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A critical appraisal of the evidence for human transmission of amyloid-β pathology

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A critical appraisal of the evidence for human transmission of amyloid-β pathology

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Abstract

Studies in experimental animals show apparent transmissibility of amyloidogenic proteins associated with prion, Alzheimer's, Parkinson's or other neurodegenerative diseases. While these data raise potential concerns for public health, convincing evidence for human iatrogenic transmission currently only exists for prions and for β-amyloid (Aβ) after systemic injections of contaminated cadaver-derived growth hormone extracts or dura mater grafts. While these procedures are now obsolete, recent reports raise the possibility of iatrogenic Aβ transmission through putatively contaminated neurosurgical equipment.

Iatrogenic Aβ-transmission appears to cause amyloid deposition in brain parenchyma and blood vessel walls, resulting in cerebral amyloid angiopathy (CAA) after several decades. CAA can cause life-threatening brain haemorrhages, yet there is currently no proof that Aβ-transmission could also lead to Alzheimer's dementia. Longer term, larger scale epidemiological studies and sensitive, cost-efficient amyloid detection tools are needed to better understand potential Aβ transmission routes and clarify whether other proteopathic seeds can be transferred iatrogenically.

Introduction

Proteinopathies are diseases characterized by the presence of misfolded proteins that adopt an aberrant conformation and can provide a template for their own polymerization. These include neurological disorders such as prion diseases and common neurodegenerative disorders such as Alzheimer's (AD), Parkinson's (PD) and Huntington's (HD) disease. While prion diseases are the prototype of transmissible proteinopathies, misfolded proteins characteristic of AD and PD (Aβ, tau or α-synuclein) also exhibit properties similar to those of prions in experimental systems: self-replicating, β-sheet rich ordered protein assemblies termed amyloids, and possible transcellular propagation[1]. In humans, such protein aggregation is associated with neurodegeneration and clinical impairments[2].

Over the last years, increasing evidence has indicated prion-like mechanisms of protein polymerization to also operate in more common amyloid-associated diseases. This has led to increasing worries with regard to the possibility of iatrogenic amyloid transmissibility in humans[1]. Two research groups reported last year cases of putative contamination by neurosurgical instruments[3,4]. This raises questions with regard to public health and safety of laboratory investigators, and makes the distinction between known infectious prions and other protein aggregates more blurred. In October 2019 a group of international experts across different fields (cellular/molecular biology, neurosurgery, blood transfusion, public health) gathered to discuss these latest findings and address the following questions: (1) What is the evidence that proteinopathies causing neurodegeneration can be transmitted between humans? (2) Under what conditions does such human-to-human transmission occur? (3) What research is needed to fully understand the potential risks and develop efficient protective measures? This personal view outlines key conclusions and priorities for further research based on a systematic review of the latest available literature.

Evidence of amyloid transmissibility from experimental inoculation of animals

While discussions on terminology are ongoing (Box 1), for the purpose of this Personal View we will use the term “prion” for agents that cause Transmissible Spongiform Encephalopathies (TSEs) and “proteopathic seed”[5] to describe all aggregated proteins that have seeding and propagation properties *in vitro* or in animals.

Apparent transmission of abnormally folded proteins associated with AD, PD, HD, amyotrophic lateral sclerosis and frontotemporal lobar degeneration has been demonstrated in animal models and cell culture[6,7]. Injection of minute amounts of proteopathic seed-containing material, especially aggregates of Aβ, into the brain are sufficient to induce cerebral amyloidosis in amyloid precursor protein overexpressing transgenic (APP) mice[8]. Formation of pathological aggregates can be distant from the injection site[8]. Moreover, Aβ seeds injected intravenously or intraperitoneally can induce CAA in rodents and primates[9,10]. Cerebral microhaemorrhage was also observed in wild-type mice after 12 months of parabiosis with their APP/human mutant presenilin 1 (PS1) transgenic littermates[11]. We refer to other publications for an in-depth overview and critical discussion of these experiments and their implications[5,6,10,12,13]. These findings in experimental models have raised concern that extracellular Aβ and

even intracellular proteins associated with neurodegenerative diseases, such as tau and α-synuclein, might be transmitted from human to human, similar to infectious prions.

