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Chronic Inflammation and Amyloidogenesis in Alzheimer's Disease – Role of Spirochetes[1]

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Abstract. Alzheimer's disease (AD) is associated with dementia, brain atrophy and the aggregation and accumulation of a cortical amyloid-β peptide (Aβ). Chronic bacterial infections are frequently associated with amyloid deposition. It had been known from a century that the spirochete *Treponema pallidum* can cause dementia in the atrophic form of general paresis. It is noteworthy that the pathological hallmarks of this atrophic form are similar to those of AD. Recent observations showed that bacteria, including spirochetes contain amyloidogenic proteins and also that Aβ deposition and tau phosphorylation can be induced *in* or *in vivo* following exposure to bacteria or LPS. Bacteria or their poorly degradable debris are powerful inflammatory cytokine inducers, activate complement, affect vascular permeability, generate nitric oxide and free radicals, induce apoptosis and are amyloidogenic. All these processes are involved in the pathogenesis of AD. Old and new observations, reviewed here, indicate that to consider the possibility that bacteria, including several types of spirochetes highly prevalent in the population at large or their persisting debris may initiate cascade of events leading to chronic inflammation and amyloid deposition in AD is important, as appropriate antibacterial and antiinflammatory therapy would be available to prevent dementia.

Keywords: Alzheimer's disease, amyloid-β, bacteria, borrelia burgdorferi, chronic inflammation, dementia, general paresis, intestinal spirochetes, LPS, lyme neuroborreliosis, neurospirochetosis, oral spirochetes, spirochetes, syphilis, treponema pallidum

INTRODUCTION

Alzheimer discovered the disorder that bears his name a century ago, when he reported the case of a 51-year-old woman (Auguste D.) who suffered from presenile dementia with characteristic changes in the cerebral cortex [2,3]. Alzheimer's disease (AD), the most common cause of dementia, is characterized by a slow, progressive decline of cortical functions, particularly cognition and memory. Terry and Davies [104] pointed out that the presenile form – with onset before age 65 – is identical to the most common form of senile dementia and suggested the term 'senile dementia of the Alzheimer type' (SDAT).

The pathological hallmarks of AD consist of a marked cortical atrophy, accumulation in the cerebral cortex of senile plaques (known also as argyrophylic or neuritic plaques), neurofibrillary tangles and neuropil threads. The occurrence of senile plaques was first reported by Blocq and Marinesco in [8] and the characteristic fibrillary changes of neuronal cells were first described and documented by Alzheimer [2,3]. Recently, particularly from the use of Gallyas silver technique [24], the accumulation of neuropil threads or curly fibers has been recognized as a characteristic cortical lesion in AD.

Fibrillary amyloid substance accumulates in senile plaques, but also in leptomeningeal and cortical vessel walls [26,50]. The major subunit of the amyloid fibrils is the 4.2-kD amyloid-β (Aβ) peptide. The small self-aggregating polypeptide was designated as Aβ because of its partial beta-pleated sheet structure. Aβ is derived by proteolytic cleavage from a larger, transmem-

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brane amyloid-β protein precursor (AβPP), which is expressed in a variety of tissues [41]. AβPP contains features characteristic of glycosylated cell-surface receptors and is revealed to be a proteoglycan core protein [87]. Neurofibrillary tangles contain paired helical filaments (PHFs) composed of the microtubule-associated protein tau. Tau is hyperphosphorylated in PHFs, which abolishes its ability to bind microtubules and promote microtubule assembly [27,95]. The pathomechanism of Aβ and tangle formation still remains unclear. The role of chronic local inflammation in AD is well established, but the factors responsible for amyloid deposition and persisting inflammation are not known.

For about a century it has been known that chronic bacterial infection, caused by the spirochete *Treponema pallidum* in the atrophic form of general paresis in syphilis can cause dementia, brain atrophy and local amyloidosis. The possibility that microorganisms may play a role in the formation of senile plaques was already discussed a century ago by Fischer, Alzheimer and their colleagues. Increasing recent evidences show that bacteria and their persisting remnants due to their biological activities may play a role in persisting inflammation and amyloid deposition in AD. The consideration that bacteria or their biologically active remnants may initiate the cascade of events leading to neurodegeneration brings together in a comprehensive way a large number of apparently diverse hypotheses which have been proposed to play a role in the pathogenesis of AD. The old and new observations reviewed here indicate that to consider and support research on the role of pathogens in AD would be important as appropriate therapy would be available. Joint antibiotic and anti-inflammatory therapies, if started early, may prevent or slow down the degenerative process.

