® Postepy Hig Med Dosw (online), 2018; 72: 830-845
e-ISSN 1732-2693

www.phmd.pl
Review

Received: 03.01.2018
Accepted: 19.07.2018
Published: 19.09.2018

Facts and speculations on the infectious nature of Alzheimer's disease

Zakaźność choroby Alzheimera – fakty i spekulacje

Katarzyna Bilińska, Patrycja Jakubowska, Agnieszka Woźniak, Rafał Butowt

Departament of Molecular Cell Genetics, Nicolaus Copernicus University in Toruń, Ludwik Rydygier Collegium Medicum in Bydgoszcz

Summary

For over 30 years, a large volume of data has been collected indicating the possibility of an infectious form of Alzheimer's disease (AD). Using various AD animal models and patients' brain extracts it has been demonstrated that amyloid Aβ (Aβ) can be an infectious agent. The similarities of Aβ and PrP^{sc} prion protein (PrP^{sc}) have been an important indicator of a potentially infective nature of AD. Nonetheless, the majority of epidemiological data have not yet supported the hypothesis of the infectious nature of this disease. It must be emphasized that AD is a very complex disease which is most likely unique to humans. The strong evidence on the infectivity and propagation of Aβ in animal models is accompanied by the uncertainty of whether the observed symptoms can be recapitulated in humans. Therefore, using currently available AD models it may not be feasible to collect data of sufficient quality clearly and unambiguously demonstrating the infectivity of the disease. We postulate that in order to gather stronger evidence for AD infectivity in humans, new experimental strategies must be considered. This approach should also lead to better understanding of the peripheral routes of Aβ infection. The aim of this review is to present the current state of knowledge and existing doubts in this important area of neurobiology and medicine. In the light of available data, AD infectivity has still not been proven, yet it should be seriously considered. The confirmation that some forms of AD are infectious may result in significant scientific, medical and social consequences.

Keywords: **Alzheimer's disease • amyloid Aβ • Aβ peptide • prion protein • neurodegenerative diseases • transmissible protein aggregates**

GICID 01.3001.0012.4938
DOI: 10.5604/01.3001.0012.4938
Word count: 13216
Tables: 2
Figures: 2
References: 111

Author's address: Rafał Butowt, Departament of Molecular Cell Genetics, Nicolaus Copernicus University in Toruń, Ludwik Rydygier Collegium Medicum in Bydgoszcz, ul. M. Skłodowskiej-Curie 9, 85-094 Bydgoszcz, e-mail: r.butowt@cm.umk.pl

*This publication has been supported by a grant of Polish National Science Centre (UMO-2013/09/B/NZ3/02359)

ALZHEIMER'S DISEASE AS THE MOST COMMON NEURODEGENERATIVE DISEASE

Alzheimer's disease (AD) was described for the first time by the German neuropathologist Alois Alzheimer in the early 20th century. It is the most widespread human neurodegenerative disorder. According to various estimates, AD accounts for 50% up to even 70% of all cases of neurodegenerative diseases and dementias. Generally, in this case we can already refer to it as a pandemic, because there are currently 46 million people in the world who suffer from AD [83]. The incidence of the disease increases significantly with age, doubling on average every 5 years after the age of 65. For this reason, it is a condition that has the biggest impact on reducing the quality of life of the elderly. In spite of intensive research conducted for several decades and extensive funds allocated for testing new therapies, the exact mechanism of the disease development is still unknown. There is also no therapy that could reverse or at least stop the development of clinical symptoms.

AD as well as many other less common neurodegenerative diseases may occur in the genetic and sporadic forms. The genetic form is caused by the presence of one of several hundred detected mutations in three genes (*APP, PSEN1* and *PSEN2*). The causes of the sporadic form are unknown, although it occurs in over 99% of all cases [10]. Since the beginning of research on AD the hypothesis of infectivity of this disease has been considered, i.e. transmitted between humans or by contact with an infectious agent present in the external environment. Seemingly such considerations may seem unwarranted, because the etiology of neurodegenerative diseases has never been specifically linked to any classic infectious agents such as bacteria or viruses. Therefore, it has long been accepted that these diseases do not occur in an infectious form. However, in the 1960s., it was proved that one of the rare endemic prion diseases known as kuru is an infectious disease [40]. Kuru does not exist any longer; its causes were associated with ritual acts of cannibalism among the Fore people of Papua New Guinea. The research on this first infectious neurodegenerative disease was recognized and honoured with Nobel Prize in 1976 in Physiology and Medicine for Daniel C. Gajdusek. Later, it turned out that another human prion disease, known as iatrogenic form of Creutzfeldt-Jacob disease (iCJD), also has infectious etiology [14]. For a long time it seemed that infectivity of prion diseases was the exception rather than the rule among neurodegenerative disorders. However, the current state of research on the mechanisms leading to the development of neurodegeneration calls for serious consideration of the occurrence of an infectious form of AD. The aim of this paper is to present the current state of knowledge in this field, with particular emphasis on the arguments for and against AD infectivity.

CONFIRMATION OF AD INFECTIVITY IS IMPORTANT FROM THE CLINICAL POINT OF VIEW

The issue of infectivity is important from the clinical point of view due to the very frequent occurrence of AD compared to rare prion diseases. In the case of the infectious form of prion disease, it was demonstrated that up to several hundred cases of infection occurred in the past because of various medical and neurosurgical procedures. An example of such a procedure may be administering cadaver-derived pituitary human growth hormone (GH) preparations to young persons to treat dwarfism in the years 1958-1985. In the late 1980s. it was proven that some of these preparations were contaminated with the pathogenic form of the prion protein which is an infectious agent. Several years up to a few decades later, the infected persons died of iCJD [14]. Similar events occurred also following corneal transplants or dura mater grafts. For this reason, the use of cadaver-derived GH was discontinued, which stopped a further increase in the incidence of iCJD. However, it should be remembered that the incidence of iCJD is several orders of magnitude lower than the incidence of AD. Therefore, the confirmation of AD infectivity may not only change the fundamental understanding of this disease, but it will also have more significant clinical consequences [1]. Proving that infections are possible, even if they were rare among all AD cases, could affect the patient's treatment and performance of medical/neurosurgical procedures [63].

VERIFICATION OF THE AD INFECTIVITY HYPOTHESIS IN PRIMATES

Infectivity of prion diseases was confirmed in chimpanzees and later in other monkeys [40]. Therefore, the first attempts to verify the AD infectivity hypothesis were made on the same experimental model. Certain clinical and histopathological similarities between prion diseases and AD contributed to this hypothesis. In addition, the co-occurrence of CJD and AD – although difficult to interpret – has been acknowledged for long time [15, 72, 104]. During these pioneer experiments it was assumed that the incubation period of AD was at least a few years, hence these experiments had to last for a relatively long time. The first results of intracerebral inoculation of brain extracts from AD patients in primates were published in 1978 [87]. They initially confirmed that this route for the spread of the disease was possible. However, 2 years later, such explicit conclusions were not reached when extended results of these studies on a larger number of animals were published [45]. This may indicate a complete absence of infectious etiology of AD. However, this could also result from the fact that AD development requires a much longer incubation period compared to prion diseases. Conducting individual experiments that last longer than 4-5 years is very difficult. At that time, antibodies that specifically recognized prion protein and Aβ plaques/aggregates had not yet been introduced into research, which in practice impeded a clear interpretation of histopathological results. Therefore, the final criterion in the above studies was the occurrence of clinical symptoms of AD, which were not convincingly detected. However, it should be taken into account that, in monkeys it may

not be possible to observe overall clinical changes that are characteristic of human patients.

Finally, in the 1980s transmissibility and infectivity of AD were considered as an open issue for debates, thus requiring further research. Some researchers at that time were inclined to postulate that AD itself was not likely to be an infectious disease [39, 42]. Supporters of the AD infectivity hypothesis stressed the importance of the recipient's genetic background as well as other potentially necessary requirements such as the presence of proinflammatory factors [94]. It was argued that the complexity of the issue may hinder proving interindividual transmissibility of AD, which, however, occurs under strictly defined conditions [107]. Then, in the 1990s., the results of many years of research on marmoset monkeys were published. The animals used in the research were analyzed after 7 years following intracerebral inoculation of extracts derived from AD patients. These data confirmed the possibility of infection by direct contact of the infectious agent with the brain [5, 6]. At that time, there was a growing awareness that the preclinical stage of AD in humans may actually last as long as 20-30 years. That is why research on transmission of AD from humans to marmoset monkeys via intracerebral inoculation became a long-term project. This resulted in further studies published in 2006 [88], in which a number of monkeys were analyzed after intervals up to 8-9 years following intracerebral inoculation of AD extracts. The results obtained again confirmed a significant positive correlation between the occurrence of Aβ plaques – typical of AD – in the brains of the marmosets and the inoculation with patient-derived brain extracts. The use of control extracts from healthy subjects did not result in significant accumulation of Aβ aggregates. In addition, in control animals of comparable age no spontaneously developing Aβ plaques were found [5, 88]. Importantly, no sporadic or genetic forms of the prion disease were observed in the group of monkeys under study. This ruled out the direct effect of the prion disease on the development of the histopathological features characteristic of AD.

The above experiments carried out in monkeys indicate a significant probability of the occurrence of the infectious form of AD in humans. It should be noted, however, that the main reference point in these studies was solely the histopathological analysis of brains with the use of immunocytochemistry. As was mentioned above, no clinical symptoms typical of AD were found in the monkeys [34]. The histopathological features as such may not be a sufficient criterion for the occurrence of AD, since in some persons senile plaques can be detected without coexisting dementia and other symptoms characteristic of AD [93]. In addition, the histopathological analysis of brains in these studies did not detect hyperphosphorylated tau tangles, which are also characteristic of AD patients. Doubts also resulted from the fact that intracerebral inoculation of synthetic Aβ in monkeys did not induce Aβ plaques, as was observed following the inoculation of human brain extracts derived from AD patients [81, 88]. Recently, chimpanzees' brain sections obtained by Daniel C. Gajdusek et al. several decades ago during the first attempts to verify the hypothesis of AD infectivity, have been subjected to retrospective analysis. It was possible because paraffin-embedded brain samples can be stored in well preserved condition for a long time. These studies were performed using state-of-the-art research tools such as a wide panel of specific monoclonal antibodies towards various Aβ conformers that were not available during the initial analysis. Similarly to marmosets, these results also indicate the infectious potential of AD [44]. As noted above, the analyzed brains belonged to monkeys that did not show any clinical symptoms of AD during the initial analysis [45]. The fulfillment of histopathological criteria in monkeys in the absence of clear clinical symptoms does not necessarily contradict the AD infectivity in humans, which is discussed briefly at the end of this paper

TRANSGENIC ANIMAL MODELS SUPPORT THE HYPOTHESIS OF AD INFECTIVITY

Experiments performed in monkeys have numerous limitations such as high costs, very long duration of experiments and difficulties with using a large number of animals. These limitations were minimized in the mid-1990s., when the technology of genetic modifications in mice developed rapidly. These transgenic mouse models have become most widely used in AD research. Most of the so-called „AD mice" show high levels of expression of APP, PS1 or PS2. Frequently, a combination of different mutations and overexpression of more than one of the above-mentioned human proteins is used in one mouse line. The endogenous mouse proteins are less frequently modified, and they are „humanized" by inserting a fragment of the appropriate human gene into their sequence [2]. Due to the fact that for each of the three aforementioned genes many mutations have been indentified that lead to the familial form of AD in humans, currently over 100 mouse models of AD are known. Although these mouse lines do not show all symptoms characteristic of AD in humans, apart from histopathological changes they also show certain behavioral and cognitive changes resembling the human disease. These include, for example, memory impairments and impaired long-term synaptic potentiation. An important difference between the brain material derived from the AD mouse model and human AD brain analyzed *post mortem* is usually the lack of atrophy of neurons in the former.