Amyloid transmissibility between and into humans

In the case of prions, human transmission has been observed in the context of mortuary feasts in Papua New Guinea as well as through medical procedures such as corneal transplantation, neurosurgical instruments, stereotactic depth electrodes, treatment with human cadaveric pituitary hormones such as growth hormone (c-hGH) and gonadotrophin, cadaveric dura mater grafts and, in the case of variant CJD, blood transfusion[14,15]. The biggest threat to public health was however bovine spongiform encephalopathy (BSE), as the bovine agent was able to cross the species barrier into human, causing the variant CJD outbreak in consumers exposed to contaminated meat and cattle products. Below we review the evidence that Aβ seeds can be transmitted through human-to-human routes (Table 1). We start with the strongest evidence first.

Growth hormone treatment and dura mater graft

Extracts of growth hormone from pituitary glands collected post-mortem were used between 1958 until the mid-1980s for treatment of growth hormone deficiency[16]. Human dura mater grafts were used until the mid-1990's, mainly for repair of dural defects during neurosurgery but also for cardiac, orthopaedic, otological, dental, urological, and gynaecological procedures[17]. In addition to prions, pathological deposits of Aβ, tau and α-synuclein may sometimes be observed in pituitary glands and dura mater, even if the tissue was collected from donors without clinical signs of neurodegenerative disease[18,19]. A first retrospective study of 796 deceased individuals treated with hGH derived from human cadavers (c-hGH) did not reveal any increased risk of AD or PD[18]. This study was limited in scope as CAA or intracerebral haemorrhage were not investigated, autopsy data were not available, and the mean duration from first treatment was 16.3 years, likely too short to detect clinical documentation of CAA-related complications. The authors accordingly recommended further monitoring of the cohorts.

This view has changed since the discovery of CAA and parenchymal Aβ pathology in patients who died of iatrogenic CJD (iCJD) (Table 1). Post-mortem histopathological analyses performed on 80 c-hGH recipients who developed iCJD, and on 12 c-hGH recipients who did not develop CJD, revealed that 31 cases (34%) exhibited Aβ deposits and/or CAA (Table 1). While sporadic CAA is typically observed in people after the sixth decade of life[20], here all affected individuals were aged between 20 and 54 years. Genetic studies did not identify any risk factors associated with early onset CAA in these iCJD patients[21]. Three additional findings argue in favour of iatrogenic transmission of Aβ seeds in these patients, independent of the prion pathology. First, several c-hGH samples prepared before 1988 were found to contain tau and Aβ peptides[10,22] and these samples accelerated Aβ plaque formation and induced CAA when injected in the brain of mice expressing a humanised Aβ domain[10]. Second, there is no evidence of increased Aβ pathology in other post-mortem prion disease cohorts (sporadic or variant CJD, inherited prion diseases)[21,23], and no evidence for cross-seeding between Aβ and prions[24]. Finally, 5 of 12 (42%) individuals who had received c-hGH treatment and did not develop CJD, showed CAA and parenchymal Aβ pathology at autopsy[25].

Similar analyses have been performed on 45 individuals who received dura mater grafts: 44 cases with a neurosurgical procedure (40 of whom later developed iCJD), and 1 case with cardiac embolisation (Table 1). Thirty-two of these individuals (70%) had CAA. In nearly all the cases, Aβ deposition was also observed in the parenchyma (Table 1). Again, most of these individuals were much younger compared to typical patients with sporadic CAA. The distribution of the Aβ deposits was consistent with propagation from the allografted dura[19,26].

Neurosurgical instruments

Experiments showing that contaminated stainless-steel wires can transmit Aβ pathology in mice[8] raised concerns that Aβ proteopathic seeds might be transmitted during neurosurgical procedures. Recent publications reported 11 patients with a medical history of neurosurgical intervention at a very young age who developed CAA-related intracerebral haemorrhages at ages 30-57[3,4,20] (Table 1). The age of onset of CAA in these patients suggests that surgical instruments may have transmitted Aβ seeds during the procedure many years earlier. This prolonged latency would be consistent with other evidence that Aβ accumulates very slowly and that it may take over two decades to develop symptomatic pathology (typically associated with extracellular Aβ and intracellular tau tangles)[27]. While the limited number of documented cases and the retrospective nature of these studies preclude conclusions of a causal relationship between early neurosurgical procedure and CAA in these young or middle-aged adults, they clearly signal the need for vigilance and further systematic study of this possible phenomenon.

