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

Elsa Lauwers, PhD[1,2,#], Giovanna Lalli, PhD[3,#], Prof. Sebastian Brandner, MD[4,5], Prof. John Collinge, MD[6], Prof. Veerle Compernolle, MD[7,8], Prof. Charles Duyckaerts, MD[9], Prof. Gustaf Edgren, MD[10,11], Stéphane Haïk, MD[9,12], Prof. John Hardy, PhD[3,13,14,15,16], Prof. Adel Helmy, MD[17], Adrian J. Ivinson, PhD[3], Zane Jaunmuktane, PhD[4,18], Prof. Mathias Jucker, PhD[19,20], Prof. Richard Knight, MD[21,22], Robin Lemmens, MD, PhD[1,2,23], I-Chun Lin, PhD[3], Prof. Seth Love, PhD[24], Prof. Simon Mead, PhD[6], Prof. V. Hugh Perry, PhD[3], James Pickett, PhD[25,26], Prof. Guy Poppy, PhD[27], Prof. Sheena E. Radford, PhD[28], Frederic Rousseau, PhD[1,29], Carol Routledge, PhD[30], Prof. Giampietro Schiavo, PhD[3,31], Joost Schymkowitz, PhD[1,29], Prof. Dennis J. Selkoe, MD[32], Prof. Colin Smith, PhD[33], Prof. Dietmar R. Thal, MD[34], Tom Theys, MD[35], Prof. Pierre Tiberghien, MD, PhD[36,37], Prof. Peter van den Burg, MD, PhD[38,39], Prof. Philippe Vandekerckhove, MD, PhD[40,41], Clare Walton, PhD[42, 43], Prof. Hans L. Zaaijer, MD[44], Prof. Henrik Zetterberg, MD, PhD[3,5,45,46], Prof. Bart De Strooper, MD, PhD[1,2,3,*]

**corresponding author # co-first authors*

Affiliations

[1]VIB-KU Leuven Center for Brain & Disease Research, 3000 Leuven, Belgium.

[2]KU Leuven, Department of Neurosciences, Leuven Brain Institute, 3000 Leuven, Belgium.

[3]UK Dementia Research Institute at University College London, London, United Kingdom.

[4]Division of Neuropathology, National Hospital for Neurology and Neurosurgery, University College London NHS Foundation Trust, Queen Square, London, WC1N 3BG, United Kingdom.

[5]Department of Neurodegenerative disease, UCL Queen Square Institute of Neurology, Queen Square, London, WC1N 3BG, UK.

[6]Medical Research Council Prion Unit at UCL, Institute of Prion Diseases, University College London, London W1W 7FF, United Kingdom.

[7]Blood Services, Belgian Red Cross-Flanders, Mechelen, Belgium.

[8]Faculty of Medicine and Health Sciences, Ghent University, Ghent, Belgium.

[9]Sorbonne Université, INSERM, CNRS UMR 7225, Institut du Cerveau et de la Moelle épinière, ICM, Paris, France; AP-HP, Hôpital de la Pitié-Salpêtrière, Laboratoire de Neuropathologie R Escourolle, Paris, France.

[10]Clinical Epidemiology Unit, Department of Medicine Solna, Karolinska Institutet, Stockholm, Sweden.

[11]Department of Cardiology, Södersjukhuset, Stockholm, Sweden.

[12]AP-HP, Cellule Nationale de Référence des maladies de Creutzfeldt-Jakob, Groupe Hospitalier Pitié-Salpêtrière, Paris, France.

[13]Department of Neurodegenerative Disease, UCL Institute of Neurology, University College London, London, United Kingdom.

[14]Reta Lila Weston Institute, UCL Queen Square Institute of Neurology, 1 Wakefield Street, London WC1N 1PJ, United Kingdom.

[15]NIHR University College London Hospitals Biomedical Research Centre, London, United Kingdom.

[16]Institute for Advanced Study, The Hong Kong University of Science and Technology, Hong Kong SAR, China.

[17]Division of Neurosurgery, Department of Clinical Neuroscience, University of Cambridge, United Kingdom.

[18]Department of Clinical and Movement Neurosciences and Queen Square Brain Bank for Neurological Disorders, Queen Square Institute of Neurology, University College London, 1 Wakefield street, London, WC1N 1PJ, United Kingdom.

[19]Hertie-Institute for Clinical Brain Research, University of Tübingen, Tübingen, Germany.

[20]German Center for Neurodegenerative Diseases, Tübingen, Germany.

[21]Centre for Clinical Brain Sciences and UK Dementia Research Institute at the University of Edinburgh, Edinburgh, United Kingdom.

[22]National Creutzfeldt-Jakob Disease Research and Surveillance Unit, Western General Hospital, Edinburgh, United Kingdom.

[23]Department of Neurology, University Hospitals Leuven, Belgium.

[24]Translational Health Sciences, Bristol Medical School, University of Bristol, Bristol, United Kingdom.

[25]Alzheimer's Society, London EC3N 2AE, United Kingdom.