One of the most popular genetically modified models is the Tg2576 mouse. This mouse line is characterized by high-level expression of amyloid precursor protein (APP) bearing the Swedish-type mutation in codons 670 and 671 [52]. Expression of the mutant protein causes the formation of significant amounts of Aβ deposits in mice aged about 9-10 months. These deposits are similar to the deposits present in the brains of AD patients. Tg2576 model was used for intracerebral inoculation

of diluted brain extracts derived from AD patients. A much faster formation of amyloid plaques containing Aβ was observed than without inoculation (Fig. 1A) [57]. Controls involving the inoculation of extracts from human healthy control subjects of similar age or from wild-type mice into the cortex of Tg2576 mice did not cause the observed changes (Fig.1C) [57]. This suggested, similarly to previous experiments in monkeys, the possibility of transmitting an infectious agent present in the inoculated extract to the recipient's brain. Significantly accelerated formation of Aβ plaques was observed only in genetically modified mice and not in wild-type mice (Fig.1A and B). The work of Kane et al. [57] initiated a series of further studies using other transgenic mouse models, and sometimes also rat models [90]. Their goal was to thoroughly verify the hypothesis of AD infectivity and to examine the mechanism of Aβ propagation in the brain. Subsequent studies performed on the APP23 and APPPS1 mouse lines confirmed the possibility of disease transmission by intracerebral inoculation of brain extracts derived from AD patients or old AD mice [66]. Using AD mice it was also demonstrated that the acceleration of Aβ plaques formation positively correlated with the time that had elapsed since inoculation and with the concentration of Aβ aggregates present in the brain extracts [68]. Importantly, immunodepletion of Aβ with anti-Aβ antibodies added to brain extracts before inoculation caused a significant reduction of acceleration of Aβ accumulation in the recipient (Fig.1D) [66]. A similar result was obtained after previous immunization of recipient mice against aggregated forms of Aβ, or removal of Aβ molecules from the brain extracts using the ASR1 reagent bound to magnetic beads [26]. This proves that in the biochemically complex brain extract, these are the various forms of Aβ that are the component specifically responsible for the process of infection and propagation of Aβ in the recipient's brain. Inoculation of AD brain extracts in wild-type mice does not result in the formation of new Aβ aggregates (Fig. 1B) [57, 66]. In contrast, injection as small amounts of Aβ as found in a million times diluted AD brain extract into the brain of Tg2576 mice also leads to accelerated accumulation of Aβ [68]. This indicates that the observed aggregates in the brains of recipient mice are not exclusively the result of a simple transfer of Aβ present in the inoculated extract. These results suggest that an amplification process occurs which causes the number of aggregates to grow in the infected brain. Two essential conclusions can be drawn from the data presented: first of all, in the experimental models applied, it is undoubtedly possible to infect a compatible recipient with Aβ present in the external environment. Secondly, the amount of Aβ in the recipient's brain is increasing, which is probably caused by amplification of the pathogenic structures of this peptide.

The ability to infect and to propagate Aβ within the mouse brain is manifested not only by brain extracts from AD patients and aged AD mice. The same properties were demonstrated by extracts derived from the elderly who had a significant number of Aβ plaques in their brains, but nevertheless did not show clinical symptoms [27]. Persons who accumulate significant amounts of Aβ plaques in their brains without concurrent cognitive changes are probably in the asymptomatic long-term preclinical stage of AD [24].

While using the AD mouse model it was also proved that, similarly to iatrogenic prion diseases, neurosurgical procedures may be a potential source of infection. This was demonstrated by initiating the process of β-amyloidosis using a steel rod, inserted in the brain of a young mouse and coated with a brain extract derived from an old AD mouse [29].

Despite many convincing observations, papers using genetically modified mouse models were often accepted with skepticism due to the lack of similar effects after intracerebral inoculation of AD extracts in wild-type mice. However, this can be explained – according to the view currently considered among neuroscientists – by the fact that AD is a disease unique to humans [34, 103]. Murine APP protein has indeed biological properties similar to the human homologue and it is subject to the same posttranslational modifications and complex proteolysis in neurons [71]. Yet, minor differences between the amino acid sequence of APP in mice and in humans result in the formation of the endogenous Aβ peptide that does not show tendencies to aggregation and β-amyloidosis [38]. Thus, to initiate the β-amyloidosis in mice, it is necessary to introduce the human APP gene or optionally to insert the sequence coding a human Aβ peptide fragment within the mouse gene. As highlighted, most of the discussed studies used transgenic mice in which human APP containing various mutations causing the genetic form of AD was overexpressed. However, it is acknowledged that the Aβ peptide derived from wild-type human APP also tends to aggregate. Therefore, the process of transmission of Aβ from the AD extract to the recipient mouse brain should also be successful if the mouse is modified with human APP without mutations. This type of mouse line (huAPP mouse) was created as early as in 2000. Unlike the mouse line with mutant APP, in the huAPP mouse, even in later stages of its life, Aβ deposits in the brain are not detected [70]. When the AD brain extract was injected into the hippocampus of this mouse, Aβ plaques formed in large areas of the brain were also visible (Fig. 1E) [69]. It means that the effects of infection and spreading of β-amyloidosis can be achieved not only in mice with expression of proteins carrying mutations characteristic of the genetic form of AD. This is also the case in genetically modified mice in which Aβ aggregates and senile plaques are never produced during lifetime. Moreover, a widely criticized aspect of AD mouse models is too high and presumably non-physiological level of expression of human transgene. One of the latest studies, however, showed that transmissibility and accelerated accumulation of Aβ can also be observed in knock-in mice in which the expression level

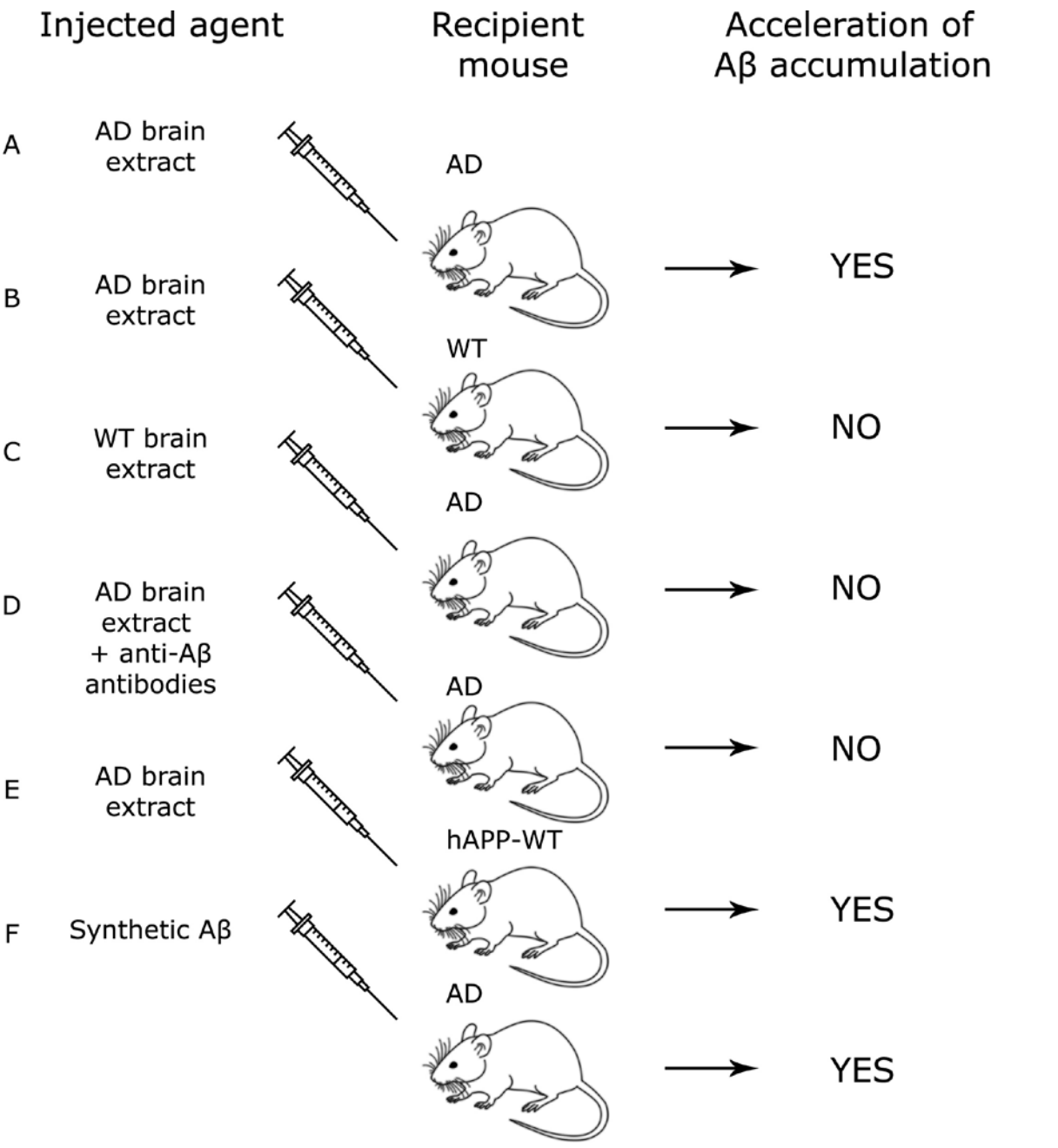

Fig. 1. Effects of intracerebral inoculation of brain extracts containing Aβ in mice

of the mutant APP gene is similar to the expression of the endogenous mouse gene [91].

Current research also indicates that intracerebral inoculation of tau protein aggregates derived from the brain of AD patients initiates the aggregation of this protein even in the brain of genetically unmodified wild-type mice [73]. Potential transmission of neurotoxic tau protein aggregates was also observed in persons who received contaminated GH preparations in early stages of their life [28]. The tau protein is the second – in addition to APP – major aggregating protein involved in the AD pathogenesis. Published data indicate that this protein demonstrates – similar to Aβ – properties of intermolecular transfer of the pathogenic conformation to native non-pathogenic molecules of this protein [4]. A potential mechanism of this process is discussed in the further part of this paper.

