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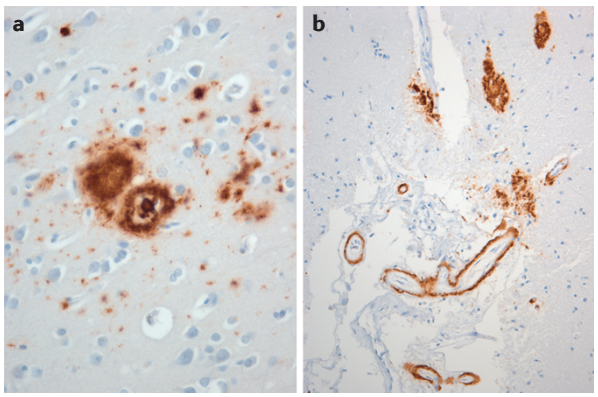
PRION DISEASE

Aβ pathology in human growth hormone recipients

> "the Aβ pathology … was not accompanied by other neuropathological hallmarks of AD"

The use of human pituitary-derived growth hormone (hGH) injections to treat growth hormone deficiency in young people has been linked to a number of cases of iatrogenic Creutzfeldt–Jakob disease (iCJD) over the past three decades. A new study published in *Acta Neuropathologica* has found evidence that in addition to the infectious prion proteins that cause CJD, the Alzheimer disease (AD)-associated peptide amyloid-β (Aβ) can be propagated iatrogenically via hGH injections.

Although the use of hGH extracted from human cadavers was outlawed by many countries in the 1980s, cases of hGH-iCJD are still coming to light owing to the long incubation period of the disease. "The first hGH recipient in the UK to develop iCJD was reported in 1985," says lead author Diane Ritchie, who is based at the National CJD Research & Surveillance Unit, University of Edinburgh, UK. "Since then, 78 cases have occurred — the most recent in 2016 — with incubation periods of over 30 years."



Cored and diffuse Aβ plaques in the brain of a patient with hGH-iCJD (**a**), and cerebral amyloid angiopathy and diffuse Aβ plaques in the brain of an hGH recipient who did not develop iCJD (**b**). Image courtesy of D. L. Ritchie.

Ritchie and colleagues used immunohistochemistry to examine post-mortem brain tissue samples from 33 individuals with hGH-iCJD, and 12 hGH recipients who had died from other causes. Parenchymal and/or perivascular Aβ deposits were observed in the brains of 18 of the patients with hGH-iCJD and five of the other hGH recipients.

This study provides the first definitive evidence that Aβ can accumulate independently of prion infection in the brains of hGH-treated individuals. "The use of non-CJD hGH recipients as controls is unique, and addresses criticisms of earlier studies that Aβ accumulation in hGH-iCJD may represent a secondary phenomenon to abnormal prion protein accumulation," points out co-author Mark Head.

The researchers noted that the Aβ pathology in their study cohort was not accompanied by other neuropathological hallmarks of AD, such as neurofibrillary tangles. Also, the patients were relatively young and had no apparent genetic predisposition to AD. These observations reinforce the idea that the Aβ 'seeds' were introduced externally by the hGH injections.

"Although there is no epidemiological evidence to suggest that AD is transmissible, our findings indicate that Aβ can spread through the human body, seed in the brain, and accumulate to form amyloid plaques," states co-author James Ironside. "Further studies of situations where Aβ might be inadvertently introduced into the body — for example, by neurosurgical instruments or blood transfusion — may help to clarify the potential for Aβ to spread from person to person and result in brain pathology."

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ORIGINAL ARTICLE Ritchie, D. L. *et al.* Amyloid-β accumulation in the CNS in human growth hormone recipients in the UK. *Acta Neuropathol.* http://dx.doi.org/10.1007/s00401-017-1703-0 (2017)

FURTHER READING Ritchie, D. L. *et al.* UK iatrogenic Creutzfeldt–Jakob disease: investigating human prion transmission across genotypic barriers using human tissue-based and molecular approaches. *Acta Neuropathol.* **133**, 579–595 (2017)