[26]Current affiliation: Epilepsy Research UK, London SE1 4YR, United Kingdom.

[27]Biological Sciences, Faculty of Environmental and Life Sciences, Life Sciences Building 85, University of Southampton, Highfield Campus, Southampton, SO17 1BJ, United Kingdom.

[28]Astbury Centre for Structural Molecular Biology and School of Molecular and Cellular Biology, Faculty of Biological Sciences, University of Leeds, Leeds LS2 9JT, United Kingdom.

[29]KU Leuven, Department of Cellular and Molecular Medicine, Leuven, 3000, Belgium.

[30]Alzheimer's Research UK, 3 Riverside Granta Park, Cambridge CB21 6AD, United Kingdom.

[31]Department of Neuromuscular Disorders, Queen Square Institute of Neurology, University College London, London, United Kingdom.

[32]Ann Romney Center for Neurologic Diseases, Department of Neurology, Brigham and Women's Hospital, and Harvard Medical School, Boston, MA 02115, United States of America.

[33]Centre for Clinical Brain Sciences, University of Edinburgh, Edinburgh, United Kingdom.

[34]Department of Pathology, University Hospitals Leuven, and Department of Imaging and Pathology, KU-Leuven, Leuven, Belgium.

[35]Department of Neurosurgery, University Hospitals Leuven, Leuven, Belgium.

[36]Etablissement Français du Sang, La Plaine St Denis, France.

[37]Université de Franche-Comté, INSERM, Etablissement Français du Sang, UMR RIGHT1098, Besançon, France.

[38]European Blood Alliance, Brussels, Belgium.

[39]Current affiliation: Department Transfusion Medicine, Sanquin, 1066 CX Amsterdam, The Netherlands.

[40]Belgian Red Cross-Flanders, B-2800 Mechelen, Belgium.

[41]KU Leuven - University of Leuven, Department of Public Health and Primary Care, B-3000 Leuven, Belgium.

[42]Alzheimer's Society, London, United Kingdom.

[43]Current affiliation: Multiple Sclerosis International Federation, London SE1 0LX, United Kingdom.

[44]Department of Blood-borne Infections, Sanquin Research, Amsterdam, Netherlands.

[45]Department of Psychiatry and Neurochemistry, Institute of Neuroscience & Physiology, the Sahlgrenska Academy at the University of Gothenburg, Mölndal, Sweden.

[46]Clinical Neurochemistry Laboratory, Sahlgrenska University Hospital, Mölndal, Sweden.

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.

Acknowledgements

The authors are grateful to the UK Dementia Research Institute (which receives its funding from UK DRI Ltd, funded by the UK Medical Research Council, Alzheimer's Society, and Alzheimer's Research UK), the Belgian Red Cross, the European Blood Alliance, the Institut du Cerveau et de la Moelle Epinière and Mission Lucidity for co-organizing and funding the 'Amyloid Transmissibility Workshop' that was held in London in October 2019 and led to the present Personal View. Work in the Schiavo laboratory is supported by funding from Wellcome Trust (107116/Z/15/Z), the European Union's Horizon 2020 Research and Innovation programme under grant agreement 739572 and a UK Dementia Research Institute Foundation award. The Switch Laboratory is supported by grants from the European Research Council under the European Union's Horizon 2020 Framework Programme ERC Grant agreement 647458 (MANGO) to J.S., the Flanders institute for biotechnology (VIB), KU Leuven, the Industrial Research Council of KU Leuven, and the Funds for Scientific Research Flanders (FWO) and the Hercules Stichting. SB and ZJ are supported by the United Kingdom Department of Health's National Institute for Health Research (NIHR) Biomedical Research Centre's funding scheme. JH, BDS and HZ are supported by the UK Dementia Research Institute. JH is also supported by the Medical Research Council (award number MR/N026004/1), the Wellcome

Trust (award number 202903/Z/16/Z), the Dolby Family Fund, the National Institute for Health Research University College London Hospitals Biomedical Research Centre and the National Institute for Health Research University College London Hospitals Biomedical Research Centre. AJI, GL, ICL, and VHP are members of the UK DRI Headquarters based at UCL and supported by the UK Dementia Research Institute.

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.

References

1 Jaunmuktane Z, Brandner S. Transmissible human proteopathies: an expanding field. *Diagn Histopathol* 2019; **25**: 16–22.

2 Duyckaerts C, Clavaguera F, Potier M-C. The prion-like propagation hypothesis in Alzheimer's and Parkinson's disease. *Curr Opin Neurol* 2019; **32**: 266–71.

3 Hamaguchi T, Komatsu J, Sakai K, *et al.* Cerebral hemorrhagic stroke associated with cerebral amyloid angiopathy in young adults about 3 decades after neurosurgeries in their infancy. *J Neurol Sci* 2019; **399**: 3–5.

4 Giaccone G, Maderna E, Marucci G, *et al.* Iatrogenic early onset cerebral amyloid angiopathy 30 years after cerebral trauma with neurosurgery: vascular amyloid deposits are made up of both Aβ40 and Aβ42. *Acta Neuropathol Commun* 2019; **7**: 70.

