Can Creutzfeldt-Jakob disease unravel the mysteries of Alzheimer?

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ABSTRACT. Recent studies on iatrogenic Creutzfeldt-Jakob disease (CJD) raised concerns that one of the hallmark lesions of Alzheimer disease (AD), amyloid-β (Aβ), may be transmitted from human-to-human. The neuropathology of AD-related lesions is complex. Therefore, many aspects need to be considered in deciding on this issue. Observations of recent studies can be summarized as follows: 1) The frequency of iatrogenic CJD cases with parencyhmal and vascular Aβ deposits is statistically higher than expected; 2) The morphology and distribution of Aβ deposition may show distinct features; 3) The pituitary and the dura mater themselves may serve as potential sources of Aβ seeds; 4) Cadaveric dura mater from 2 examined cases shows Aβ deposition; and 5) There is a lack of evidence that the clinical phenotype of AD appears following the application of cadaveric pituitary hormone or dura mater transplantation. These studies support the notion that neurodegenerative diseases have common features regarding propagation of disease-associated proteins as seeds. However, until further evidence emerges, prions of transmissible spongiform encephalopathies are the only neurodegenerative disease-related proteins proven to propagate clinicopathological phenotypes.

KEYWORDS. Alzheimer disease, Amyloid-β, dura mater, iatrogenic Creutzfeldt-Jakob disease, pituitary, prion

INTRODUCTION

Creutzfedt-Jakob disease (CJD) is a human prion disease characterized by progressive loss of neurons together with spongiform change of the neuropil and deposition of disease-associated prion protein (PrP$^{\text{Sc}}$), the abnormal conformer of the physiological cellular prion protein. Although very rare, CJD has been in the center of scientific interest due to the fact that it is transmissible even between humans. However, the majority of

CJD cases are sporadic. Less frequently, mutations in the prion protein gene (*PRNP*) cause prion disease. Very rarely medical interventions, such as application of cadaveric pituitary hormones or transplantation of cadaveric dura mater, lead to the development of iatrogenic CJD.[1]

Other neurodegenerative diseases, such as Alzheimer disease (AD) and Parkinson disease, are more frequent than CJD. Like PrP, most of the neurodegenerative conditions are characterized also by the deposition of physicochemically modified disease-related proteins, such as amyloid-β (Aβ), α-synuclein, tau or TAR-DNA-binding protein 43 kDa (TDP-43).[2] The concept of protein-based classification of neurodegenerative diseases is widely accepted.[2] It seems that misfolding of endogenous proteins can lead to proteinaceous seeds, which can serve as self-propagating agents associated with the progression of the specific disease.[3] Experimental models and studies on humans revealed that cell–to-cell transmission of disease-associated proteins may lead to sequential dissemination of pathological protein aggregates[4] reminiscent of that reported by Fraser in 1982 for the scrapie agent in the retino-tectal pathway.[5]

Aβ and tau deposition is characteristic for AD but can be found in a wide range of disorders; furthermore, genetic predisposing factors, such as the ε4 allele of Apolipoprotein E (*APOE*), influence disease risk. The presence of Aβ and tau pathology is not unusual in sporadic and genetic CJD brains.[6-8] Accordingly, is the increased attention on reports on the detection of Aβ deposition in iatrogenic CJD warranted?

Neuropathology of Alzheimer Disease

AD is characterized by the intraneuronal deposition of pathological tau in the form of neurofibrillary tangles (NFTs) and neuropil threads and extracellular accumulation of Aβ in the form of Aβ plaques.[9] Both are needed to be detected simultaneously to allow definite diagnosis of AD.[10] Neuronal tau pathology can be detected from early adulthood, particularly in the brainstem.[11] Based on imaging and cerebrospinal fluid biomarkers of Aβ, the concept of preclinical AD has been proposed.[12] Indeed, Aβ plaques can be detected in cognitively normal individuals from 30 y of age,[11] particularly associated with the ε4 allele of the *APOE* gene.[13] In young patients with widespread Aβ pathology, mutations in the amyloid precursor protein gene (*APP*) and presenilin (*PSEN*) 1 and 2 must be also excluded.[14] Furthermore, Aβ can deposit in the cerebral blood vessels in the form of cerebral amyloid angiopathy (CAA), which can associate with AD but can also be seen independent of AD.[15]