Overall, 74 cases of suspected iatrogenic transmission of Aβ pathology have been published (Table 1), 57 of which concern individuals below the age of 50. Together with the inconsistent tau pathology (Table 1), the absence of cognitive impairment in these 74 individuals argues against transmission of a full AD neuropathological and clinical phenotype. Importantly, however, there is a considerable latency - in most cases well in excess of 20 years - between the presumed iatrogenic exposure and the manifestation of vascular Aβ pathology and the link between such clinical manifestation and very early neurosurgery might have escaped attention in many cases. These considerations raise the possibility that the present data may underestimate the risk of potential iatrogenic transmission of Aβ seeds.

Blood transfusion

While 4 cases of probable blood transfusion-mediated transmission of variant CJD - before the introduction of blood product leucodepletion throughout Europe - have been reported, there is no evidence for such transmission of sporadic CJD[28]. Importantly, epidemiological analysis of the cause of death of more than 6,000 haemophiliacs (who received abundant blood products via plasma protein therapy throughout their lives) did not detect an increased risk of central nervous system disease compared with the general population[29]. The most rigorous study took advantage of the excellent documentation of blood banking in Denmark and Sweden: the Scandinavian Donations and Transfusions (SCANDAT2) electronic database. Among 1,465,845 individuals transfused between 1968 and 2012, 2.9% received at least 1 unit of blood from a donor who was diagnosed with a neurodegenerative disorder (AD, PD, or unspecified dementia) within 20 years after donation (median follow-up: 10.4 years). The authors found no evidence of transmission of AD by blood transfusion - there was no disease concordance

between donors and their recipients, nor between recipients of blood from the same donor[30]. An obvious limitation is that no autopsy or biomarker data were available to support the diagnoses in donors or recipients. Association between blood transfusion and CAA (i.e. brain haemorrhage suggestive of or histological evidence of CAA) was not studied. Continued long term follow-up with a focus on the prevalence of both neurodegenerative disorders and CAA in patients receiving blood transfusions is needed.

Future research priorities

The use of c-hGH was terminated in the mid-1980s, and the use of cadaver-derived dura mater products for medical procedures was discontinued more than 20 years ago. Blood transfusion and neurosurgery on the other hand are lifesaving to millions of patients worldwide every year. Given the high prevalence of neurodegenerative diseases such as AD, especially in elderly populations[31], more systematic monitoring of the risk of Aβ pathology transmission in these common procedures is needed. For other amyloids, such as α-synuclein, tau, Htt, SOD1 or TDP43[6,7], the absence of evidence for transmission between humans (e.g. the lack of statistical difference between tau neuronal pathology in iatrogenic and sporadic CJD[23,25,32]) is not evidence of absence of risk. Since such proteopathic seeds are apparently efficiently transferred after extracellular injections in experimental animals[6,7], this possibility must be evaluated more closely in humans.

One of the biggest gaps in our knowledge is the lack of understanding of the molecular nature of proteopathic seeds. While only 36 human proteins are officially recognized as amyloids causing aggregates associated with diseases[33], there are aggregation-determining (amyloid-like) regions in most proteins[34]. Recent cryo-EM and solid-state NMR studies have started to unravel the complex heterogeneity of protein aggregates involved in neurodegenerative disorders[35]. It is crucial to continue this work and to determine the structural conformations of different proteopathic seeds, correlating their structural and biochemical characteristics with their neurotoxic properties and propensity to spread. This will require the development of physiologically relevant dose-response toxicity assays, both *in vitro* and *in vivo*. It is worth noting that synthetic Aβ aggregates generally have poor seeding capacity[36], suggesting that other factors may accelerate the seeding process and lead to neurodegeneration. Cell biological studies are also needed to fully understand amyloid pathology spreading, including the role of proteins possibly involved in modulating spreading and toxicity, such as the cellular prion protein[37,38]. Identifying the environmental and physicochemical/cellular host factors promoting or delaying the development of pathology (apart from the ageing process) will contribute to uncovering risk factors, and to devising strategies to prevent seed formation and polymerization *in vivo*.