SYNTHETIC AB AS THE FINAL TEST IDENTIFYING AN INFECTIOUS AGENT

In order to induce β-amyloidosis in the recipient, diluted brain extracts derived from AD patients or from old AD mice were used in majority of studies conducted in primates and genetically modified mice. Such extracts, in

addition to Aβ, also contain numerous low molecular weight chemical compounds and macromolecules which can be an important factor initiating or modulating the amyloidogenesis of Aβ. As mentioned above, experiments, in which immunodepletion of Aβ was performed using specific antibodies added to brain extracts prior to inoculation or immunization of the recipient mouse against Aβ, almost completely inhibited the development of Aβ aggregates (Fig. 1D) [31, 66]. This suggests that Aβ is the main initiator of β-amyloidosis in the recipient. There is a consensus that the final evidence confirming these results would be the induction of histopathological features characteristic of AD using synthetically produced Aβ. Initial attempts to induce infection and propagation in the recipient's brain with the Aβ peptide produced in cell-free system and aggregated *in vitro* gave negative results both in monkeys [81, 88] and in AD mice [66, 77]. Until now, two groups of researchers have managed to induce infection and propagation of Aβ in the brain of AD mice with such a synthetic agent (Fig.1F) [59, 99]. However, the infectious activity of Aβ thus produced is at least two orders of magnitude lower than the brain extracts containing a comparable amount of this peptide [98, 99]. Therefore, additional factors are probably necessary to obtain *in vitro* the spatial structure of Aβ that would be optimal for the infection and initiation of β-amyloidosis. Such factors supporting the process of polymerization and aggregation of Aβ are likely present in living cells, especially in neurons [77]. A similar situation occurs in the process of *in vitro* production of synthetic PrP^{sc}. In this case, many cofactors supporting the production of a pathogenic conformation, such as some phospholipids or RNA molecules, were detected [110]. Therefore, to obtain synthetic Aβ with much higher infectious potential, it is necessary to characterize additional factors affecting the process of Aβ aggregation in living neurons.

THE MOST RECENT CHAPTER OF THE DEBATE – RETROSPECTIVE STUDIES OF HUMAN BRAIN

In spite of existing controversies, the general outcome of research performed in monkeys and with genetically modified animal models clearly suggests that in addition to the genetic and sporadic forms, the infectious form of AD may also exist. So far, no data from human brains have been found, because similar experiments as those carried out in animals could not, obviously, be performed in humans. However, it is possible to retrospectively analyze the preserved brain materials derived from deceased persons who were in contact with an agent that could potentially cause AD transmission from one person to another. For this purpose, one can, for example, analyze paraffin-embedded brain samples of persons who died of iCJD caused by the administration of improperly purified preparations derived from human brain.

Due to the fact that brain samples derived from different persons were processed together, the processing technology leading to iCJD was very conducive to infections. This material is therefore a unique model for testing a potential transmission of not only prion disease but also other neurodegenerative diseases. As early as in 2006, a case of a 28-year-old patient was described, in whom after the cadaver-derived dura mater graft an infectious form of iCJD developed. In this patient, despite such a young age, symptoms of developing AD neuropathology were also observed (Table 1) [82]. The publication containing this data remained almost unnoticed as it concerned a single clinical case. The authors themselves speculated that the cause of the histopathological development of AD in this patient could be brain damage in early childhood, and not the transmission of the infectious agent from the dura mater graft [82].

The results of the work published in the last two years strengthened the hypothesis of AD infectivity. Researchers from the John Collinge's and Sebastian Brandner's laboratories carried out a retrospective immunocytochemical analysis of brain samples of patients who died of iCJD [54]. Such persons are very closely monitored in the UK and their brains are stored for many years. The development of iCJD in these people was caused by injections of contaminated cadaver-derived pituitary GH preparations in the past. Therefore, during the GH administration, these patients were repeatedly administered potentially infectious human brain extracts via the circulatory system. Surprisingly, Aβ aggregates and plaques characteristic of AD were found in the brain samples of most of individuals under study [54] (Table 1). What is important, these persons died at a much too early age to develop sporadic AD. Aβ deposits are observed in AD-asymptomatic persons, but these individuals are always at an advanced age [21]. Therefore, the logical reason for the detection of Aβ aggregates in the analyzed samples was the induction of β-amyloidosis by Aβ found in GH preparations administered to these persons in the past. Following the above, these individuals probably did not develop full clinical symptoms of AD, because they had died earlier due to a faster-developing iCJD prion disease. According to an alternative scenario consistent with the controversial hypothesis of the so-called cross-seeding, aggregation of Aβ could be initiated by the previously generated aggregates of pathogenic PrP^{sc}. However, the analysis of control materials derived from persons who died of sporadic CJD (sCJD) at a similar age did not show statistically significant presence of aggregates and Aβ plaques [54]. Previous studies also failed to prove a cause-and-effect relationship between prion diseases and AD, although this possibility was suggested by some *in vitro* obtained data [47,101]. For example, the analysis of 110 cases of CJD has led to the conclusion that the co-occurrence of histopathological features of CJD and AD is accidental and rather associated with advanced age [47]. Although some earlier studies have shown that Aβ deposits are frequent in prion diseases, they are difficult to interpret because they mainly affect the genetic form of CJD [41, 104] or elderly patients who are frequently known to have Aβ deposits without the clinical symptoms of

Table 1. Comparison of the results of histopathological analysis of human brain samples from iCJD patients performed for the hallmarks of AD

References	Preusser et al., 2006 [82]	Jaunmuktane et al., 2015 [54]	Frontzek et al., 2016 [37]	Kovacs el al., 2016 [58]	Hamaguchi et al., 2016 [48]	Ritchie et al., 2017 [89]	Duyckaerts et al., 2018 [28]	Cali et al., 2018 [19]
Clinical phenotype	CJD	CJD	CJD	CJD	CJD	CJD	CJD	CJD
Cause of iCJD	hDM	hGH	hDM	hDM	hDM	hGH	hGH	hGH and hDM
Number of cases examined	1	8	7	2	16	33	24	21
Number of cases with Aβ parenchymal deposits	1	6	5	2	13	12	1	5
Number of cases with Aß CAA deposits	1	4	5	2	11	14	1	11
Age of cases with Aß deposits	28	40 – 51	28 – 63	28-33	35 – 81	20 – 38	23-39	23-54

[a] All the results except publications [82] were statistically significant, [b] All studies except [37] performed genetic testing which excluded mutations involved in familial AD, [c] In the studies[28, 48, 89] deposition of hyperphosphorylated tau has been shown.

AD [46]. Summing up, the results of Jaunmuktane et al. [54] evidence against *de novo* induction of Aβ aggregates by pathogenic prion protein, although they do not completely exclude this possibility. Clearly, however, they suggest the possibility of infection and, consequently, the initiation of β-amyloidosis by exogenous forms of Aβ found in human GH pituitary preparations. Some researchers speculate that both processes may even occur simultaneously [63]. It would be advisable in this case to analyze GH preparations used in the past for their Aβ content. In practice, this is difficult because in 1985 their use in medicine was discontinued. Only in one study such analysis was performed, thus confirming the presence of aggregated potentially toxic Aβ in these preparations [28]. In addition, the presence of Aβ aggregates has been demonstrated in some pituitaries derived both from patients and healthy controls that have never been used for GH administration [53, 54]. This clearly indicates the possibility of transmitting pathogenic Aβ aggregates as a result of using human pituitary preparations.

Jaunmuktane et al. [54] initiated a new chapter in the debate on the infectious form of AD [1]. Soon, independent analyses of similar brain samples derived from persons who died of iCJD were initiated in other laboratories. Over the past few years, the results of 6 additional studies have been published which significantly confirm the key assumptions made by Jaunmuktane et al. [54] (Table 1). In one of the studies, Ritchie et al. [89] have recently analyzed brains derived from a much larger number of persons who died of iCJD because of having taken pituitary preparations. Similarly, a very high correlation was found between the prion disease infection and Aβ plaques that are typical of AD. Control brain samples from persons who died of other forms of CJD showed no significant accumulation of Aβ deposits. About half of the brain materials from persons who had taken contaminated pituitary preparations but died of a different reason than iCJD also contained Aβ aggregates [89]. This is an important observation, which also undermines the hypothesis about the potential initiation of Aβ aggregation by the pathological prion protein. It should be emphasized that in the above studies microscopic colocalization of both types of protein aggregates was not observed, which evidences against the hypothesis claiming that the pathological prion protein is a factor causing the formation of Aβ aggregates. There are previous reports of colocalization of PrP^{sc} and Aβ but they usually concern single cases and/or patients at an advanced age [79,104]. Another factor, apart from exogenous Aβ infection, that could initiate spontaneous formation of Aβ aggregates at an early age is the occurrence of a mutation characteristic of the genetic form of AD. In earlier studies suggesting the effect of PrP^{sc} on the formation of Aβ deposits, the occurrence of mutations that could possibly promote the aggregation of Aβ was not verified [104]. However, in recent studies, including a retrospective analysis of brains derived from persons who died of iCJD, a wide range of this type of genetic analyses was carried out. Sequencing of DNA isolated from brain samples did not confirm the presence of mutations that cause accumulation of Aβ [54, 89]. It is worth noting that many different mutations were analyzed, not only those related to the development of AD, but also mutations that affect other neurodegenerative disorders [54]. In addition, the polymorphisms increasing the likelihood of AD, such as the presence of the

ApoEε4 allele, were also verified. This allele is a widely accepted genetic factor that increases the risk of AD.

Brain samples from persons who died of iCJD are not readily available and therefore such analyses cannot be widely performed in many independent laboratories. This stems from the fact that most cases of iCJD infection have been reported so far in the UK, France and the USA. In other countries, these were only single cases [13, 14]. As it is already known, however, taking pituitary preparations is not the only possible iatrogenic route of CJD infection. Such infections also occurred in the past following cadaver-derived dura mater grafts. When brain sections, derived from persons who died later of iCJD, were analyzed with a view to the presence of plaques and Aβ aggregates, a very frequent occurrence of the histopathological features characteristic of AD was also observed [37, 48, 50, 58]. As in the case of brains from persons taking pituitary preparations, controls' analysis did not show statistically significant correlations. According to the authors, this precluded the initiation of Aβ aggregation by pathogenic PrP^{sc} found in dura mater grafts. No mutations characteristic of the genetic form of AD were found. There was also no significant correlation between the occurrence of Aβ aggregates and the presence of the ApoEε4 allele which increases the probability of their formation. The results of the latest study in which the subject of concurrent analysis were brain samples from patients coming from different countries who were infected with contaminated pituitary preparations or dura mater grafts indicate that the accumulation of Aβ aggregates in cerebral vessels and the absence of tau protein aggregates are a shared feature [19]. Perhaps, Aβ in humans demonstrates a greater potential for infection and/or induction of its own β-amyloidosis compared to toxic forms of the tau protein. On the other hand, the first analysis of a group of 24 French patients who died of iCJD as a result of the administration of contaminated GH preparations showed only one case of Aβ pathology and it was rather in the parenchyma of the brain, and not in the vessels [28]. The authors of this study are of the opinion that this is due to the much shorter incubation period of iCJD in this group of patients compared to the UK patients. Due to the more rapid death of iCJD, there was probably not enough time for Aβ to accumulate and aggregate in their brains [28]. It is also possible that the procedures for the purification of cadaver-derived pituitary GH preparations used in France have been more effective in eliminating toxic forms of Aβ compared to the procedures used in the United Kingdom.