5 Jucker M, Walker LC. Propagation and spread of pathogenic protein assemblies in neurodegenerative diseases. *Nat Neurosci* 2018; **21**: 1341–9.

6 Vaquer-Alicea J, Diamond MI. Propagation of Protein Aggregation in Neurodegenerative Diseases. *Annu Rev Biochem* 2019; **88**: 785–810.

7 McAlary L, Plotkin SS, Yerbury JJ, Cashman NR. Prion-Like Propagation of Protein Misfolding and Aggregation in Amyotrophic Lateral Sclerosis. *Front Mol Neurosci* 2019; **12**: 262.

8 Eisele YS, Bolmont T, Heikenwalder M, *et al.* Induction of cerebral β-amyloidosis: Intracerebral versus systemic Aβ inoculation. *Proc Natl Acad Sci U S A* 2009; **106**: 12926–31.

9 Burwinkel M, Lutzenberger M, Heppner FL, Schulz-Schaeffer W, Baier M. Intravenous injection of beta-amyloid seeds promotes cerebral amyloid angiopathy (CAA). *Acta Neuropathol Commun* 2018; **6**: 23.

10 Purro SA, Farrow MA, Linehan J, *et al.* Transmission of amyloid-β protein pathology from cadaveric pituitary growth hormone. *Nature* 2018; **564**: 415–9.

11 Bu X-L, Xiang Y, Jin W-S, *et al.* Blood-derived amyloid-β protein induces Alzheimer's disease pathologies. *Mol Psychiatry* 2018; **23**: 1948–56.

12 Collinge J. Mammalian prions and their wider relevance in neurodegenerative diseases. *Nature* 2016; **539**: 217–26.

13 Walsh DM, Selkoe DJ. A critical appraisal of the pathogenic protein spread hypothesis of neurodegeneration. Nature Reviews Neuroscience. 2016; **17**: 251–60.

14 Ironside JW, Ritchie DL, Head MW. Prion diseases. *Handb Clin Neurol* 2017; **145**: 393–403.

15 Urwin PJM, Mackenzie JM, Llewelyn CA, Will RG, Hewitt PE. Creutzfeldt-Jakob disease and blood transfusion: updated results of the UK Transfusion Medicine Epidemiology Review Study. Vox Sanguinis. 2016; **110**: 310–6.

16 Ranke MB, Wit JM. Growth hormone - past, present and future. *Nat Rev Endocrinol* 2018; **14**: 285–300.

17 Brooke FJ, Boyd A, Klug GM, Masters CL, Collins SJ. Lyodura use and the risk of iatrogenic Creutzfeldt–Jakob disease in Australia. *Med J Aust* 2004; **180**: 177–81.

18 Irwin DJ, Abrams JY, Schonberger LB, *et al.* Evaluation of potential infectivity of Alzheimer and Parkinson disease proteins in recipients of cadaver-derived human growth hormone. *JAMA Neurol* 2013; **70**: 462–8.

19 Kovacs GG, Lutz MI, Ricken G, *et al.* Dura mater is a potential source of Aβ seeds. *Acta Neuropathol* 2016; **131**: 911–23.

20 Jaunmuktane Z, Quaegebeur A, Taipa R, *et al.* Evidence of amyloid-β cerebral amyloid angiopathy transmission through neurosurgery. *Acta Neuropathol* 2018; **135**: 671–9.

21 Jaunmuktane Z, Mead S, Ellis M, *et al.* Evidence for human transmission of amyloid-β pathology and cerebral amyloid angiopathy. *Nature* 2015; **525**: 247–50.

22 Duyckaerts C, Sazdovitch V, Ando K, *et al.* Neuropathology of iatrogenic Creutzfeldt--Jakob disease and immunoassay of French cadaver-sourced growth hormone batches suggest possible transmission of tauopathy and long incubation periods for the transmission of Abeta pathology. *Acta Neuropathol* 2018; **135**: 201–12.

23 Cali I, Cohen ML, Haik S, *et al.* Iatrogenic Creutzfeldt-Jakob disease with Amyloid-β pathology: an international study. *Acta Neuropathol Commun* 2018; **6**: 5.

24 Rasmussen J, Krasemann S, Altmeppen H, *et al.* Infectious prions do not induce Aβ deposition in an in vivo seeding model. *Acta Neuropathol* 2018; **135**: 965–7.

25 Ritchie DL, Adlard P, Peden AH, *et al.* Amyloid-β accumulation in the CNS in human growth hormone recipients in the UK. *Acta Neuropathol* 2017; **134**: 221–40.

26 Hervé D, Porché M, Cabrejo L, *et al.* Fatal Aβ cerebral amyloid angiopathy 4 decades after a dural graft at the age of 2 years. *Acta Neuropathol* 2018; **135**: 801–3.

27 McDade E, Bateman RJ. Stop Alzheimer's before it starts. *Nature* 2017; **547**: 153–5.

28 Holmqvist J, Wikman A, Pedersen OBV, *et al.* No evidence of transfusion transmitted sporadic Creutzfeldt-Jakob disease: results from a bi-national cohort study. Transfusion. 2020; **60**: 694–7.