A precise description of the molecular nature of proteopathic seeds will also help devise novel detection tools that could lead to scalable, practical 'ELISA-like' assays to screen blood, CSF and other biological samples, with important implications for public health, diagnosis and therapeutic development. As aggregation is a sequence-specific process nucleated by specific short aggregation-prone sequences, such interactions could be exploited instead of, or in addition to classic antibody-based assays to detect and

potentially prevent amyloid formation[39]. Other potentially useful approaches include Protein Misfolded Cyclic Amplification (PMCA), a labour-intensive process which is however 100% sensitive and 99% analytically specific for detection of prions in the plasma of individuals with (pre)symptomatic variant CJD[40,41]. PCMA can also be used to distinguish between different α-synuclein strains[42], and reproduce some aspects of α-synuclein aggregation and seeded propagation[43]. Recently, the use of Real-Time Quaking Induced Conversion (RT-QuIC), which has significantly improved the diagnosis of sporadic CJD in CSF, olfactory-mucosa and skin, showed promise in detecting the seeding activity associated with synucleinopathies and tauopathies[44–48]. The development of low-cost, high-throughput, sensitive assays for proteopathic seeds would eventually enable direct testing for the presence of proteopathic seeds on neurosurgical instruments[49].

In parallel, larger epidemiological studies are needed to ascertain the prevalence of CAA pathology in patients with a medical history of neurosurgery in early life. Such investigations must take into account that it may take at least two decades to develop pathologically detectable Aβ deposits and even longer to manifest clinically as CAA. These studies could employ Magnetic Resonance Imaging (MRI) and amyloid PET imaging to define the prevalence of CAA in younger adults (<50 years) following neurosurgical procedures in childhood. At the same time, retrospective studies mining healthcare record systems to check prior history of neurosurgical intervention in all patients presenting with early onset CAA could help to ascertain the cause and extent of iatrogenic CAA. Testing and evaluating surgical tool decontamination procedures with affordable enzyme-based detergents similar to those previously developed for prion decontamination[50] may also help to limit the potential risk of surgical instrument-based transmission of proteopathic seeds that are known to resist conventional sterilization procedures.

Regarding the potential risk of blood-based amyloid transmissibility, building longitudinal cohorts of individuals at potential risk (*e.g.* haemophiliacs who may repeatedly receive large amount of plasma-derived medicinal products) with periodic follow-ups including MRI and/or amyloid PET imaging and extending long-term vigilance studies based on the SCANDAT model[30] could help provide definitive evidence. Rigorous health record systems enable tracking of donor/recipients for other therapies that might carry a risk of proteopathic seed transmission, such as future neural stem cell transplantation. Moreover, biobanks of both blood donors and recipients could be tested using the rapidly improving blood tests for neurodegenerative pathologies[40], including neurofilament light chain (general neurodegeneration), phosphorylated tau (Aβ and tau pathology), $A\beta_{42}/A\beta_{40}$ ratio (amyloid pathology)[51,52] and phosphorylated Ser129 or C-terminally truncated α-synuclein[53]. Further studies on animal models, such as blood transfer from aged mice with brain amyloid pathology to wild-type recipient animals and parabiosis paradigms[11], could also help investigate potential transmissibility mechanisms in more detail.

Finally, transparent communication on the nature of the potential risk based on the available scientific evidence and on the areas of remaining uncertainty, together with clear statements on which measures/research are undertaken, are crucial. Governments and health agencies also need to relay scientific information to the general public, health workers and patients, perform scientifically founded risk assessment, and regularly re-evaluate policies in the light of epidemiological information accumulating over time and the emergence of key novel evidence. At this moment there is no scientific

evidence that supports more drastic measures than the ones we summarize in the Supplementary material (appendix, p1-p4).