In the light of the above research, both the results of studies based on the brain material from persons infected with „pituitary" preparations and dura mater grafts lead to the same conclusion. These studies show that not only is the infectious form of PrP^{sc} transmitted to humans, but also an additional infectious agent causing slow development of AD pathology is transmitted (Table 1).

POSSIBLE ROUTES OF INFECTION WITH AB

From the data presented, it can be concluded that in some AD patients an Aβ infection could have occurred and the infectious agent could enter the body via various routes. Table 2 shows potential routes of infection with Aβ and their relative infection potential has been estimated. The direct contact with the central nervous system is considered to be the most effective route of infection. It occurs, for example, during neurosurgical procedures, such as the above mentioned dura mater grafts. After such procedures patients were infected with the pathogenic prion protein and in some cases probably also with Aβ. They died of iCJD disease because this disease is characterized by a shorter incubation period compared to AD. It should be noted that the iatrogenic form is one of the fastest-growing forms of CJD disease. Its incubation period after direct contact of the infectious agent with the brain lasts between a few to 24 months on average [62]. Therefore, presumably in this case, the incubation period of AD may also be shorter than that of most other sporadic AD cases. Certainly, however, these are years rather than months, as long-term incubation periods were required in previously discussed experiments with intracerebral Aβ inoculation in monkeys [88]. In addition, recent studies carried out in the laboratory of Sebastian Brandner indicate a positive correlation between the occurrence of amyloid aggregates characteristic of AD in the brain of middle-aged patients and the various neurosurgical procedures performed in their childhood [55]. These studies were done in a group of patients that did not show any pathology associated with prion protein aggregates [55]. Also these patients were too young to have Aβ aggregates and plaques occurring spontaneously. In this case, the time from performing the neurosurgical procedure until the occurrence of significant amounts of Aβ was ca. 30-40 years.

Other potential pathways of Aβ infection are also considered. The intravenous route is less thoroughly described but also very likely; it was used when patients were given cadaver-derived pituitary GH preparations. As discussed above, in the brains of many of these patients, a statistically significant prevalence of histopathological features of AD was observed. It can be assumed that the clinical symptoms of AD would have developed if they had not died earlier due to iCJD. Incubation of iCJD as a result of infection with GH preparations takes, on average, up to over a dozen years. However, in the case of AD the preclinical stage is probably longer [62]. On the other hand, in the AD mice model the transmission of Aβ via the intravenous route has been described so far in two cases. This was obtained for the first time after multiple intravenous injections of 100 μg of synthetic Aβ [59]. Therefore, in order to cause infection and accelerated aggregation of Aβ, at least several dozen times more synthetic factor should be administered via the circulatory system than via the intracerebral route [59, 99]. In the second study, AD mice were injected intravenously with brain extracts derived from AD patients and, after

Table 2. Possible routes of infection and assessment of the relative infectivity of Aβ

Routes of inoculation	Relative infectivity	References
Intracerebral	****	[37, 55, 57, 66, 87]
Intraperitoneal	***	[31, 32]
Intraocular	*	[29]
Intranasal	*	[29]
Oral	*	[29]
Intravenous	***	[16, 17, 54, 59]

180 days, significant accumulation of Aβ aggregates was observed [17]. This result was not achieved after the administration of extracts from healthy controls who were, at their death, at a similar age.

An additional argument indicating the possibility of Aβ infection via the intravenous route is Aβ's ability to cross the blood-brain barrier [111]. In addition, it has also been proved that it is possible to transmit Aβ from the blood of AD mice to the brain of wild mice through the combined blood systems of two individuals [16]. However, repeated epidemiological analyses on groups of persons with a history of frequent blood transfusions do not corroborate an increase in the risk of developing AD [11, 25]. Nevertheless, many researchers are of the opinion that epidemiological analyses do not document AD infectivity due to the complexity, heterogeneity, very long preclinical stage and other unique features of this disease. In addition, in the light of recent studies, the main difficulty in interpreting the impact of multiple blood transfusions may be the fact that these procedures can potentially have an opposite effect on the risk of developing AD. In mouse models, it was shown that after connecting blood systems of the young wild mouse and the old AD mouse, clinical symptoms of AD were reduced and/or the number of Aβ aggregates in the brain of the ill mouse was reduced as well [67, 108]. For this reason, administering plasma, derived from young persons to AD patients is now considered as a potential new treatment.

When using the AD mouse model, the possibility of intraperitoneal infection was also demonstrated [31, 32] (Table 2). The potential for infection and propagation of Aβ in the brain after peritoneal injection is significantly lower as compared to intracerebral inoculation of an identical extract in the same AD mouse model. In order to achieve an effect similar to intracerebral inoculation, approximately 40 times more AD extract was administered to the APP23 mice into the peritoneum [32]. As in the case of transmissibility by direct contact with the brain, the efficacy of the intraperitoneal route also depends on the concentration of Aβ in the extract used and the level of expression of the human mutant APP in the recipient mouse brain [31] (Table 2). However, it does not depend on the level of this protein expression in peripheral tissues, as it was shown using 3 different lines of AD mice [31].

Other peripheral AD infection routes remain almost unexplored and it is a surprising gap in this intriguing field of research. Until now, they have been the focus of only one study in which ineffectiveness of intranasal, oral and intraocular infection [29] was demonstrated by using the AD mouse model. This suggests low effectiveness of these infection routes, yet does not completely exclude them (Table 2). For example, some population studies analyzing the effects of anaesthesia and surgical procedures in the cardiovascular system suggest an increase in the risk of dementia and/or AD within a few to several years later [61, 75]. However, similar analyses of patients undergoing prostate and hernia surgery did not show an increase in the risk of dementia and AD later in life [102]. In addition, the analysis of the causes of death in the neurosurgeons' population showed that these persons were more likely to die of Alzheimer's disease compared to the general population's average [64]. One possible explanation for this phenomenon is a peripheral infection with Aβ, which can potentially occur during surgical procedures. In addition, the risk of developing AD increases more than six times when one of the co-habiting spouses is already suffering from this disease [76]. This may be related to peripheral pathogenic Aβ infection from a spouse suffering from the disease. Therefore, the issue of peripheral routes of Aβ infection is still poorly recognized and requires further detailed studies.

PrP^{Sc} AND Aβ SHOW SIMILARITIES IN THEIR BIOLOGICAL PROPERTIES

Extensive research on prion diseases over the last several decades has led to the confirmation of the concept of „prion" as a proteinaceous infectious particle that does not require DNA to propagate. This understanding of „prion" was already suggested in the early 1980s. by Stanley Prusiner [84]. Prion diseases, although very rare, have become a model and reference point that can facilitate understanding of more common neurodegenerative disorders. In simple terms, it is assumed that PrP is present in neurons in two basic spatial conformations: native, i.e. physiologically normal (PrP^{c}) and pathogenic, referred to as PrP^{sc}. Under the influence of endogenous or environmental factors, some of the molecules of native PrP^{c} may undergo a conversion into a less soluble and more aggregated form of PrP^{sc}. The results of many studies have shown that

after the development of seeds that initiate the generation of misfolded PrP^{sc}, this process has autocatalytic properties. The PrP^{sc} molecules are a kind of template that transmits its pathogenic conformation to native PrP^{c} molecules. As a result, many more PrP^{c} molecules are converted into a pathogenic form in the process of seed nucleation. The progressive accumulation of PrP^{sc} results in large aggregates of this protein being accumulated, as it may be observed histopathologically under the microscope. All molecular details of this process are still unknown. It is acknowledged that further propagation occurs along the neural connections to the neighbouring neurons and gradually covers other areas of the brain [56, 105]. The pathogenic forms of the prion protein are extremely chemically stable and resistant to degradation. As a result, they can survive in the external environment for a long time. That is why they are capable of transmitting the infection from one organism to another, for example by the intravenous, oral or the aforementioned cerebral route [95].

Currently, the term „prion" or „prion protein" is used not only in a narrower sense referring exclusively to PrP. In a broader sense, the term refers to a group of proteins that manifest abilities of transition between two different yet thermodynamically beneficial conformation states. Hence, such proteins or peptides are referred to as prion-like or prionoid proteins. It is believed that the conversion between two conformation states is dependent on the presence of prion-like domains enriched in asparagine/glutamine, which have been found so far in many completely different proteins [7]. In some cases, each of the two spatial states may be associated with another, not necessarily toxic, physiological function of a given „prion" protein [51]. In neurodegenerative diseases, only one of the spatial states of this protein is beneficial for the body, while the other is harmful. Many recent experimental data obtained both *in vitro* and *in vivo* indicate that Aβ displays such prion-like properties. Therefore, it is able to self-replicate inside neurons and slowly spread to connected cells [56, 68, 105] (Fig. 2).

The seed nucleation process and prion-like propagation was also demonstrated for Aβ in invertebrates, using the *Drosophila* nervous system [96].

The propagation of aggregates to neighbouring neurons is not only due to the process of seed nucleation and self-replication that leads to the generation of the pathogenic form of Aβ. The active axonal transport of Aβ molecules also participates in this process [12]. The use of axonal transport for propagation in the brain is also a feature of the prion protein [18]. Similar ‚prion' properties are also displayed by other important proteins associated with neurodegenerative processes, such as tau protein or α-synuclein that is associated with Parkinson's disease [43]. Aβ in its aggregated and β-sheet rich structure is, similarly as PrP^{sc}, resistant to digestion with proteinase K and to many other environmental factors [66, 99]. In addition, both types of pathogenic aggregates show high affinity to azo organic dyes such as Congo red [35]. These dyes recognize hydrophobic domains in proteins that tend to aggregate regardless of the primary structure. Moreover, both PrP^{sc} and Aβ deposits are located mainly in the extracellular space of the brain, although other aggregating proteins in neurodegenerative diseases form rather intracellular aggregates.

The data presented allow us to assume that another similarity to PrP^{sc} may be the ability of Aβ to initiate its own self-replication also in the infected body. Considering the prion properties of Aβ, it can be assumed that the mechanism leading to infection of the new organism is the same as the mechanism of Aβ propagation between neurons inside the patient's brain (Fig. 2) [30]. In both cases, pathological conformers of Aβ transmit their toxic spatial structure to the native soluble molecules of the Aβ peptide present in the yet unaffected neuron. The possibility of this scenario is evidenced by the results of previously discussed studies performed in monkeys and transgenic mice, as well as retrospective analyses of brains from persons infected with transmissible prion disease.