Development of protein depositions composed of pathological tau and Aβ has 2 aspects. First, the deposit itself undergoes "maturation;" second, the anatomical distribution shows sequential involvement of different regions. The intracellular development of tau pathology starts from fine granular deposition of hyperphosphorylated tau in the form of pretangles, which become ubiquitinated and argyrophilic when showing the classic morphology of NFTs.[16] Extracellular Aβ deposits also show different morphologies.[9] Fine granular perineuronal and diffuse deposits are the earliest lesions. These are not detectable with thioflavin S and Congo red staining. Furthermore, focal deposits can be distinguished, which may be associated or not to a neuritic corona. A subset of focal deposits may be detected only by immunohistochemistry for Aβ while further ones are additionally congophilic and thioflavine S-positive. Dystrophic neurites are important components of a subset of plaques. Although rare tau positive dots and thin neurites appear already in some diffuse deposits, degenerating neurites are visible in the corona of focal deposits called mature senile plaques.[17] These plaques can be grouped based on the presence or lack of chromogranin A, synaptic markers, amyloid precursor protein, ubiquitin, and tau immunoreactivity in the dystrophic component.[9,18-20] Tau-positive dystrophic neurites mostly appear to be associated with plaques only in so far as NFTs appear in those regions where the plaque forms.[20] The whole spectrum of these tau and Aβ immunoreactivities are seen in typical AD cases.

The anatomical distribution of tau and Aβ deposits show distinct patterns in early stages (tau) and phases (Aβ). Later these pathologies converge and affect the same anatomical regions. Neuronal tau pathology first involves specific brainstem nuclei and later proceed to involve limbic and neocortical areas.[11,21] Aβ plaques appear first in neocortical areas and later the hippocampus, subcortical nuclei, brainstem and cerebellum become sequentially involved.[22]

Aβ and Tau in Sporadic and Genetic CJD

Tau and Aβ deposition is not rare in sporadic and genetic CJD. One aspect needs to be emphasized: phospho-tau-positive small neuritic dots (1–3 μm; smaller than the tau-positive dystrophic neurites around Aβ plaques in AD) are seen in nearly all cases of sporadic and genetic CJD.[6,23] These might be triggered by PrP itself,[23] or simply reflect the degeneration of neurons with consequently damaged neurites.[6] In the following sections on CJD, the term tau pathology will be used to refer to all morphological types of neuronal or glial tau immunoreactivities except these tau-positive neuritic dots.

Tau-positive NFTs and Aβ plaques in CJD is indicative of concomitant AD; the frequency is not high.[6,7] The morphology of Aβ plaques is similar to AD or that seen in cognitively normal individuals.[9,13, 23] The anatomical involvement follows the stages and phases seen in AD [21,22] irrespective of the distribution of PrP deposits. This argues against cross-seeding of disease-associated PrP and Aβ in human brains. CAA is not seen frequently in sporadic CJD. In certain forms of genetic CJD (e.g., E200K mutation), even in younger patients (<55 years), Aβ deposition similar to that seen in AD has been reported.[8,24] Importantly, neuronal and glial tau pathology without Aβ deposition is more frequent in sporadic CJD than Aβ deposition alone or with NFTs.[6] In addition, widespread tau pathologies (neuronal and glial) have been reported in genetic but also in sporadic CJD cases.[6,8]

Based on these observations, it is difficult to determine whether human-to-human transmission of AD-related pathology occurred in association with the iatrogenic transmission of CJD. Thus, in addition to employing statistical approaches on the frequency of AD-related pathology, the cadaveric tissue must be examined, distinctive morphological features of brain pathology must be sought and genetic or other predisposing factors have to be excluded, to allow for a more definitive conclusion.

Aβ and Tau in Iatrogenic CJD

There are 4 published studies reporting the examination of AD-related pathologies in iatrogenic CJD cases (summarized in Table 1). The first study reported an increased frequency of parenchymal and vascular Aβ in relatively young iatrogenic CJD cases treated with cadaveric growth hormone (GH) as compared to genetic and sporadic CJD cases.[25] This study excluded possible genetic predisposing factors and emphasized the lack of tau positive NFTs. Although the study demonstrated a higher load of parenchymal Aβ deposition and CAA in iatrogenic CJD, it did not comment on potentially distinctive morphological features of Aβ pathology in the iatrogenic CJD cases. Finally, the study did not have the opportunity to examine cadaveric samples for the presence of Aβ; however, it did confirm previous observations that the pituitary itself can exhibit Aβ deposits.[25,26]

The second study focused on iatrogenic CJD cases following dura mater transplantation.[27] It compared the frequency of Aβ deposition in iatrogenic CJD and sporadic CJD and reported that CAA and brain parenchymal Aβ plaques are more frequent in iatrogenic than sporadic CJD. No conspicuous tau pathology could be observed in iatrogenic CJD cases.[27] This study provided further evidence that Aβ deposits can be potentially transmitted from human-to-human.