29 Darby SC, Kan SW, Spooner RJ, *et al.* Mortality rates, life expectancy, and causes of death in people with hemophilia A or B in the United Kingdom who were not infected with HIV. *Blood* 2007; **110**: 815–25.

30 Edgren G, Hjalgrim H, Rostgaard K, *et al.* Transmission of Neurodegenerative Disorders Through Blood Transfusion: A Cohort Study. *Ann Intern Med* 2016; **165**: 316–24.

31 Prince MJ. World Alzheimer Report 2015: the global impact of dementia: an analysis of prevalence, incidence, cost and trends. Alzheimer's Disease International, 2015.

32 Hamaguchi T, Taniguchi Y, Sakai K, *et al.* Significant association of cadaveric dura mater grafting with subpial Aβ deposition and meningeal amyloid angiopathy. *Acta Neuropathol* 2016; **132**: 313–5.

33 Benson MD, Buxbaum JN, Eisenberg DS, *et al.* Amyloid nomenclature 2018: recommendations by the International Society of Amyloidosis (ISA) nomenclature committee. *Amyloid* 2018; **25**: 215–9.

34 Chiti F, Dobson CM. Protein Misfolding, Amyloid Formation, and Human Disease: A Summary of Progress Over the Last Decade. *Annu Rev Biochem* 2017; **86**: 27–68.

35 Gallardo R, Ranson NA, Radford SE. Amyloid structures: much more than just a cross-β fold. *Curr Opin Struct Biol* 2019; **60**: 7–16.

36 Stöhr J, Watts JC, Mensinger ZL, *et al.* Purified and synthetic Alzheimer's amyloid beta (Aβ) prions. *Proc Natl Acad Sci U S A* 2012; **109**: 11025–30.

37 Gomes LA, Hipp SA, Rijal Upadhaya A, *et al.* Aβ-induced acceleration of Alzheimer-related τ-pathology spreading and its association with prion protein. *Acta Neuropathol* 2019; **138**: 913–41.

38 Corbett GT, Wang Z, Hong W, *et al.* PrP is a central player in toxicity mediated by soluble aggregates of neurodegeneration-causing proteins. *Acta Neuropathol* 2020; **139**: 503–26.

39 Khodaparast L, Khodaparast L, Gallardo R, *et al.* Aggregating sequences that occur in many proteins constitute weak spots of bacterial proteostasis. *Nat Commun* 2018; **9**: 866.

40 Bougard D, Brandel J-P, Bélondrade M, *et al.* Detection of prions in the plasma of presymptomatic and symptomatic patients with variant Creutzfeldt-Jakob disease. *Sci Transl Med* 2016; **8**: 370ra182.

41 Lyon A, Mays CE, Borriello F, Telling GC, Soto C, Pritzkow S. Application of PMCA to screen for prion infection in a human cell line used to produce biological therapeutics. *Sci Rep* 2019; **9**: 4847.

42 Shahnawaz M, Mukherjee A, Pritzkow S, *et al.* Discriminating α-synuclein strains in Parkinson's disease and multiple system atrophy. *Nature* 2020; **578**: 273–7.

43 Nicot S, Verchère J, Bélondrade M, *et al.* Seeded propagation of α-synuclein aggregation in mouse brain using protein misfolding cyclic amplification. *FASEB J* 2019; **33**: 12073–86.

44 Zanusso G, Monaco S, Pocchiari M, Caughey B. Advanced tests for early and accurate diagnosis of Creutzfeldt–Jakob disease. *Nat Rev Neurol* 2016; **12**: 325–33.

45 Fairfoul G, McGuire LI, Pal S, *et al.* Alpha-synuclein RT-Qu IC in the CSF of patients with alpha-synucleinopathies. *Annals of clinical and translational neurology* 2016; **3**: 812–8.

46 Kraus A, Saijo E, Metrick MA 2nd, *et al.* Seeding selectivity and ultrasensitive detection of tau aggregate conformers of Alzheimer disease. *Acta Neuropathol* 2019; **137**: 585–98.

47 Saijo E, Metrick MA 2nd, Koga S, *et al.* 4-Repeat tau seeds and templating subtypes as brain and CSF biomarkers of frontotemporal lobar degeneration. *Acta Neuropathol* 2020; **139**: 63–77.

48 Orrú CD, Yuan J, Appleby BS, *et al.* Prion seeding activity and infectivity in skin samples from patients with sporadic Creutzfeldt-Jakob disease. *Sci Transl Med* 2017; **9**. DOI:10.1126/scitranslmed.aam7785.

49 Smith A, Winter S, Lappin D, *et al.* Reducing the risk of iatrogenic Creutzfeldt-Jakob disease by improving the cleaning of neurosurgical instruments. *J Hosp Infect* 2018; **100**: e70–6.

Table 1

Table 1. Overview of all reported cases of suspected iatrogenic contamination by Aβ.