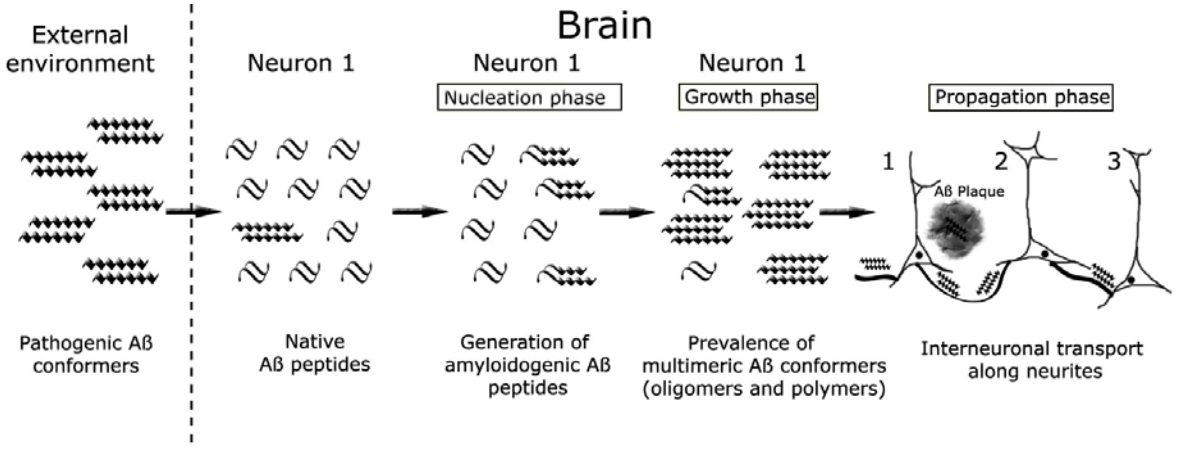

Fig. 2. Diagram of the infection process, nucleation and self-replication of Aβ in the nervous system

It is believed that, similarly as PrP^{sc}, also pathogenic Aβ exists in many different spatial conformations [49, 80]. In other words, there is no one pathogenic strain of Aβ, but many of its conformers or morphotypes. It is worth noting that such prion-like properties of Aβ could explain the long-observed interindividual variability at the histopathological and clinical level among AD patients [22, 86]. Presumably, various pathological Aβ conformers/morphotypes may lead to the development of AD with slightly different clinical symptoms. Aβ is known to be present in endogenous samples (brain extracts of AD patients or AD mice) as well as in preparations obtained *in vitro* as a complex mixture of many spatial forms differing in their degree of polymerization. It is not known exactly which of these multimers exhibit the strongest "prion" properties, and thus are mainly responsible for transmitting the aberrant conformation to subsequent native molecules of soluble and monomeric Aβ peptide. It is assumed that these may be some oligomeric conformers, and not highly aggregated polymeric forms that accumulate in the parenchyma and walls of cerebral vessels as senile plaques [78].

On the basis of these observations, it is increasingly accepted that despite differences in the amino acid sequence, both PrP and Aβ share many key biological properties. Both macromolecules belong to the same class of „prion-like" polypeptides exhibiting the feature of autocatalytic and self-replicating formation of amyloid aggregates [68, 105]. When assessing this issue from this perspective, the potential infectivity of Aβ is not surprising, because the ability of pathogenic conformers of PrP^{sc} to infect animals and humans has already been convincingly proved. It is worth adding that some aspects of the seed nucleation and aggregation process differ among the macromolecules discussed. For example, pathogenic forms of PrP^{sc} can now be obtained in completely cell-free system by the so-called method of cyclic amplification of protein misfolding known as the PMCA (Protein Misfolding Cyclic Amplification) technique [92]. So far, this technique has failed to achieve synthetic Aβ with an equally high degree of pathogenicity, as this may require the presence of other cofactors, compared to PrP^{sc} that is generated with the use of this technique. Aβ is probably not the only protein involved in the development of neurodegenerative processes that demonstrates „prion" properties. Currently, it is assumed that this is the nature of other important proteins associated with neurodegenerative processes, such as tau protein or α-synuclein [43].

INACTIVATION OF PATHOGENIC FORMS OF Aβ PRESENT IN THE EXTERNAL ENVIRONMENT

If, according to the data presented, we assume that the pathogenic forms of Aβ may cause the development of the infectious form of AD, it is important to know whether they can be effectively inactivated by routine methods. Studies using AD mice have shown that standard heat sterilization techniques may not be effective and only partially inhibit the induction of β-amyloidosis in the recipient [29, 66]. As with PrP^{sc}, non-standard sterilization techniques should also be used to inactivate Aβ. In order to completely inhibit the potential of brain extracts containing Aβ for the induction of the pathogenesis process, it is effective to use plasma sterilization [29]. It is worth noting that such cytotoxic compounds as formaldehyde do not completely inactivate the ability of pathogenic Aβ conformers to infect the recipient brain [36]. Similarly as PrP^{sc}, many polymeric forms of Aβ have a relative resistance to digestion with proteinase K [99]. They retain the properties of inducing β-amyloidosis despite digestion with this protease even for 30 minutes [60]. These data indicate an exceptional stability of infectious and pathogenic forms of Aβ in the external environment and in brain extracts. Thus, also in this respect, the properties of Aβ resemble pathogenic PrP^{sc}. In addition, pathogenic forms of Aβ can survive as dormant for a long period of time in the brain of an incompatible recipient, in whom they do not induce the formation of amyloid aggregates and still retain the ability to infect. An APP knockout mouse can be such a model incompatible recipient. The lack of APP results in the absence of native molecules of soluble Aβ peptide, to which the pathogenic conformation could be transmitted. Thus, the process of seed nucleation and self-replication of Aβ cannot take place. When the brain extracts of such mice were then used for the intracerebral inoculation in the AD mice, infection and accelerated formation of Aβ aggregates were nevertheless observed [109]. From the medical point of view, another undesirable property of Aβ aggregates is the ability to strongly adhere to metal surfaces, such as surgical instruments [29]. Nevertheless, it is possible to effectively inactivate pathogenic Aβ, as it is sensitive to protein-denaturing conditions, such as e.g. formic acid or strong alkaline compounds [66, 100].

THE FINAL EVIDENCE OF AD INFECTIVITY REQUIRES THE DEVELOPMENT OF NEW EXPERIMENTAL MODELS

As presented above, Aβ, which is likely to play one of the main roles in the pathogenesis of Alzheimer's disease, has many properties characteristic of prion protein [105]. For this reason, the possibility of Aβ infectivity is discussed according to the criteria previously adopted for PrP^{sc}. This classification includes four levels of infectivity: (i) molecular, i.e. the occurrence of a pathogenic form capable of initiating the transition of native forms of this protein into pathogenic forms inside the neuron, (ii) interneuronal, involving the spread of this protein within the nervous tissue, (iii) transport inside the body through intercellular connections and perhaps diffusion from peripheral tissues to the brain and (iv) the ability to transmit an infectious agent from one organism to another [30]. Currently, many studies postulate that Aβ is „infectious" on the first three levels mentioned above, but for many years it has not been possible to obtain final evidence that infection with Aβ is possible from human to human. Earlier studies discussing the use of apes and rodents suggested this possibility, but also

raised certain doubts. A new chapter in this long-term debate was opened by the study of Jaunmuktane et al. [54], in which atypical histopathological features characteristic of AD were observed in brains derived from iCJD patients. On this basis, the possibility of transmitting Aβ to human brain via contaminated preparations of cadaver-derived growth hormone was postulated [54]. Other researchers independently confirmed these results in groups of patients who died of iCJD due to grafts of cadaver-derived dura mater. Still, not all data on this subject are consistent and understandable. This is mainly due to the limitations of experimental models used and very high complexity of the Alzheimer's disease.

One of the main problems impeding finding the solution to the Alzheimer's disease is a considerable difficulty associated with modelling this disease in animals. It is believed that AD, in contrast to transmissible prion diseases, is a disease unique to human [34]. Rodents do not naturally suffer from AD and no deposits of Aβ are observed, even in older animals [8]. It seems that this is due to the difference of three amino acids' location in the 42-amino acid sequence of the mouse and human Aβ peptide [38]. In genetically modified AD mouse models, only some of the clinical symptoms characteristic of humans such as inhibition of long-term synaptic potentiation and changes in various types of memory are observed. In general, however, no tau tangles or a significant loss of neurons are detected. In the case of apes, the phenomenon of aggregation of senile Aβ plaques increasing with age has been observed, although mainly in long-living animals in captivity [34]. To date, no hyperphosphorylated tau protein tangles or clear clinical symptoms of the disease have been found in them [103]. All this means that AD animal models are characterized by significant limitations. On the other hand, without animal models, it is impossible to perform many basic experiments that are necessary to broaden our knowledge about potential infectivity of AD and to verify the concept of Aβ as a „prion-like" molecule.

Although well-defined criteria for AD in humans exist, such as the CERAD scores, there is little agreement among researchers which criteria are sufficient in animal models. It is believed that aggregation and deposition of Aβ plaques is a major process in the pathogenesis of Alzheimer's disease. However, it should be remembered that this is not a sufficient criterion. Nevertheless, it is widely accepted in studies using animal models. It has long been known that accumulation of Aβ plaques is observed in many elderly people, although some of them do not show cognitive symptoms characteristic of AD [21, 85]. Currently, it is assumed that Aβ accumulation significantly precedes cognitive changes and is a necessary but not the only condition for the development of full-blown AD [74]. It is assumed that one of additionally required processes is the formation of tau protein tangles, which occurs later than the aggregation of Aβ [97]. Therefore, caution should be taken when interpreting certain results, as some of the studies suggesting the transmissibility and infectivity of AD may in fact document only the process of Aβ aggregation in the recipient. It does not have to be synonymous with the occurrence of a fully developed human disease. It is possible that the development of all clinical symptoms would require additional factors or steps that may not be present in the recipients. Eespecially when it comes to a model non-human recipient such as mouse that never shows clinical symptoms without experimental manipulations. Thus, currently it is likely not possible to prove the AD infectivity hypothesis clearly and unambiguously.

It should be emphasized that currently, due to the lack of success of many therapies and clinical trials focusing on various forms of Aβ, the possibility that this factor may not be the main or sole cause of sporadic AD [3] is being more frequently considered. Due to the fact that the amount of collected data indicating high importance of APP and its derivative Aβ in the pathogenesis of AD is enormous, it can be assumed with high probability that Aβ is a necessary yet an insufficient factor for the development of this disease [65]. In addition to the aggregation of the Aβ peptide, at least three additional pathogenic pathways are present in the nervous system during the development of neurodegeneration. These include the development of severe inflammation, mitochondrial damage and increased oxidative stress [106]. Thus, perhaps at least four parallel molecular mechanisms that interact with one another are involved in the development of AD. In this respect, AD as well as other similar neurodegenerative disease seems to be unique. If this is the case, transmission of infectious Aβ from the environment to the human brain does not necessarily mean that AD develops, but may be one of conditions required for the full development of the disease. Therefore, nowadays the necessity to test combination therapies is often suggested. These therapies should target several mechanisms of pathogenesis at the same time, and not just different Aβ spatial conformers [106].

