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RESEARCH HIGHLIGHT

Is Alzheimer's Disease Transmissible in Humans?

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Alzheimer's disease (AD), the most common type of dementia, has been identified as a protein misfolding disease with the accumulation of abnormally folded amyloid-β (Aβ) protein and hyperphosphorylated tau protein in the brain [1, 2]. Aβ is known to play a crucial role in the pathogenesis of AD. Deposition of Aβ protein in the brain parenchyma causing senile plaques is the obligatory event in AD pathogenesis. Aβ protein is also deposited in the media and adventitia of small and mid-sized cerebral arteries leading to cerebral amyloid angiopathy (CAA), which is also present in the large majority of AD patents. Creutzfeldt-Jakob disease (CJD) is a typical misfolded protein disease that can spread through blood transfusions or meat products contaminated with prion proteins. AD shares some characteristics with prion diseases, considering that Aβ is prone to misfold and seed the aggregation like prions. It has been suggested that Aβ is transmissible within the brains of AD patient. This raises the critical question of whether AD is also transmissible from person to person. Three years ago, researchers led by John Collinge and Sebastian Brandner found that abundant Aβ deposition was present in the brain parenchyma and blood vessels of patients who died of iatrogenic CJD (iCJD) following childhood treatment with human cadaveric pituitary-derived growth hormone (c-hGH) that contained both prions and Aβ [3], suggesting the possibility that Aβ seeds could propagate from one person to another.

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Recently, a report by John Collinge *et al.* published in *Nature* further revealed that injection of c-hGH containing Aβ seeds as well as prions was able to accelerate Aβ plaques and CAA in a transgenic mouse model of AD [4]. In this study, researchers gave a biochemical analysis of the c-hGH received by adolescents with short stature who developed iCJD later, and found that $A\beta_{X\text{-}40}$, $A\beta_{X\text{-}42}$, and tau protein was present in almost all c-hGH vials. Then they determined the seeding activity of c-hGH in homozygous amyloid precursor protein NL-F knock-in ($APP^{NL\text{-}F/NL\text{-}F}$) mice. First, they showed the time course of CAA and Aβ deposition in $APP^{NL\text{-}F/NL\text{-}F}$ mice induced by intracerebral injection of brain homogenates from autopsy-confirmed AD cases. After inoculation with brain homogenates from AD patients, normal controls, or phosphate-buffered saline (PBS) into $APP^{NL\text{-}F/NL\text{-}F}$ mice at 6–8 weeks of age, amounts of CAA as well as brain parenchymal plaques appeared in AD-brain-inoculated mice 240 days after infection, while PBS- and normal-brain-inoculated mice had almost no CAA but parenchymal Aβ deposits that was remarkable fewer than those in AD-brain-inoculated mice. Histological evaluation 360 days after injection showed that CAA was present only in some dorsal meningeal blood vessels over the cerebral cortex of PBS- and normal-brain-inoculated mice, while it was detected in almost all the meningeal blood vessels of AD-brain-inoculated mice. Next, they intracerebrally injected c-hGH and recombinant hGH (rec-hGH) into $APP^{NL\text{-}F/NL\text{-}F}$ and wild-type mice at 6–8 weeks of age and culled them after 240 days for analysis. No CAA and Aβ plaques were found in wild-type mice. And the CAA and Aβ deposits were similar in PBS-, normal-brain-, and rec-hGH-inoculated $APP^{NL\text{-}F/NL\text{-}F}$ mice, demonstrating that growth hormone itself is not capable of inducing Aβ deposition. However, the CAA and Aβ deposits were evident in the $APP^{NL\text{-}F/NL\text{-}F}$ mice injected

with c-hGH, but the amounts were less than in AD-brain-inoculated mice. This study indicates that the Aβ seeding activity can last for decades, and provides new evidence on the transmission of Aβ pathology between persons.

However, the mechanisms underlying the prion-like activity of Aβ seeds, and why there is a long incubation period after infection with Aβ is not clear. Although histopathological staining showed that prions did not co-localize with Aβ deposits in the brains of iCJD cases, we cannot exclude the possibility that prions somehow interact and seed Aβ aggregation. Evidence from injection of c-hGH from pure AD patients (without iCJD) is needed to answer this question. Neurofibrillary tangles consisting of hyperphosphorylated tau are also histopathological hallmarks of AD [5]. Although c-hGH contained tau proteins, none of the iCJD cases with Aβ pathology had neurofibrillary tangle pathology. Whether there is no transmission of tau or the tau transmission takes much longer to appear needs further study.

Growing evidence from experimental animal models has implicated the propagation and spread of Aβ proteins in the pathogenesis of AD. In a transgenic mouse model of AD, brain Aβ plaques and CAA can be prematurely induced by intracerebral injection of Aβ-rich brain homogenates from AD patients or aged transgenic AD mice, suggesting a prion-like activity of Aβ [6, 7]. It seems that the expression of human Aβ by the transgenic host is necessary for triggering cerebral amyloidosis by exogenous Aβ [8]. And the exogenous induction of Aβ deposition is dependent on the timing and the Aβ concentration of brain homogenates [7]. These animal studies raise the possibility that Aβ aggregates may be transmissible and behave like prions. The aforementioned two reports of John Collinge and Sebastian Brandner's team published in *Nature* demonstrates that human cadaveric pituitary-derived growth hormone containing Aβ contaminants has seeding properties, and confirms that Aβ aggregates from one brain can seed the prion-like spread of Aβ in another.

As prion diseases like CJD can spread *via* blood products and surgical equipment, whether AD could be transmissible in humans has become an important public health issue. A retrospective study reviewed the health records of 1,465,845 patients to assess whether those who received blood transfusions eventually developed neurodegenerative disorders the same as those the donors later suffered from, and found no evidence of an increased risk of AD due to blood transfusion [9]. It has been reported that the CAA and brain parenchymal Aβ plaques are more frequent in iCJD cases after dural grafting than in sporadic CJD [10]. So human dura mater grafts are also able to induce cerebral amyloidosis decades later. This raises the possibility that contaminated surgical equipment in neurosurgery may contribute to the induction of Aβ pathology. So far, no valid evidence indicates that AD is capable of spreading *via* blood transfusions or surgical equipment.

It has been shown that brain Aβ plaques and CAA can be prematurely induced in a transgenic mouse model of AD after intraperitoneal inoculation with Aβ-rich brain homogenates from AD patients or aged transgenic AD mice [11, 12], suggesting that peripheral Aβ seeds can also exacerbate disease pathogenesis. It seems that cerebral amyloidosis can only be induced in AD transgenic mice expressing mutant human APP but not in wild-type mice. However, in our recent study, using a model of parabiosis between AD model transgenic mice and wild-type mice, we found that circulating Aβ was able to enter the brain and cause cerebral amyloidosis and neurodegeneration in the wild-type mice [13], revealing that blood Aβ also contributes to brain AD pathophysiology. This study provides novel insight into the understanding of AD pathogenesis and implies that AD can also start from the periphery, not just the brain.

In conclusion, Aβ aggregates may be transmissible in a prion-like infectious manner between persons. However, none of the iCJD patients with Aβ pathology manifested clinical symptoms of AD. Perhaps they may have developed AD symptoms if they had lived longer. Further studies are needed to establish whether Aβ seeds are indeed able to induce the pathological and clinical manifestations of AD. And whether AD can be transmitted by other routes should also be determined.

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Conflict of interest The authors declare no financial or other conflicts of interests.

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