Suspected iatrogenic exposure: c-hGH - 31 reported cases						
Age (years)*	**Sex**	**Country**	**Exposure (years)***	**Aβ pathology**	**tau pathology**	**References**
50 [44-54]	3 M	US	37.3 [32.5-41.5][a]	CAA, 2 cases with plaques	Mild NFT, 1 case with mild DN	[23]
32.5 [20-45]	5 F, 18 M	UK	18.4 [9-32] (NA for 5 cases without CJD)	7 cases with CAA only, 7 cases with parenchymal Aβ deposits only, 9 cases with both	No NFT	[25]
39	M	France	25.4[b]	CAA and plaques	Tau-positive neurites around prion plaques	[22]
5-6th decade of life	1 F, 3 M	UK	[27.9–38.9][b]	parenchymal Aβ deposits, 3 cases also with CAA	No NFT	[21]
Suspected iatrogenic exposure: dura mater graft - 32 reported cases						
Age (years)*	**Sex**	**Country**	**Exposure (years)***	**Aβ pathology**	**tau pathology**	**References**
50 [26-75]	3 F, 5 M	Australia, France, Italy, USA	12.8 [4-25]	CAA, 3 cases with parenchymal Aβ deposits	Several aged cases with NFT	[23] and references therein
30.5 [28-33]	1 F, 1 M	Austria	23.5 [22-25]	CAA and parenchymal Aβ deposits	Sparse small neuritic plaques, no NFT	[19] and references therein
60.5 [35-81]	5 F, 6 M	Japan	20.5 [10.2-29.3]	CAA	Tau-positive neurites around prion plaques	[32]
39	F	Japan	20	CAA and parenchymal Aβ deposits	Limited (Braak NFTs stage 1)	[61]
44,5 [28-63]	3 F, 2 M	Switzerland, Austria	[21-25]	CAA and parenchymal Aβ deposits	Negative	[62]
46	F	France	44	CAA and parenchymal Aβ deposits	Few positive neurites, rare NFTs	[26]
40 [34-48]	1 F, 2 M	UK	36 [34-37]	2 cases with CAA, 2 cases with parenchymal Aβ deposits	2 cases negative, 1 case not tested	[63]
37	1 M	France	35	CAA, parenchymal Aβ	Negative	[64]

				deposits		
Suspected iatrogenic exposure: neurosurgery - 11 reported cases						
Age (years)*	**Sex**	**Country**	**Exposure (years)***	**Aβ pathology**	**tau pathology**	**References**
40 [31-57]	3 F, 5 M	Austria, Belgium, Germany, Japan, Portugal, UK	[20-40]	CAA, 3 cases with parenchymal Aβ deposits	1 case with NFTs (Braak stage 2)	[20]and references therein
30	2 M	Japan	30	CAA	Not tested	[3]
30	1 M	Italy	29[c]	CAA	Few positive neurites, no NFT	[4]

*mean and/or [range]. [a]Duration since middle of the treatment. [b] Duration since first treatment. [c]No data available to confirm or exclude the use of cadaveric dura mater graft. Abbreviations: DN: dystrophic neurites, NFT: neurofibrillary tangles.

Supplementary Material

Much remains uncertain with regard to the human transmissibility of proteopathic seeds and the evidence as summarized in the accompanying publication does not warrant drastic measurements to be taken. Nevertheless, it seems logical and good practice to adapt a series of proactive safety measures with good cost-to-potential-risk ratio. The suggestions are inspired by established guidelines to handle prions, and are meant to stimulate discussions among all relevant stakeholders.

Implications for research laboratories and biobanks

Research using biological material containing proteopathic seeds, such as cell cultures, transgenic animals, or human tissue samples, are routinely performed under biosafety level 2 conditions. Common sense precautions to avoid spills, cuts and needle pricks, and use of standard protective equipment are assumed to be sufficient to avoid contamination of personnel and laboratory equipment.

Activities that aim at purifying and enriching proteopathic seeds, may however present an increased risk and demand extra caution. Staff should work within a safety cabinet, wear a mouth and nose mask and safety goggles to protect mucosa from splashes, and water-proof protective clothing when manipulating large volumes. In the event of a cut or prick wound, not much advice can be given apart from rinsing abundantly under running cold water. Waste should be handled carefully, given the apparent resistance of proteopathic seeds to standard autoclaving and sterilization methods[1–3]. Disinfectants containing aldehydes do not destroy proteopathic seeding activity[2] and may actually enhance their stability. Several decontamination procedures, including some based on commercially available reagents, have been tested for their ability to remove proteopathic seeds from different materials. While corrosive agents such as 2M NaOH or 20% (v/v) sodium hypochlorite (bleach), enzyme-based methods, 1% SDS solution or a mixture of 0.2% SDS and 0.3% NaOH[3–5] appear efficient, they are almost certainly unsuitable for most metal equipment[4,6]. Finally, aerosols - for example resulting from sonication of concentrated seeds in open vials - should be avoided. If necessary, procedures that generate aerosols should be performed in a suitable safety cabinet.