However, there were still missing pieces to the puzzle. Indeed, there was a lack of literature data whether Aβ can deposit in the dura mater at all; hence, to be able to act as a

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TABLE 1. Comparison of studies on iatrogenic Creutzfeldt-Jakob disease (iCJD) and Aβ deposition. AD: Alzheimer disease; GH: growth hormone; NA: not addressed in the study; Nr: number. * Indicates that these cases were included in Study 2 also.

Study	Study 1	Study 2	Study 3	Study 4
Type of iCJD	Pituitary-derived GH	Dura mater	Dura mater	Dura mater
Number of iCJD cases examined	8	7	2*	16
Nr. of iCJD with parenchymal Aβ deposits	4 + 2 focal	5	2*	13
Distinct morphology or distribution of parenchymal Aβ	NA	NA	Yes	Subpial accumulation emphasized. Morphology of parenchymal plaques not commented.
Nr. of iCJD with CAA	3 + 1 focal	5	2*	11
Cadaveric tissue examined	No	No	Yes	No
Non-cadaveric tissue examined	Yes: pituitary (55 samples)	No	Yes: dura mater (84 samples)	No
AD related tau pathology	No	No	No	Yes - details not provided
Genetic aspects	*APOE* + AD genes	NA	*APOE* + AD genes	*APOE*
Statistical difference when compared to sCJD	Yes	Yes	NA	Yes
Age of iCJD cases with parenchymal Aβ	4th decade to 51	28–63	28, 33	35–81
Age of iCJD cases with CAA	5th decade to 51	28–63	28, 33	35–81
Age of cases < 40 y with parenchymal Aβ deposits	36 (focal)	28, 33	28, 33	35, 39
Age of cases < 40 y with CAA	–	28, 33	28, 33	35, 39
Clinical phenotype	CJD	CJD	CJD	CJD
Reference	25	27	28	29

source of transmissible protein seeds. Moreover, it was still not known whether 1) the cadaveric tissue used in these iatrogenic CJD cases exhibit Aβ depositions, and 2) there are any distinctive features of brain pathology in these cases. To answer these questions, we performed an additional study on 2 cases.[28] We used 4 anti-Aβ antibodies (clones 6F/3D, 4G8, anti-Aβ_{1-40}, and anti-Aβ_{1-42}) to provide unequivocal results and not misinterpret nonspecific stainings. Our observations on 84 dura mater samples obtained in a longitudinal community-based aging study provided evidence for the first time that the dura mater may harbor Aβ deposits in the form of CAA or amorphous aggregates. Furthermore, this study is the only one, which compared cadaveric and host dura mater samples and demonstrated the presence of Aβ only in the cadaveric dura mater sample in addition to the brain tissue of the host.[28] Importantly, these cases are the

youngest reported with iatrogenic CJD and Aβ deposition, and we excluded genetic predisposing factors (*APOE, APPP, PSEN 1, 2*). Meticulous analysis of Aβ morphologies suggested peculiar features. First of all, in contrast to disease-associated PrP, which was found widespread in the brain, Aβ deposits were accentuated close to the operation site. In these cases the subpial cortical area near to the traumatic lesion and the surgical intervention showed tissue damage. Strikingly, the morphological spectrum of Aβ depositions in these 2 cases was much more limited and different as compared to that seen in AD, other forms of CJD, traumatic brain injury, and cognitively normal individuals.[28] Instead of diffuse plaques, we observed focal deposits and congophilic cored plaques with and without a neuritic corona. Dystrophic neurites around the plaques accumulated ubiquitin but not hyperphosphorylated tau. We observed clusters

away from the lesion site or columnar alignment of Aβ plaques close to the lesion.[28] We also emphasized that NFTs were completely lacking even in subcortical areas where it may be seen in young individuals.[11] However, we noted the tau immunoreactive small neuritic profiles as seen in all CJD forms.[28]