Conclusions

There is currently no evidence to suggest that AD or other human neurodegenerative diseases (except variant CJD) are transmissible via iatrogenic ways. However, the potential iatrogenic transmission of Aβ pathology (CAA) calls for more systematic monitoring of individuals subject to early life neurosurgical procedures and for longer-term vigilance studies on blood transfusion. In addition, understanding the molecular nature of the proteopathic seeds and the development of scalable assays for seed detection will be crucial to provide definitive evidence on the risk of amyloid transmissibility. Further work is also needed to carefully monitor the possible spreading of other proteopathic seeds like alpha-synuclein and Tau from patient to patient, although currently no evidence apart from animal experimentation is available.

Box 1. Terminology

There is currently no generally accepted, standard terminology for protein aggregates characteristic of proteinopathies. Two diverging trends exist in the field[54], with a focus either on the similarities - in terms of protein structure and ability to template their own polymerization - or differences - in terms of infectivity - between the original "prions" and other misfolded proteins associated with neurodegenerative diseases.

- **Prions** were defined as proteinaceous infectious particles in 1982[55], originally to designate the agents causing transmissible spongiform encephalopathies (TSEs). Over the years, the term has been semantically broadened and is now sometimes used irrespective of their infectivity[56].
- **Prion-like**[57]**, prionoid**[58] **and quasi-prion**[59] are the most frequent alternative names for proteins that have properties reminiscent of prions, in particular regarding their ability to seed proteins of the same kind and transmit between cells. We do not use them here as they are stressing the similarities between amyloids and prions, which might create confusion in the public. For instance while the prion disease Bovine spongiform encephaloptahy can be transmitted orally by eating contaminated meat, this is not yet observed with any of the proteins that are causing neurodegenerative disorders like AD or PD.

- **Propagons**[60] was proposed by the yeast research community instead of the term "yeast prions" for the non-pathogenic, transmissible amyloids that mediate protein-based epigenetic inheritance.
- **Proteopathic seeds**[5] is used here in this Personal View. It is a more neutral term indicating the abnormally folded proteins that cause neurodegenerative disorders.

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Declaration of interests

AJI is a consultant of Sun Pharma Advanced Research Company, Ltd. DJS is a director and consultant of Prothena Biosciences. DRT reports grants from FWO, during the conduct of the study; non-financial support from GE Healthcare, non-financial support from Novartis, grants from Janssen Pharmaceutical companies, non-financial support from Probiodrug, other from UCB, all outside the submitted work. He received speaker honoraria or travel reimbursement for invited talks from Novartis (Switzerland), GE-Healthcare (UK), and UCB (Belgium). GP is the Chief Scientific Adviser to the Food Standards Agency and the Director of the UKRI SPF programme on `'A food systems approach for healthy people and a healthy planet`'. He contributed to this paper as a University Professor and not in the capacity as a Government Adviser or Director. GS is a consultant of Fastox. HZ has served at scientific advisory boards for Denali, Roche Diagnostics, Wave, Samumed and CogRx, and has given lectures in symposia sponsored by Fujirebio, Alzecure and Biogen (all outside submitted work). JC reports financial relationship with D-Gen Limited, outside of the submitted work. MJ served at scientific advisory boards for Roche (Switzerland). PT is employed by the French transfusion public service (Etablissement Français du Sang) in charge of collecting, preparing and issuing blood products in France. All other authors declare no competing interests. SH has received research support from Institut de Recherche Servier, LFB Biomedicaments and MedDay Pharmaceuticals.

Search strategy and selection criteria

References for this Personal View were identified by searching PubMed (6, 3, 2019 - 18, 5, 2020) for articles, case reports and clinical studies. The search terms used were “Abeta” or “amyloid” in combination with the terms “iatrogenic” and “dura mater” or “growth hormone”. There were no language restrictions. Further publications were identified by searching the list of references cited in the articles that were reviewed. The final reference list, including all search results reporting histopathological analysis of human biomaterial for the presence of amyloids, was generated on the basis of relevance to the topic of this Personal View by the participants to the Amyloid Transmissibility Workshop held in London on October 7-8, 2019.

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