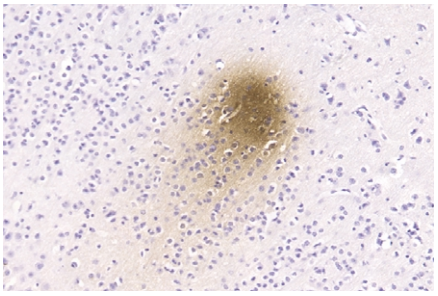
Recently published research [1] has shown a link between the common respiratory intracellular bacteria *Chlyamidia pneumoniae*, which infects as many as 70% of the world's population, and the amyloid plaques found in the brains of people who have sporadic, non-hereditary Alzheimer's disease (AD). The incentive to find out the mechanism of AD and how to treat it has increased because people are now living longer and its prevalence is rising. Changes in the brain that accompany AD memory loss are being disentangled; however, the underlying cause remains a mystery. 'As we have not yet identified what causes the majority of AD cases … insight into infectious risk or causation is highly significant.' says Brian Balin, lead researcher on the recent study.

Internal or external?

There are two distinct forms of AD: familial and sporadic. The defining neuropathology of both forms includes neuritic senile plaques (consisting primarily of amyloid β protein) and neurofibrillary tangles (the major component being modified *tau* protein). Whereas the familial form is due to genetic mutations at several loci, those individuals who succumb to sporadic AD, accounting for the vast majority of cases, do not possess mutations in these genes. Although risk factors have been identified, the early initiating events leading to disease development have not been identified.

Most research has focussed on the assumption that the cause is internal, that is, genetic or the side effect of the general wear and tear accompanying aging. However, infection has been implicated as a potential trigger in the initiation of sporadic AD because



An amyloid plaque formed in a normal mouse brain four months post-intranasal infection with *Chlamydia pneumoniae*, obtained following culture from an Alzheimer's disease brain. Image courtesy of Brian J. Balin, Philadelphia College of Osteopathic Medicine (http://www.pcom.edu)

infectious agents, such as *C. pneumoniae* and herpes simplex virus-1, have been associated with AD. Earlier research by a group at Philadelphia College of Osteopathic Medicine's Center for the Study of Chronic Diseases of Aging (http://www.pcom.edu/) found *C. pneumoniae* within 90% of AD brains, and in areas of the brain exhibiting AD pathology (only one non-AD brain had the bacteria). Although attempts to replicate this observation have met with mixed results, this raised the controversial possibility that AD is sometimes caused by an infection.

Infection and AD pathogenesis

The same group have now intranasally infected non-transgenic BALB/c mice with *C. pneumoniae*. They found amyloid β deposits in their brains up to three months post-infection, with the density, size and number of deposits increasing as the infection progressed, showing that in animals with no genetic modifications, infection with *C. pneumoniae* alone is sufficient to induce AD-like pathology and might be a trigger in AD pathology. This research could provide a useful model for furthering our understanding of mechanisms, linked to infection, that are involved in the initiation of sporadic AD pathogenesis.

Balin says: 'It is very difficult to pinpoint an infectious cause for a progressive, chronic disease. We also believe that our isolation of *C. pneumoniae* from the human Alzheimer's diseased brain and induction of pathology in normal mice is proof of principle that this can be a causative mechanism on pathology'. If he is right, the implications could be huge.

Doubts

Ashley Bush, Director and Associate Professor at the Genetics and Aging Research Unit at Harvard, MA, USA (http://neuro-www.mgh.harvard.edu/) has doubts, however: 'I am concerned that this is an uncorroborated elevation in amyloid …The rodent brain is notorious for developing deposits that mimic plaques, but do not withstand closer scrutiny. It is not surprising that an infected brain develops some non-specific changes, and even some elevated production of amyloid (which is a normal protein). I await more confirmation.'

Balin and co-lead researcher Denah Appelt are already looking further ahead, towards setting up clinical trials in patients with late-onset AD to investigate the effect of typical antibiotics used for treating *C. pneumoniae* infections. Their feeling is, however, that a combined approach of antibiotics and anti-inflammatory drugs might be the most realistic approach and could be instrumental in treating AD.

Reference

1 Little, C.S. *et al.* (2004) *Chlamydia pneumoniae* induces Alzheimer-like amyloid plaques in brains of BALB/c mice. *Neurobiol. Aging* 25, 419–429

1359-6446/04/$ – see front matter PII: S1359-6446(04)03123-X