A fourth study has been recently reported from Japan.[29] They did not find a higher frequency in iatrogenic CJD as compared to sporadic CJD; however, their study included elderly patients (up to 81 years). The youngest iatrogenic CJD cases did show more Aβ than the youngest sporadic CJD cases. The study demonstrated significant association of cadaveric dura mater grafting with subpial Aβ deposition and meningeal amyloid angiopathy using the anti-Aβ antibody 4G8.[29] They discussed the possibility that Aβ pathology propagated from the superficial portions of the brain in the patients with iatrogenic CJD.[29] The immunohistochemical studies were performed only on sections of the frontal, parietal, temporal, and occipital lobes and it was not clear how the Aβ deposits related to the site of the surgical intervention. This study did not provide details on distinctive morphological features of parenchymal Aβ deposits. However, the cohort included 11 cases (from 16 examined) above the age of 60 and some carrying ε4 alleles of the *APOE* gene, which could potentially limit any interpretation of this aspect. It is also not surprising that the study documented NFTs following Braak stages,[29] which might also be compatible with findings in the general population of this age group.[11]

In summary, not all aspects needed for exact comparisons have been presented in these studies (Table 1). The question why not all iatrogenic CJD cases show Aβ deposition raises the possibility that cadaver samples with or without Aβ had been used or there are yet unidentified susceptibility/protective factors. Frontzek et al. suggested that the longer latency might be associated with Aβ deposition,[27] which seems to be supported also by the observation that the incubation period between dura mater grafting and death significantly correlated with the degree of subpial Aβ deposition and CAA.[29] The confirmation of Aβ in cadaveric dura mater could

be complemented by studies on the samples of cadaveric pituitary (see also Irwin et al.[26]), or the derived GH used for therapy in iatrogenic CJD cases. Furthermore, potential distinguishing morphological features of human cadaveric GH–related iatrogenic CJD merits further studies. Finally, the exact mechanism by which the external Aβ deposits propagate in the brain tissue and in particular how they induce CAA in humans could not be addressed.

In spite these missing pieces we can conclude, however, that: 1) The frequency of cases with parenchymal and vascular Aβ deposits is high in iatrogenic CJD with cadaveric pituitary-derived GH and cadaveric dura mater transplantation (statistical level), even after excluding an effect of genetic predisposing factors; 2) The morphology and distribution of Aβ deposition shows distinct features at least in the 2 cases where this was commented on in details; 3) The pituitary and the dura mater themselves may harbor Aβ deposits and thus may serve as potential sources of Aβ seeds; 4) The cadaveric dura mater shows Aβ deposition at least in the 2 cases where this was examined; and finally that 5) None of the studies reported iatrogenic CJD cases with the typical AD-type clinical phenotype.

CONCLUSIONS

When talking about an infectious nature of a protein different levels can be defined (see recent reviews on Aβ).[3,17,30] Experimental observations suggest that Aβ may propagate (as suggested to be called as ´propagon)[17] its conformation on a molecular level and has the ability to spread within and, in a limited manner, across tissues.[3,17,30] The observations on human iatrogenic CJD with Aβ deposition suggest that Aβ, in addition to prions of CJD, may act as an infectious seed between individuals. However, there are still differences between prions and Aβ seeds. The complete clinicopathological phenotype of AD has not been proven to be transmitted by Aβ, in contrast to prions in CJD. Thus only prions of CJD are 'phenotype propagons'.[28] Although it could be argued that perhaps Aβ could be also classified

as such if more time given. Another explanation could be that classical AD requires an altered microenvironment, including the presence of tau appearing first at a distant location from Aβ. In the rare situation when an Aβ seed is placed in the brain (i.e. "external" source), the microenvironment might not be conducive for the development of the classical AD phenotype. Again, in the 2 young cases reported by our group,[28] even the brainstem nuclei, which are thought to be the earliest to develop neuronal tau pathology during AD,[11] did not show any tau immunoreactivity.[28] Experimental studies have shown that injection of Aβ42 fibrils into the brains of P301L mutant tau transgenic mice caused prominent increases in the numbers of NFTs.[31] On one hand this can be interpreted that Aβ is needed to accelerate tau pathology, but on the other hand this could mean also that the microenvironment (mutant tau transgenic mice) was favorable for Aβ to achieve this.

It is conceivable that the term ´prion-like´ could be used to refer to some of the pathogenic aspects resembling prion diseases where it was first described. However, in addition to the studies reviewed here, further observations on humans could not provide unequivocal evidence that the clinical phenotype of AD is transmissible between humans through blood transfusion or cadaver human growth hormone.[26,32] Therefore, until further evidence emerges on the transmissibility of clinicopathological phenotypes between humans, the term ´prion disease´ is still most compatible with disorders described also as transmissible spongiform encephalopathies characterized by the deposition of the abnormal form of PrP.

DISCLOSURE OF POTENTIAL CONFLICTS OF INTEREST

No potential conflicts of interest were disclosed.

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