PATHOGENESIS OF ALZHEIMER'S DISEASE

Although the first description of AD, which is the most frequent cause of dementia, dates back to a century ago, and despite of the enormous progress made in AD research, the elucidation of the cellular-molecular mechanisms involved in the degenerative process of AD is still unclear and the treatment unresolved [68].

A variety of scientific hypotheses were proposed to explain the pathogenesis of AD [5,68,88,89,92,102].

Three genes are implicated in inherited forms of AD, with onset between ages 28–50 years. These are genes of AβPP located on chromosome 21, presenilin 1 (PS1) located on chromosome 14 and presenilin 2 (PS2) located on chromosome 1. The number of cases with these genetic mutations is low. There are less than 100 known individuals worldwide carrying the AβPP717 mutation [85,103]. All these mutations appear to increase the production of Aβ. A fourth gene, apolipoprotein E (ApoE), is located on chromosome 19 and its E4 allele revealed to be a risk factor for late onset AD [86]. Finally, there is an association between AD and various polymorphisms in other genes, including a growing number of new genes implicated in immune defense mechanisms [53], which seem to have influence on the pathogenesis of AD.

The relation between Aβ and hyperphosphorylation of tau in AD is not yet fully elucidated. "Baptists" against "tauoists" claim the pathogenic role of Aβ versus tau. Extracellular, pre-amyloid Aβ protofibrils, versus intracellular Aβ accumulation for a direct role in AD pathology is discussed. The amyloid cascade hypothesis postulates that neurotoxicity of Aβ would cause the damage to neurons. Recent observations showed an interaction between Aβ and tau suggesting an important link between these major biological markers of AD [31] which is in agreement with previous observations that AβPP is an integral component of neurofibrillary tangles [77].

The role of ubiquitin; glycosylation end products; several neurotransmitters (e.g., the cholinergic hypothesis); hormones; neurotrophic factors, several metals, changes in calcium homeostasis and oxidative damage [70] to proteins, lipids and nucleic acids are other proposed alternative hypotheses. Several environmental factors; cardio-vascular risk factors such as cholesterolaemia, hypertension, cerebral hypoperfusion; mitochondrial abnormalities; disturbed signaling pathways (e.g., related to tau phosphorylation); are all factors which are implicated in the degenerative process in AD. Many other important factors not cited here, including cranio-cerebral trauma play an important role in the pathogenesis of AD.

CHRONIC INFLAMMATION IN ALZHEIMER'S DISEASE

Until recently, immune mechanisms in the pathogenesis of AD have been largely overlooked. Following the pioneer work of McGeer, Rogers and Griffin it is today generally accepted that cellular and molecular components of immune system reactions are associated with AD [28,51,55,56]. Activated microglia

(the brain's representatives of the phagocytic cells that are designed to clean up debris and foreign bacteria) surround senile plaques and extracellular neurofibrillary tangles. AD lesions are characterized by the presence of a series of inflammatory mediators, including cytokines, chemokines, proteases, adhesion molecules, free radicals, pentraxins, prostaglandins, anaphylatoxins, and activated complement proteins [52,54].

It has been assumed that lymphocytic infiltration does not occur in AD. However, using specific immunohistochemical markers, both T-helper/inducer and T-cytotoxic/suppressor lymphocytes have been observed. Of particular importance is the association of the membrane attack complex (MAC, C5b-9) intended to lyse foreign cells, such as bacteria, with dystrophic neurites [55,108]. The conclusion that inflammation exacerbates AD pathology is now supported by more than 20 epidemiological studies showing that individuals were protected from AD if they have been taking anti-inflammatory drugs or have suffered from unrelated conditions for which such drugs are routinely used [56, 105]. This effect has been particularly evident in people using nonsteroidal anti-inflammatory drugs (NSAIDs). Three large epidemiological studies showed a reduction of risk of 55–80% for AD [96,105,113].