Very long time of asymptomatic preclinical stage of AD in humans also substantially hinders providing explicit evidence of AD infectivity. It is assumed that this is a period of at least 15 to even 30 years [20, 23]. Such long latent incubation periods are difficult to reproduce in laboratory conditions, which may explain the failure of some early experiments to transmit Aβ from humans to monkeys, or the difficulty in obtaining reliable epidemiological data. In transgenic mouse models high-level expression of human APP is most commonly used [33]. As a result, aggregation and accumulation of various forms of Aβ can be achieved during a relatively short lifetime of mice. However, it should be noted that the use of genetic manipulations can potentially distort the examined disease.

So far, relatively few papers have been published, that may deny the existence of a infectious form of AD.

These studies also have their weaknesses. A frequently cited paper presenting the opposite point of view is a study (from the laboratory of John Trojanowski [53]) on a group of people who received GH preparations in the past. It contains a statistical comparison of several hundred death certificates and the patients' medical history in the US population. This analysis did not show a significant increase in the incidence of AD [53]. It is worth noting, however, that medical records are often incomplete, and doctors are not always able to diagnose AD sufficiently early. This is due to aforementioned very long preclinical stage and high probability of death of other causes, despite the concurrent slow development of AD dementia. In addition, it should be emphasized that the incidence of infection with iCJD after the administration of GH pituitary preparations showed a significant variability between countries. These differences ranged from 0.4% to as much as 6.5% [14], which probably resulted from differences in GH biochemical purification protocols. This led to varying amounts of pathogenic prion protein and probably also of Aβ in the GH preparations administered later to humans. In the USA, infection with pituitary preparations was relatively scarce compared to, for example, the UK and France. This hinders the interpretation of epidemiological analyses of US patients.

Despite doubts, general implications of most studies conducted in monkeys and mice, as well as the latest data based on the retrospective analysis of human brains support the AD infectivity hypothesis. Perhaps only a small proportion of cases of sporadic AD is due to infection with pathogenic Aβ. However, it cannot currently be ruled out that the infection with exogenous Aβ is a frequent but difficult to detect phenomenon leading to the development of many cases of sporadic AD. The infection may have occurred in the past, for example, through a contaminated pituitary preparation or a fragment of the dura mater. It can be assumed that infections are also possible by other routes, because Aβ is extremely stable and can survive in the external environment for a long period of time. Despite the clear progress of research, controversies still exist and should be clarified in the future by means of using other control groups and new models. For example, it has long been acknowledged that France is the country where the highest percentage of iCJD infections has been reported after administration of cadaver-derived pituitary preparations [14]. So far, the analysis of French patients was made only in one study that presented surprising differences compared to the UK population [28, 54, 89]. Therefore, it would be important to carry out more detailed analyses of the French population in order to explain the reasons for the observed differences. Other researchers, such as Mathias Jucker, postulate the use of completely new experimental and control groups. Such a group could gather patients who underwent neurosurgical procedures for the treatment of epilepsy in the past [1]. Such procedures could potentially increase the risk of the infection due to insufficient sterilization of the tools and equipment used. Therefore, other groups of persons with a potentially increased risk of developing AD should also be identified and analyzed. Some of the risk groups previously used in epidemiological studies, such as persons with a history of multiple blood transfusions, may – contrary to earlier expectations – not preclude achieving clear and unambiguous results.

CONCLUSIONS

It follows from the above considerations that despite the inability to conduct direct experiments in humans, still alternative ways exist to conduct experimental studies that could help explain the doubts. AD is a very complex and heterogeneous disorder that can have possible various causes. This disorder may possible be affected by even several independent yet interacting mechanisms of pathogenesis [9, 106]. The very long time of incubation of the disease and its uniqueness to humans, prevent from developing ideal animal models that fully reflect all clinical symptoms occurring in humans. For these and other reasons, to get clear evidence of the intriguing hypothesis that some cases of sporadic AD are infectious is not easy and perhaps this is currently not possible to prove beyond any doubts. However, mounting evidence suggests that this possibility is very probable and should be considered seriously. It is worth emphasizing that a positive answer to the question about AD infectivity can modify the standards of patient care and affect the course of certain medical procedures as well as the search for new therapies.

REFERENCES

[1] Abbott A.: The red-hot debate about transmissible Alzheimer's. Nature, 2016; 531: 294-297

[2] Ameen-Ali K.E., Wharton S.B., Simpson J.E., Heath P.R., Sharp P., Berwick J.: Review: Neuropathology and behavioural features of transgenic murine models of Alzheimer's disease. Neuropathol. Appl. Neurobiol., 2017; 43: 553-570

[3] Armstrong R.A.: A critical analysis of the ‚amyloid cascade hypothesis'. Folia Neuropathol., 2014; 52: 211-225

[4] Ayers J.I., Giasson B.I., Borchelt D.R.: Prion-like spreading in tauopathies. Biol. Psychiatry, 2018: 83: 337-346

[5] Baker H.F., Ridley R.M., Duchen L.W., Crow T.J., Bruton C.J.: Evidence for the experimental transmission of cerebral beta-amyloidosis to primates. Int. J. Exp. Pathol., 1993; 74: 441-454

[6] Baker H.F., Ridley R.M., Duchen L.W., Crow T.J., Bruton C.J.: Induction of β(A4)-amyloid in primates by injection of Alzheimer's disease brain homogenate. Comparison with transmission of spongiform

encephalopathy. Mol. Neurobiol., 1994; 8: 25-39

[7] Batlle C., Iglesias V., Navarro S., Ventura S.: Prion-like proteins and their computational identification in proteomes. Expert Rev. Proteomics, 2017; 14: 335-350

[8] Beekes M., Thomzig A., Schulz-Schaeffer W.J., Burger R.: Is there a risk of prion-like disease transmission by Alzheimer – or Parkinson-associated protein particles? Acta Neuropathol., 2014; 128: 463-476

[9] Besson F.L., La Joie R., Doeuvre L., Gaubert M., Mézenge F., Egret S., Landeau B., Barré L., Abbas A., Ibazizene M., de La Sayette V., Desgranges B., Eustache F., Chételat G.: Cognitive and brain profiles associated with current neuroimaging biomarkers of preclinical Alzheimer's disease. J. Neurosci., 2015; 35: 10402-10411

[10] Blennow K., de Leon M.J., Zetterberg H.: Alzheimer's disease. Lancet, 2006; 368: 387-403

[11] Bohnen N.I., Warner M.A., Kokmen E., Beard C.M., Kurland L.T.: Prior blood transfusions and Alzheimer's disease. Neurology, 1994; 44: 1159-1160

[12] Brahic M., Bousset L., Bieri G., Melki R., Gitler A.D.: Axonal transport and secretion of fibrillar forms of α-synuclein, Aβ42 peptide and HTTExon 1. Acta Neuropathol., 2016; 131: 539-548

[13] Brown P., Brandel J.P., Preece M., Sato T.: Iatrogenic Creutzfeldt-Jakob disease: the waning of an era. Neurology, 2006; 67: 389-393

[14] Brown P., Brandel J.P., Sato T., Nakamura Y., MacKenzie J., Will R.G., Ladogana A., Pocchiari M., Leschek E.W., Schonberger L.B.: Iatrogenic Creutzfeldt-Jakob disease, final assessment. Emerg. Infect. Dis., 2012; 18: 901-907

[15] Brown P., Jannotta F., Gibbs C.J.Jr., Baron H., Guiroy D.C., Gajdusek D.C.: Coexistence of Creutzfeldt-Jakob disease and Alzheimer's disease in the same patient. Neurology, 1990; 40: 226-228

[16] Bu X.L., Xiang Y., Jin W.S., Wang J., Shen L.L., Huang Z.L., Zhang K., Liu Y.H., Zeng F., Liu J.H., Sun H.L., Zhuang Z.Q., Chen S.H., Yao X.Q., Giunta B., et al.: Blood-derived amyloid-beta protein induces Alzheimer's disease pathologies. Mol. Psychiatry, 2017 (in print)

[17] Burwinkel M., Lutzenberger M., Heppner F.L., Schulz-Schaeffer W., Baier M.: Intravenous injection of β-amyloid seeds promotes cerebral amyloid angiopathy (CAA). Acta Neuropathol. Commun., 2018; 6: 23

[18] Butowt R., Davies P., Brown D.R.: Anterograde axonal transport of chicken cellular prion protein (PrP^c) in vivo requires its N-terminal part. J. Neurosci. Res., 2007; 85: 2567-2579

[19] Cali I., Cohen M.L., Haik S., Parchi P., Giaccone G., Collins S.J., Kofskey D., Wang H., McLean C.A., Brandel J.P., Privat N., Sazdovitch V., Duyckaerts C., Kitamoto T., Belay E.D., et al.: Iatrogenic Creutzfeldt-Jakob disease with amyloid-β pathology: an international study. Acta Neuropathol. Commun., 2018; 6: 5

[20] Caselli R.J., Beach T.G., Knopman D.S., Graff-Radford N.R.: Alzheimer disease: scientific breakthroughs and translational challenges. Mayo Clin. Proc., 2017; 92: 978-994

[21] Chételat G., La Joie R., Villain N., Perrotin A., de La Sayette V., Eustache F., Vandenberghe R.: Amyloid imaging in cognitively normal individuals, at-risk populations and preclinical Alzheimer's disease. Neuroimage Clin., 2013; 2: 356-365

[22] Cohen M., Appleby B., Safar J.G.: Distinct prion-like strains of amyloid beta implicated in phenotypic diversity of Alzheimer's disease. Prion, 2016; 10: 9-17

[23] Collinge J., Whitfield J., McKintosh E., Beck J., Mead S., Thomas D.J., Alpers M.P.: Kuru in the 21st century – an acquired human prion disease with very long incubation periods. Lancet, 2006; 367: 2068-2074

[24] Crous-Bou M., Minguillón C., Gramunt N., Molinuevo J.L.: Alzheimer's disease prevention: from risk factors to early intervention. Alzheimers Res. Ther., 2017; 9: 71

[25] Darby S.C., Kan S.W., Spooner R.J., Giangrande P.L., Hill F.G., Hay C.R., Lee C.A., Ludlam C.A., Williams M.: 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: 815-825

[26] Duran-Aniotz C., Morales R., Moreno-Gonzalez I., Hu P.P., Fedynyshyn J., Soto C.: Aggregate-depleted brain fails to induce Aβ deposition in a mouse model of Alzheimer's disease. PLoS One, 2014; 9: e89014

[27] Duran-Aniotz C., Morales R., Moreno-Gonzalez I., Hu P.P., Soto C.: Brains from non-Alzheimer's individuals containing amyloid deposits accelerate Aβ deposition *in vivo*. Acta Neuropathol. Commun., 2013; 1: 76

[28] Duyckaerts C., Sazdovitch V., Ando K., Seilhean D., Privat N., Yilmaz Z., Peckeu L., Amar E., Comoy E., Maceski A., Lehmann S., Brion J.P., Brandel J.P., Haik S.: 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: 201-212

[29] Eisele Y.S., Bolmont T., Heikenwalder M., Langer F., Jacobson L.H., Yan Z.X., Roth K., Aguzzi A., Staufenbiel M., Walker L.C., Jucker M.: Induction of cerebral β-amyloidosis: intracerebral versus systemic Aβ inoculation. Proc. Natl. Acad. Sci. USA, 2009; 106: 12926-12931