Further advice can be obtained from the recommendations made in most European countries for the handling of prions that cause TSEs such as CJD (EU Directive EC 2000/54 and corresponding national regulations). Currently available evidence would not enforce working at full L3 containment levels with amyloid seeds, unless prion contamination is also suspected.

Implications for neurosurgery

In the light of the limited and inconclusive evidence for transmission of Aβ pathology through neurosurgical instruments (Table 1), and given the tendency of amyloids to stick to metals and their resistance to standard sterilisation procedures (see above), the risk of iatrogenic transmission of Aβ needs to be considered. In particular neurosurgical procedures on elderly patients might contaminate instruments and using those later for procedures on children and young adults, might introduce a risk, especially when taking into account the very long 'incubation periods' that seem to underlie CAA. Aβ has

a demonstrated ability to stick to metal surgical instruments, and resists standard sterilisation procedures (see above).

Most important at this moment is to monitor this risk much more strictly (see Future directions). In the meantime, a pragmatic approach to minimize potential risks without impacting patient decision-making or increasing the ethical burden on patient screening and counselling, is indicated. We refer to current precautionary measures to reduce protein seed contamination of surgical instruments from France (French Ministry of Health, Labour and Welfare - Instruction DGS/R13 2011-449), Germany (Guidelines from the Commission for Hospital Hygiene and Infection Prevention (KRINKO) - Hygiene Requirements for the Reprocessing of Medical Devices) and prion contamination in the UK (NICE Guidance IPG666 - Reducing the risk of transmission of Creutzfeldt–Jakob disease (CJD) from surgical instruments used for interventional procedures on high-risk tissues).

- Conventional decontamination and sterilization procedures are insufficient to clean proteopathic seed-contaminated instruments. Several decontamination methods exist[1–3] and these should be further assessed for neurosurgical instruments. Aldehydes, high temperatures or any agent having fixating properties should be avoided.

- Given the long incubation time (from 20-40 years - Table 1) and the current uncertainty regarding the magnitude of the risk, one could consider avoiding instruments used before for adult neurosurgery in paediatric neurosurgical procedures.

- Given the incidence of Aβ pathology and neurodegeneration in the general population aged above 60[7], it might be desirable to implement an electronic tracking system for non-disposable neurosurgical instruments, although this would have significant logistical and financial implications. This would enable the retrospective identification of patients operated on with a given set of instruments and would facilitate research into possible transmissible agents, as well as the retrospective identification of patients at risk.

Implications for blood banks

There is currently no cost-effective, sufficiently sensitive and specific test available to assess the presence of various amyloid seeds in blood samples, despite being an active area of ongoing research[8]. Recent studies suggest that plasma phosphorylated-tau concentration may serve as a sensitive and specific test to detect the presence of cerebral Aβ pathology, including in pre-dementia disease stages[9,10], although more research is needed before screening could be considered or recommended. Current pathogen reduction technologies used to increase blood safety are methodologically also unable to eliminate proteopathic seeds, as they focus on nucleic acid inactivation. Based on the limited amount of data on the long-term outcomes of potential amyloid transmission via blood donation, a revision of the blood donor selection criteria might be considered. The European Commission Directive 2004/33/EC, which lays down technical requirements to prevent the transmission of diseases by blood and blood components, suggests that the following donors should be permanently excluded from allogeneic donations:

- Persons who have received human pituitary-derived hormones, or grafts of human dura mater or cornea.
- Persons with a history of serious central nervous system disease.
- Persons who have a family history, which places them at risk of developing a TSE such as CJD (*i.e.* persons with a genetic test diagnosis of inherited prion disease, or with two or more blood relatives who developed a prion disease).

These ineligibility criteria could be extended to:

- Persons who have received grafts of human sclera or other ocular tissue.
- Persons identified as members of a family at risk of neurodegenerative disease associated with proteopathic seeds. By analogy with the position of the UK Blood Services regarding prion disease, this would be either carriers of autosomal dominant mutations in disease-genes, or persons with two or more first-degree relatives who developed an early-onset neurodegenerative disorder.

Since the risk of developing a neurodegenerative disease such as AD or PD increases with age, a conceptually simple measure is lowering the maximum donor age limit. However, this imposes serious logistical hurdles and drastically decreases blood availability: 18% of all blood donors worldwide are over 45 years of age, and this proportion is typically around 40% or higher in western countries (World Health Organization). Moreover, there is also ample data showing that donor age does not affect patient long-term survival[11,12]. We therefore do not currently recommend revising the maximum donor age limit. However, if further studies were to substantiate a potential transfusion-mediated transmission risk, additional safety measures may include the avoidance of transfusing children or young adults with blood from donors over a certain age.

It is worth noting that no observational studies report on stable plasma-derived medicinal products (PDMP) such as albumin, coagulation factors and immunoglobulins, all of which theoretically pose a high risk. Such risk is introduced by using global logistics chains, pooling of a large number of blood units derived from multiple different patients, and use of fractionation, and inactivation methods which preserve protein structure and activity. Recording the use of these products in the same way as regular blood products seems a prerequisite.

