Editorial

New evidence suggests link between prion disease and alzheimer's disease

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Among many neurodegenerative diseases, two have always attracted much attention: prion disease and Alzheimer's disease (AD). Prion disease is named by its unique infectious agent, prion protein (PrP), a mis-folded protein with the ability to transmit its conformation to normally folded counterpart proteins thus to self-propagate. Creutzfeldt-Jakob disease (CJD) is the major form of human prion disease. Most of CJD cases are caused by genetic mutations:[1] sporadic CJD (sCJD) as the result of somatic mutation and familial CJD (fCJD) as the result of an autosomal dominant germline mutation. Some CJD cases are acquired, including iatrogenic CJD (iCJD) resulted from prion-contaminated medical treatments such as transplantations of dura matter and human growth hormone derived from human cadavers (c-hGH),[2] recently emerging variant CJD (vCJD) with bovine prion (from mad cow disease) as a suspected cause, and Kuru among the Fore tribe of Papua New Guinea via funerary cannibalism. The accumulation of the abnormal PrP causes neuronal death and microscopic holes in the brain and gives the brain a sponge-like appearance, therefore CJD is categorized as a type of transmissible spongiform encephalopathy (TSE).[3] Eventually, CJD causes deterioration of cognitive, mental, and physical abilities. There is no treatment available to date and the mean survival time is only 5-14months after the onset of the illness.[4] On the other hand, Alzheimer's disease is the most prevalent cause of dementia in the world's aging populations.[5] The hallmark of AD pathology is the accumulation of protein aggregates, called plaques, of abnormally folded amyloid-beta (Aβ) in the extracellular space and intracellular aggregated fibrillary tangles of phosphorylated tau protein. Tau pathology occurs after Aβ plaques thus is postulated as induced by Aβ plaques.[6] The major risk factors of AD include age, apolipoprotein E ε4 (APOE) gene (over 60% of AD patients have at least one allele), and sex (60% of AD patients are female).[7]

Recently, three studies showed some connections between the pathologies of the two diseases. Published in September 2015, Jaunmuktane et al.[8] performed a brain autopsy study with histology and immunoblotting on eight iCJD patients, who received prion-contaminated c-hGH treatment between 1958 and 1985 and deceased in the 20-64 age range with incubation periods of 18.8-30.8years after the last treatment. Surprisingly, in addition to and at locations different from the presence of PrP, in seven of the eight patients, various levels of Aβ deposits were found in the gray matter of the brain as well as in the blood vessel walls. Next-generation sequencing showed none of them carried APOE; only three carried few possible risk factors but non-causal mutations related to AD, thus genetic causes were ruled out. They compared the Aβ load in this iCJD group with data from other autopsy studies obtained from patients with other prion diseases and found only the iCJD group exhibited the Aβ load at such young ages. Following these findings, another study[9] published in January 2016 confirmed the results. Using immunocytochemistry, Frontzek et al.[9] detected Aβ plaques in the brain gray matter and meningeal vessels in five of seven iCJD patients, who received prion-contaminated dural

He Liu
Department of Biology, Gannon University, USA

Correspondence: He Liu, Department of Biology, Morosky College of Health Professions and Sciences, Gannon University, Erie, PA, USA, Tel 8148717871, Email liu017@gannon.edu

grafting. The frequency of Aβ seen in these iCJD cases is significantly higher than the frequency in age-matched sCJD cases.

Two alternative but non-exclusive hypotheses may explain the observations. First, as the authors proposed, the Aβ "seeds" may have been transmitted to the iCJD patients in parallel to the prion contamination by the same c-hGH treatments. Jaunmuktane et al.[8] also observed frequent presence of Aβ in the pituitary glands of patients with cerebral Aβ pathology, as 7 out of 49 examined pituitary samples contained Aβ. There are also numerous experiments conducted with animal models to support this hypothesis, as Aβ seeds can transmit within the body after injected.[10–18]

However, these lines of evidence still cannot rule out an alternative hypothesis that the prion incubation induced the mis-folding and accumulation of Aβ de novo. Another report,[19] published in September 2015 by Tousseyn et al.[19] supports this hypothesis by the discovery of AD-like changes in sCJD patients. Human brain aggregates (BrnAggs) prepared from 16-week fetal brain tissues, which did not contain extracellular Aβ plaques, were exposed to the thalamus homogenate from a sCJD patient for 35days. In addition to the presence of PrP, the BrnAggs also showed a higher level of Aβ and an overwhelmingly large amount of phosphorylated tau, both of which were not seen in the control BrnAggs exposed to normal brain homogenate. The authors also observed that 17% of 266 prion disease cases showed extracellular Aβ plaques, although no control data in the general population with same ages was included for comparison.

The three recent reports raised more questions about the pathology of the two diseases. Was the c-hGH contaminated with Aβ, and the injected Aβ seeds stayed dormant in the recipients but eventually self-propagated in the central nervous system? Or do prion diseases such as sCJD have the nature to induce Aβ plaques? Maybe both are true. As the authors pointed out, the answers probably do not matter to the prion disease patients as most prion disease patients die within a year of disease onset. However, additional caution should be taken when human proteins are transferred between individuals such as blood transfusion. Or even the clinical sterilization methods need to be re-examined as Aβ resists formalin and a commonly used disinfectant per acetic acid.[20,21] More mechanistic studies on the apparent links between the two diseases may provide more insight of the pathology of AD, and hopefully some clues for the prevention of AD in the aging global population.

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