[30] Eisele Y.S., Duyckaerts C.: Propagation of Aβ pathology: hypotheses, discoveries, and yet unresolved questions from experimental and human brain studies. Acta Neuropathol., 2016; 131: 5-25

[31] Eisele Y.S., Fritschi S.K., Hamaguchi T., Obermüller U., Füger P., Skodras A., Schäfer C., Odenthal J., Heikenwalder M., Staufenbiel M., Jucker M.: Multiple factors contribute to the peripheral induction of cerebral β-amyloidosis. J. Neurosci., 2014; 34: 10264-10273

[32] Eisele Y.S., Obermüller U., Heilbronner G., Baumann F., Kaeser S.A., Wolburg H., Walker L.C., Staufenbiel M., Heikenwalder M., Jucker M.: Peripherally applied Aβ-containing inoculates induce cerebral β-amyloidosis. Science, 2010; 330: 980-982

[33] Esquerda-Canals G., Montoliu-Gaya L., Güell-Bosch J., Villegas S.: Mouse models of Alzheimer's disease. J. Alzheimers Dis., 2017; 57: 1171-1183

[34] Finch C.E., Austad S.N.: Commentary: is Alzheimer's disease uniquely human? Neurobiol. Aging, 2015; 36: 553-555

[35] Frid P., Anisimov S.V., Popovic N.: Congo red and protein aggregation in neurodegenerative diseases. Brain Res. Rev., 2007; 53: 135-160

[36] Fritschi S.K., Langer F., Kaeser S.A., Maia L.F., Portelius E., Pinotsi D., Kaminski C.F., Winkler D.T., Maetzler W., Keyvani K., Spitzer P., Wiltfang J., Kaminski Schierle G.S., Zetterberg H., Staufenbiel M., Jucker M.: Highly potent soluble amyloid-β seeds in human Alzheimer brain but not cerebrospinal fluid. Brain, 2014; 137: 2909-2915

[37] Frontzek K., Lutz M.I., Aguzzi A., Kovacs G.G., Budka H.: Amyloid-β pathology and cerebral amyloid angiopathy are frequent in iatrogenic Creutzfeldt-Jakob disease after dural grafting. Swiss Med. Wkly., 2016; 146: w14287

[38] Fung J., Frost D., Chakrabartty A., McLaurin J.: Interaction of human and mouse Aβ peptides. J. Neurochem., 2004; 91: 1398-1403

[39] Gajdusek D.C.: Transmissible and non-transmissible amyloidoses: autocatalytic post-translational conversion of host precursor proteins to β-pleated sheet configurations. J. Neuroimmunol., 1988; 20: 95-110

[40] Gajdusek D.C., Gibbs C.J., Alpers M.: Experimental transmission of a kuru-like syndrome to chimpanzees. Nature, 1966; 209: 794-796

[41] Ghoshal N., Cali I., Perrin R.J., Josephson S.A., Sun N., Gambetti P., Morris J.C.: Codistribution of amyloid β plaques and spongiform degeneration in familial Creutzfeldt-Jakob disease with the E200K-129M haplotype. Arch. Neurol., 2009; 66: 1240-1246

[42] Godec M.S., Asher D.M., Masters C.L., Kozachuk W.E., Friedland R.P., Gibbs C.J.Jr., Gajdusek D.C., Rapoport S.I., Schapiro M.B.: Evidence against the transmissibility of Alzheimer's disease. Neurology, 1991; 41: 1320

[43] Goedert M., Masuda-Suzukake M., Falcon B.: Like prions: the propagation of aggregated tau and α-synuclein in neurodegeneration. Brain, 2017; 140: 266-278

[44] Goldgaber D., Davies P., Gambetti P., Walker L.C., Friedland R.P., White L.R., Piccardo P., Asher D.M.: Transmission of Alzheimer amyloidosis to chimpanzees and monkeys: Revisited. Alzheimer's & Dementia, 2010; 6: S250

[45] Goudsmit J., Morrow C.H., Asher D.M., Yanagihara R.T., Masters C.L., Gibbs C.J.Jr., Gajdusek D.C.: Evidence for and against the transmissibility of Alzheimer disease. Neurology, 1980; 30: 945-950

[46] Gray F., Chrétien F., Cesaro P., Chatelain J., Beaudry P., Laplanche J.L., Mikol J., Bell J., Gambetti P., Degos J.D.: Creutzfeldt-Jakob disease and cerebral amyloid angiopathy. Acta Neuropathol., 1994; 88: 106-111

[47] Hainfellner J.A., Wanschitz J., Jellinger K., Liberski P.P., Gullotta F., Budka H.: Coexistence of Alzheimer-type neuropathology in Creutzfeldt-Jakob disease. Acta Neuropathol., 1998; 96: 116-122

[48] Hamaguchi T., Taniguchi Y., Sakai K., Kitamoto T., Takao M., Murayama S., Iwasaki Y., Yoshida M., Shimizu H., Kakita A., Takahashi H., Suzuki H., Naiki H., Sanjo N., Mizusawa H., Yamada M.: Significant association of cadaveric dura mater grafting with subpial Aβ deposition and meningeal amyloid angiopathy. Acta Neuropathol., 2016; 132: 313-315

[49] Heilbronner G., Eisele Y.S., Langer F., Kaeser S.A., Novotny R., Nagarathinam A., Aslund A., Hammarström P., Nilsson K.P., Jucker M.: Seeded strain-like transmission of β-amyloid morphotypes in APP transgenic mice. EMBO Rep., 2013; 14: 1017-1022

[50] Hervé D., Porché M., Cabrejo L., Guidoux C., Tournier-Lasserve E., Nicolas G., Adle-Biassette H., Plu I., Chabriat H., Duyckaerts C.: Fatal Aβ cerebral amyloid angiopathy 4 decades after a dural graft at the age of 2 years. Acta Neuropathol., 2018; 135: 801-803

[51] Hou F., Sun L., Zheng H., Skaug B., Jiang Q.X., Chen Z.J.: MAVS forms functional prion-like aggregates to activate and propagate antiviral innate immune response. Cell, 2011; 146: 448-461

[52] Hsiao K., Chapman P., Nilsen S., Eckman C., Harigaya Y., Younkin S., Yang F., Cole G.: Correlative memory deficits, Aβ elevation, and amyloid plaques in transgenic mice. Science, 1996; 274: 99-102

[53] Irwin D.J., Abrams J.Y., Schonberger L.B., Leschek E.W., Mills J.L., Lee V.M., Trojanowski J.Q.: Evaluation of potential infectivity of Alzheimer and Parkinson disease proteins in recipients of cadaver-derived human growth hormone. JAMA Neurol, 2013; 70: 462-468

[54] Jaunmuktane Z., Mead S., Ellis M., Wadsworth J.D., Nicoll A.J., Kenny J., Launchbury F., Linehan J., Richard-Loendt A., Walker A.S., Rudge P., Collinge J., Brandner S.: Evidence for human transmission of amyloid-β pathology and cerebral amyloid angiopathy. Nature, 2015; 525: 247-250

[55] Jaunmuktane Z., Quaegebeur A., Taipa R., Viana-Baptista M., Barbosa R., Koriath C., Sciot R., Mead S., Brandner S.: Evidence of amyloid-β cerebral amyloid angiopathy transmission through neurosurgery. Acta Neuropathol., 2018; 135: 671-679

[56] Jucker M., Walker L.C.: Self-propagation of pathogenic protein aggregates in neurodegenerative diseases. Nature, 2013; 501: 45-51

[57] Kane M.D., Lipinski W.J., Callahan M.J., Bian F., Durham R.A., Schwarz R.D., Roher A.E., Walker L.C.: Evidence for seeding of β-amyloid by intracerebral infusion of Alzheimer brain extracts in β-amyloid precursor protein-transgenic mice. J. Neurosci., 2000; 20: 3606-3611

[58] Kovacs G.G., Lutz M.I., Ricken G., Ströbel T., Höftberger R., Preusser M., Regelsberger G., Hönigschnabl S., Reiner A., Fischer P., Budka H., Hainfellner J.A.: Dura mater is a potential source of Aβ seeds. Acta Neuropathol., 2016; 131: 911-923

[59] Kozin S.A., Cheglakov I.B., Ovsepyan A.A., Telegin G.B., Tsvetkov P.O., Lisitsa A.V., Makarov A.A.: Peripherally applied synthetic peptide isoAsp7-Aβ(1-42) triggers cerebral β-amyloidosis. Neurotox. Res., 2013; 24: 370-376

[60] Langer F., Eisele Y.S., Fritschi S.K., Staufenbiel M., Walker L.C., Jucker M.: Soluble Aβ seeds are potent inducers of cerebral β-amyloid deposition. J. Neurosci., 2011; 31: 14488-14495

[61] Lee T.A., Wolozin B., Weiss K.B., Bednar M.M.: Assessment of the emergence of Alzheimer's disease following coronary artery bypass graft surgery or percutaneous transluminal coronary angioplasty. J. Alzheimers Dis., 2005; 7: 319-324

[62] Liberski P.P., Bratosiewicz-Wasik J., Budka H., Ironside J.W., Sikorska B.: Transmissible spongiform encephalopathies or prion diseases – update 2007. Aktualnosci Neurologiczne, 2007; 7: 158-187

[63] Liu H.: New evidence suggests link between prion disease and Alzheimer's disease. MOJ Cell Sci. Rep., 2016; 3: 00056

[64] Lollis S.S., Valdes P.A., Li Z., Ball P.A., Roberts D.W.: Cause-specific mortality among neurosurgeons. J. Neurosurg., 2010; 113: 474-478

[65] McCaulley M.E., Grush K.A.: Seeking a new paradigm for Alzheimer's disease: considering the roles of inflammation, blood-brain barrier dysfunction, and prion disease. Int. J. Alzheimers Dis., 2017; 2017: 2438901

[66] Meyer-Luehmann M., Coomaraswamy J., Bolmont T., Kaeser S., Schaefer C., Kilger E., Neuenschwander A., Abramowski D., Frey P., Jaton A.L., Vigouret J.M., Paganetti P., Walsh D.M., Mathews P.M., Ghiso J., et al.: Exogenous induction of cerebral β-amyloidogenesis is governed by agent and host. Science, 2006; 313: 1781-1784

[67] Middeldorp J., Lehallier B., Villeda S.A., Miedema S.S., Evans E., Czirr E., Zhang H., Luo J., Stan T., Mosher K.I., Masliah E., Wyss-Coray T.: Preclinical assessment of young blood plasma for Alzheimer disease. JAMA Neurol, 2016; 73: 1325-1333

[68] Morales R., Bravo-Alegria J., Duran-Aniotz C., Soto C.: Titration of biologically active amyloid-β seeds in a transgenic mouse model of Alzheimer's disease. Sci. Rep., 2015; 5: 9349

[69] Morales R., Duran-Aniotz C., Castilla J., Estrada L.D., Soto C.: *De novo* induction of amyloid-β deposition *in vivo*. Mol. Psychiatry, 2012; 17: 1347-1353