Of note some countries store small blood samples from each donation to allow *a posteriori* biological control experiments. In France, for instance, two additional 1 ml plasma samples are collected at the time of each donation and stored. In Flanders (Belgium), one 750 µl sample is stored indefinitely (with the oldest samples collected over 10 years ago). Similar systems are in place elsewhere in other countries. Such biobanks allow the assessment of disease-specific biomarkers during pre-symptomatic phases of diseases[13] and are invaluable for medical research. The ability to track health outcomes in donors and recipients over many decades is vitally important. The SCANDAT2 database (http://www.scandat.se/) provides a link between donors and recipients and their detailed clinical follow-up across Sweden and Denmark[14]. Importantly, given the long incubation periods of neurodegenerative diseases, both biobanks and donor-recipient databases must be set up for long-term maintenance (*i.e.* several decades) with appropriate patients' consent. Conversely, when patients present with CAA at a young age (under 60

years, when such pathology is rare[15]), physicians should consider medical procedures with cadaver derived tissues, neurosurgery but also blood transfusions during childhood as potential risk factors.

Implications for organ transplantation and cell therapy

APP and enzymes required for Aβ production are widely expressed in somatic organs such as kidney, pancreas, spleen, intestines, skin and lung[16–18]. α-synuclein can also be found in peripheral tissues[19,20], and there is some evidence that α-synuclein pathology may spread in a stereotyped fashion from the gastrointestinal tract via the vagus nerve to the ventral midbrain, leading to selective degeneration of dopaminergic neurons in humans and animal models[21–23]. However, there is currently, no documentation on the ability of proteopathic seeds to propagate after organ transplantation. Important risk/benefit issues also need to be considered: organ transplantation continues to provide the last chance of survival for many patients - in the case of transmissible proteopathic seeds, the patient would need to survive for decades (assuming incubation times of 10-30 years) before the manifestation of overt pathology. The question arises whether it is ethical to preclude transplantation of potentially compromised organs given the paucity of organs available for transplantation and the high mortality risk incurred in absence of transplantation.

In 2008, two studies reported the occurrence of α-synuclein inclusions, or Lewy bodies, in foetal dopaminergic cells transplanted into the striatum of patients with PD[24,25], suggesting that misfolded α-synuclein in the host could have been propagated into grafted cells and trigger α-synuclein aggregation. Some subsequent reports showed transfer of aggregated α-synuclein between cultured cells and from host to engrafted cells[26,27]. Tau pathology can also manifest in originally healthy neural tissue transplanted into the brains of patients with PD and HD[28], although formal proof of transmission from the host is lacking. Mutant huntingtin aggregates have been observed within healthy foetal neural allografts in the brains of patients with advanced HD[29], but again proof of amplification of transmitted seeds is lacking. These observations suggest that some grafted cells could be affected by the disease process, thereby limiting the long-term clinical benefit of this type of therapeutic approach. However, the number of reported cases remains small, and further studies, including a number of ongoing clinical trials using stem cell transplantation in neurodegenerative disorders, are expected to shed more light on this possibility.

References

1 Eisele YS, Bolmont T, Heikenwalder M, *et al.* Induction of cerebral β-amyloidosis: Intracerebral versus systemic Aβ inoculation. *Proc Natl Acad Sci U S A* 2009; **106**: 12926–31.

2 Fritschi SK, Cintron A, Ye L, *et al.* Aβ seeds resist inactivation by formaldehyde. *Acta Neuropathol* 2014; **128**: 477–84.

3 Edgeworth JA, Sicilia A, Linehan J, Brandner S, Jackson GS, Collinge J. A standardized comparison of commercially available prion decontamination reagents using the Standard Steel-Binding Assay. *J*

Gen Virol 2011; **92**: 718–26.

4 Fenyi A, Coens A, Bellande T, Melki R, Bousset L. Assessment of the efficacy of different procedures that remove and disassemble alpha-synuclein, tau and A-beta fibrils from laboratory material and surfaces. *Sci Rep* 2018; **8**: 10788.

5 Thomzig A, Wagenführ K, Daus ML, *et al.* Decontamination of medical devices from pathological amyloid-β-, tau- and α-synuclein aggregates. *Acta Neuropathol Commun* 2014; **2**: 151.

6 Jackson GS, McKintosh E, Flechsig E, *et al.* An enzyme--detergent method for effective prion decontamination of surgical steel. *J Gen Virol* 2005; **86**: 869–78.

7 Jack CR Jr, Wiste HJ, Weigand SD, *et al.* Age-specific population frequencies of cerebral β-amyloidosis and neurodegeneration among people with normal cognitive function aged 50-89 years: a cross-sectional study. *Lancet Neurol* 2014; **13**: 997–1005.

8 Schindler SE, Bollinger JG, Ovod V, *et al.* High-precision plasma β-amyloid 42/40 predicts current and future brain amyloidosis. *Neurology* 2019; **93**: e1647–59.

9 La Joie R Wolf A Strom A Wang P Iaccarino L TE. Diagnostic value of plasma phosphorylated tau181 in Alzheimer's disease and frontotemporal lobar degeneration. *Nat Med*; **in press**.

10 Janelidze S, Mattsson N, Palmqvist S, Insel P, Smith R, Eichenlaub U. Plasma P-tau181 in Alzheimer's disease: relationship to other biomarkers, differential diagnosis, neuropathology and longitudinal progression to Alzheimer's dementia. *Nat Med*; **in press**.

11 Vasan SK, Chiesa F, Rostgaard K, *et al.* Lack of association between blood donor age and survival of transfused patients. Blood. 2016; **127**: 658–61.

12 Edgren G, Ullum H, Rostgaard K, *et al.* Association of Donor Age and Sex With Survival of Patients Receiving Transfusions. *JAMA Intern Med* 2017; **177**: 854–60.

13 Bougard D, Brandel J-P, Bélondrade M, *et al.* Detection of prions in the plasma of presymptomatic and symptomatic patients with variant Creutzfeldt-Jakob disease. *Sci Transl Med* 2016; **8**: 370ra182.

14 Edgren G, Hjalgrim H, Rostgaard K, *et al.* Transmission of Neurodegenerative Disorders Through Blood Transfusion: A Cohort Study. *Ann Intern Med* 2016; **165**: 316–24.

15 Jaunmuktane Z, Quaegebeur A, Taipa R, *et al.* Evidence of amyloid-β cerebral amyloid angiopathy transmission through neurosurgery. *Acta Neuropathol* 2018; **135**: 671–9.

16 Citron M, Vigo-Pelfrey C, Teplow DB. Excessive production of amyloid beta-protein by peripheral cells of symptomatic and presymptomatic patients carrying the Swedish familial Alzheimer disease mutation. *Proceedings of the National Academy of Sciences of the United States of America* 1994; **91**: 11993–7.

17 Selkoe DJ, Podlisny MB, Joachim CL, *et al.* Beta-amyloid precursor protein of Alzheimer disease occurs as 110- to 135-kilodalton membrane-associated proteins in neural and nonneural tissues. *Proc Natl Acad Sci U S A* 1988; **85**: 7341–5.

18 Sandbrink R, Masters CL, Beyreuther K. Beta A4-amyloid protein precursor mRNA isoforms without exon 15 are ubiquitously expressed in rat tissues including brain, but not in neurons. *J Biol Chem* 1994; **269**: 1510–7.

19 Malek N, Swallow D, Grosset KA, Anichtchik O, Spillantini M, Grosset DG. Alpha-synuclein in peripheral tissues and body fluids as a biomarker for P arkinson's disease--a systematic review. *Acta Neurol Scand* 2014; **130**: 59–72.

20 Beach TG, Adler CH, Sue LI, *et al.* Multi-organ distribution of phosphorylated alpha-synuclein histopathology in subjects with Lewy body disorders. *Acta Neuropathol* 2010; **119**: 689–702.

21 Kim S, Kwon S-H, Kam T-I, *et al.* Transneuronal Propagation of Pathologic α-Synuclein from the Gut to the Brain Models Parkinson's Disease. *Neuron* 2019; **103**: 627–41.e7.

22 Braak H, Rüb U, Gai WP, Del Tredici K. Idiopathic Parkinson's disease: possible routes by which vulnerable neuronal types may be subject to neuroinvasion by an unknown pathogen. *J Neural Transm* 2003; **110**: 517–36.

23 Braak H, Del Tredici K, Rüb U, de Vos RAI, Jansen Steur ENH, Braak E. Staging of brain pathology related to sporadic Parkinson's disease. *Neurobiol Aging* 2003; **24**: 197–211.

24 Li J-Y, Englund E, Holton JL, *et al.* Lewy bodies in grafted neurons in subjects with Parkinson's disease suggest host-to-graft disease propagation. *Nat Med* 2008; **14**: 501–3.

25 Kordower JH, Chu Y, Hauser RA, Freeman TB, Warren Olanow C. Lewy body–like pathology in long-term embryonic nigral transplants in Parkinson's disease. *Nat Med* 2008; **14**: 504–6.

26 Desplats P, Lee H-J, Bae E-J, *et al.* Inclusion formation and neuronal cell death through neuron-to-neuron transmission of alpha-synuclein. *Proc Natl Acad Sci U S A* 2009; **106**: 13010–5.

27 Hansen C, Angot E, Bergström A-L, *et al.* α-Synuclein propagates from mouse brain to grafted dopaminergic neurons and seeds aggregation in cultured human cells. *J Clin Invest* 2011; **121**: 715–25.

28 Cisbani G, Maxan A, Kordower JH, Planel E, Freeman TB, Cicchetti F. Presence of tau pathology within foetal neural allografts in patients with Huntington's and Parkinson's disease. *Brain* 2017; **140**: 2982–92.

29 Cicchetti F, Lacroix S, Cisbani G, *et al.* Mutant huntingtin is present in neuronal grafts in Huntington disease patients. *Ann Neurol* 2014; **76**: 31–42.