[70] Mucke L., Masliah E., Yu G.Q., Mallory M., Rockenstein E.M., Tatsuno G., Hu K., Kholodenko D., Johnson-Wood K., McConlogue L.: High-level neuronal expression of $A\beta_{1-42}$ in wild-type human amyloid protein precursor transgenic mice: synaptotoxicity without plaque formation. J. Neurosci., 2000; 20: 4050-4058

[71] Müller U.C., Deller T., Korte M.: Not just amyloid: physiological functions of the amyloid precursor protein family. Nat. Rev. Neurosci., 2017; 18: 281-298

[72] Muramoto T., Kitamoto T., Koga H., Tateishi J.: The coexistence of Alzheimer's disease and Creutzfeldt-Jakob disease in a patient with dementia of long duration. Acta Neuropathol., 1992; 84: 686-689

[73] Narasimhan S., Guo J.L., Changolkar L., Stieber A., McBride J.D., Silva L.V., He Z., Zhang B., Gathagan R.J., Trojanowski J.Q., Lee V.M.: Pathological tau strains from human brains recapitulate the diversity of tauopathies in non-transgenic mouse brain. J. Neurosci., 2017; 37: 11406-11423

[74] Nelson P.T., Alafuzoff I., Bigio E.H., Bouras C., Braak H., Cairns N.J., Castellani R.J., Crain B.J., Davies P., Del Tredici K., Duyckaerts C., Frosch M.P., Haroutunian V., Hof P.R., Hulette C.M., et al.: Correlation of Alzheimer disease neuropathologic changes with cognitive status: a review of the literature. J. Neuropathol. Exp. Neurol., 2012; 71: 362-381

[75] Newman M.F., Kirchner J.L., Phillips-Bute B., Gaver V., Grocott H., Jones R.H., Mark D.B., Reves J.G., Blumenthal J.A.: Longitudinal assessment of neurocognitive function after coronary-artery bypass surgery. N. Engl. J. Med., 2001; 344: 395-402

[76] Norton M.C., Smith K.R., Østbye T., Tschanz J.T., Corcoran C., Schwartz S., Piercy K.W., Rabins P.V., Steffens D.C., Skoog I., Breitner J.C., Welsh-Bohmer K.A., Cache County Investigators: Greater risk of dementia when spouse has dementia? The Cache County study. J. Am. Geriatr. Soc., 2010; 58: 895-900

[77] Novotny R., Langer F., Mahler J., Skodras A., Vlachos A., Wegenast-Braun B.M., Kaeser S.A., Neher J.J., Eisele Y.S., Pietrowski M.J., Nilsson K.P., Deller T., Staufenbiel M., Heimrich B., Jucker M.: Conversion of synthetic Aβ to *in vivo* active seeds and amyloid plaque formation in a hippocampal slice culture model. J. Neurosci., 2016; 36: 5084-5093

[78] Ono K.: Alzheimer's disease as oligomeropathy. Neurochem. Int., 2017 (in print)

[79] Paquet C., Privat N., Kaci R., Polivka M., Dupont O., Haik S., Laplanche J.L., Hauw J.J., Gray F.: Cerebral amyloid angiopathy with co-localization of prion protein and beta-amyloid in an 85-year-old patient with sporadic Creutzfeldt-Jakob disease. Acta Neuropathol., 2008; 116: 567-573

[80] Petkova A.T., Leapman R.D., Guo Z., Yau W.M., Mattson M.P., Tycko R.: Self-propagating, molecular-level polymorphism in Alzheimer's β-amyloid fibrils. Science, 2005; 307: 262-265

[81] Podlisny M.B., Stephenson D.T., Frosch M.P., Tolan D.R., Lieberburg I., Clemens J.A., Selkoe D.J.: Microinjection of synthetic amyloid beta-protein in monkey cerebral cortex fails to produce acute neurotoxicity. Am. J. Pathol., 1993; 142: 17-24

[82] Preusser M., Ströbel T., Gelpi E., Eiler M., Broessner G., Schmutzhard E., Budka H.: Alzheimer-type neuropathology in a 28 year old patient with iatrogenic Creutzfeldt-Jakob disease after dural grafting. J. Neurol. Neurosurg. Psychiatry, 2006; 77: 413-416

[83] Prince M.C., Knapp M., Guerchet M., Karagiannidou M.: World Alzheimer Report 2016. Improving healthcare for people living with dementia coverage, quality and costs now and in the future. 2016.

[84] Prusiner S.B.: Novel proteinaceous infectious particles cause scrapie. Science, 1982; 216: 136-144

[85] Rafalowska J., Barcikowska M., Wen G.Y., Wisniewski H.M.: Laminar distribution of neuritic plaques in normal aging, Alzheimer's disease and Down's syndrome. Acta Neuropathol., 1988; 77: 21-25

[86] Rasmussen J., Jucker M., Walker L.C.: Aβ seeds and prions: How close the fit? Prion, 2017; 11: 215-225

[87] Rewcastle N.B., Gibbs C.J.Jr., Gajdusek D.C.: Transmission of familial Alzheimer's disease to primates. J. Neuropathol. Exp. Neurol., 1978; 37: 679

[88] Ridley R.M., Baker H.F., Windle C.P., Cummings R.M.: Very long term studies of the seeding of β-amyloidosis in primates. J. Neural. Transm., 2006; 113: 1243-1251

[89] Ritchie D.L., Adlard P., Peden A.H., Lowrie S., Le Grice M., Burns K., Jackson R.J., Yull H., Keogh M.J., Wei W., Chinnery P.F., Head M.W., Ironside J.W.: Amyloid-β accumulation in the CNS in human growth hormone recipients in the UK. Acta Neuropathol., 2017; 134: 221-240

[90] Rosen R.F., Fritz J.J., Dooyema J., Cintron A.F., Hamaguchi T., Lah J.J., LeVine H.3rd, Jucker M., Walker L.C.: Exogenous seeding of cerebral β-amyloid deposition in βAPP-transgenic rats. J. Neurochem., 2012; 120: 660-666

[91] Ruiz-Riquelme A., Lau H.H.C., Stuart E., Goczi A.N., Wang Z., Schmitt-Ulms G., Watts J.C.: Prion-like propagation of β-amyloid aggregates in the absence of APP overexpression. Acta Neuropathol. Commun., 2018; 6: 26

[92] Saá P., Cervenakova L.: Protein misfolding cyclic amplification (PMCA): Current status and future directions. Virus Res., 2015; 207: 47-61

[93] SantaCruz K.S., Sonnen J.A., Pezhouh M.K., Desrosiers M.F., Nelson P.T., Tyas S.L.: Alzheimer disease pathology in subjects without dementia in 2 studies of aging: the Nun Study and the Adult Changes in Thought Study. J. Neuropathol. Exp. Neurol., 2011; 70: 832-840

[94] Sigurdsson E.M., Wisniewski T., Frangione B.: Infectivity of amyloid diseases. Trends Mol. Med., 2002; 8: 411-413

[95] Sikorska B., Knight R., Ironside J.W., Liberski P.P.: Creutzfeldt-Jakob disease. Adv. Exp. Med. Biol., 2012; 724: 76-90

[96] Sowade R.F., Jahn T.R.: Seed-induced acceleration of amyloid-β mediated neurotoxicity in vivo. Nat Commun, 2017; 8: 512

[97] Stancu I.C., Vasconcelos B., Terwel D., Dewachter I.: Models of β-amyloid induced Tau-pathology: the long and „folded" road to understand the mechanism. Mol. Neurodegener., 2014; 9: 51

[98] Stöhr J., Condello C., Watts J.C., Bloch L., Oehler A., Nick M., DeArmond S.J., Giles K., DeGrado W.F., Prusiner S.B.: Distinct synthetic Aβ prion strains producing different amyloid deposits in bigenic mice. Proc. Natl. Acad. Sci. USA, 2014; 111: 10329-10334

[99] Stöhr J., Watts J.C., Mensinger Z.L., Oehler A., Grillo S.K., DeArmond S.J., Prusiner S.B., Giles K.: Purified and synthetic Alzheimer's amyloid β (Aβ) prions. Proc. Natl. Acad. Sci. USA, 2012; 109: 11025-11030

[100] Thomzig A., Wagenführ K., Daus M.L., Joncic M., Schulz-Schaeffer W.J., Thanheiser M., Mielke M., Beekes M.: Decontamination of medical devices from pathological amyloid-β-, tau – and α-synuclein aggregates. Acta Neuropathol. Commun., 2014; 2: 151

[101] Tousseyn T., Bajsarowicz K., Sánchez H., Gheyara A., Oehler A., Geschwind M., DeArmond B., DeArmond S.J.: Prion disease induces Alzheimer disease-like neuropathologic changes. J. Neuropathol. Exp. Neurol., 2015; 74: 873-888

[102] Vanderweyde T., Bednar M.M., Forman S.A., Wolozin B.: Iatrogenic risk factors for Alzheimer's disease: surgery and anesthesia. J. Alzheimers Dis., 2010; 22: 91-104

[103] Walker L.C., Jucker M.: The exceptional vulnerability of humans to Alzheimer's disease. Trends Mol. Med., 2017; 23: 534-545

[104] Watanabe R., Duchen L.W.: Cerebral amyloid in human prion disease. Neuropathol. Appl. Neurobiol., 1993; 19: 253-260

[105] Watts J.C., Prusiner S.B.: β-Amyloid prions and the pathobiology of Alzheimer's disease. Cold Spring Harb. Perspect. Med., 2018; 8: a023507

[106] Weinstein J.D.: A new direction for Alzheimer's research. Neural Regen. Res., 2018; 13: 190-193

[107] Wisniewski H.M., Merz G.S., Carp R.I.: Senile dementia of the Alzheimer type: possibility of infectious etiology in genetically susceptible individuals. Acta Neurol. Scand., 1984; 69: 91-97

[108] Xiang Y., Bu X.L., Liu Y.H., Zhu C., Shen L.L., Jiao S.S., Zhu X.Y., Giunta B., Tan J., Song W.H., Zhou H.D., Zhou X.F., Wang Y.J.: Physiological amyloid-beta clearance in the periphery and its therapeutic potential for Alzheimer's disease. Acta Neuropathol., 2015; 130: 487-499

[109] Ye L., Fritschi S.K., Schelle J., Obermüller U., Degenhardt K., Kaeser S.A., Eisele Y.S., Walker L.C., Baumann F., Staufenbiel M., Jucker M.: Persistence of Aβ seeds in APP null mouse brain. Nat. Neurosci., 2015; 18: 1559-1561

[110] Zhang Z., Zhang Y., Wang F., Wang X., Xu Y., Yang H., Yu G., Yuan C., Ma J.: De novo generation of infectious prions with bacterially expressed recombinant prion protein. FASEB J., 2013; 27: 4768-4775

[111] Zlokovic B.V., Martel C.L., Mackic J.B., Matsubara E., Wisniewski T., McComb J.G., Frangione B., Ghiso J.: Brain uptake of circulating apolipoproteins J and E complexed to Alzheimer's amyloid β. Biochem. Biophys. Res. Commun., 1994; 205: 1431-1437

The authors have no potential conflicts of interest to declare.