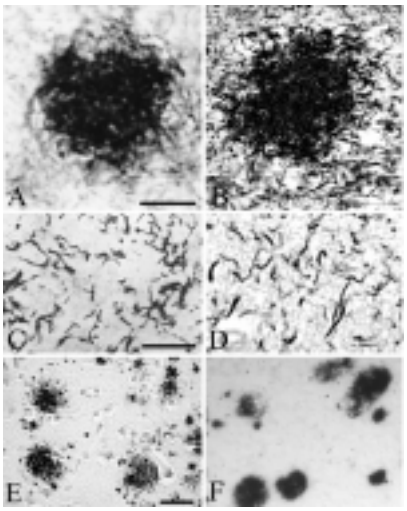

Fig. 1. The pathological hallmarks of AD are similar to those occurring in the atrophic form of general paresis, a chronic bacterial infection caused by *Treponema pallidum*. A: Mass or colony of spirochetes visualized by the silver impregnation method of Dieterle for spirochetes in the cerebral cortex of a patient with general paresis. Reproduced by the kind permission of the publisher from R.R. Dieterle, Spirochetosis of the central nervous system in general paralysis, *Am. J. Psych.* **7** (1928), 37–67. B: Morphology of a senile plaque silver-stained with Bielschowsky technique for senile plaques. C and D show the similar morphology between silver impregnated Treponema pallidum spirochetes in the cerebral cortex of a patient with general paresis and cortical curly fibers or neuropil threads in a patient with sporadic AD (Gallyas silver technique). E and F show similar distribution of beta amyloid in the cerebral cortex of a patient with the atrophic form of general paresis (E) and of a patient with AD (F). Bars: A = 80 μm and is the same for B; C = 25 μm and is the same for D; E = 120 μm and is the same F.

DEMENTIA, CORTICAL ATROPHY AND AMYLOID DEPOSITION CAUSED BY CHRONIC BACTERIAL INFECTION

Noguchi and Moor [69] were the first who demonstrated the persistence of *Treponema pallidum* spirochete in the brains of syphilitic patients suffering from general paresis. This important discovery established a direct pathogenic link between bacterial infection and dementia. Based on their observations it is now generally accepted that *Treponema pallidum* can cause chronic neuropsychiatric disorders including dementia.

In the long standing or atrophic form of general paresis *Treponema pallidum* causes slowly progressive dementia, cortical atrophy, microgliosis and amyloid deposition. Intriguingly, the clinical and pathological hallmarks of the atrophic form of general paresis are similar to those occurring in AD (Fig. 1). Alzheimer himself referred to a similarity of the clinical picture in one of his AD patients with presenile dementia [3]. With respect to the histopathological changes, multiple authors have described *Treponema pallida* colonies confined to the cerebral cortex in patients with general paresis [37,38,74,75]. The morphology, distribution and histochemical properties of these colonies are identical to those of the senile plaques in AD. Senile plaques and spirochetal colonies both were described and called "miliary necroses" in the beginning of the last century [19,98]. Neurofibrillary tangles have also been described in dementia paralytica [9,78,106] just as cortical and vascular amyloid deposition [107]. Recent characterization revealed that the aggregated amyloid substance corresponds to Aβ (Fig. 1E) [67].

BACTERIA ARE POWERFUL STIMULATORS OF INFLAMMATION AND ARE AMYLOIDOGENIC

It is well known that several bacteria, on interaction with the mammalian immune-system, induce chronic inflammation and amyloid deposition. Bacteria and their toxins are powerful inducers of inflammatory cytokines and activators of the complement pathway [22,

44]. It has been known from almost a century that chronic bacterial infections (e.g. rheumatoid arthritis, leprosy, tuberculosis, syphilis, osteomyelitis) are frequently associated with amyloid deposits in the infected tissues. It has also been known from almost a century that experimental amyloidosis can be induced by injecting living, attenuated or killed bacteria or bacterial components to experimental animals [79]. The bacterial inflammatory surface molecule lipopolysaccharide (LPS), a bacterial endotoxin is a powerful inflammatory and amyloidogenic factor of Gram negative bacteria. LPS is used world wide in experimental *in* and *in vivo* models of inflammation and amyloidosis. In bacteria (Prokaryotes), the cell wall consists of peptidoglycan, a complex polysaccharide composed of two sugar derivatives, N-acetylglucosamine and N-acetylmuramic acid and a small group of amino acids which comprise D-amino acids. Bacterial peptidoglycan is present only in bacteria, and is found in the wall of virtually all Eubacteria. It is absent in the evolutionary higher plant and animal cells (Eukaryotes). Poorly degradable "bacterial remnants" or alternatively, "dormant" fastidious bacteria may persist indefinitely in the affected organs [22]. LPS and bacterial cell wall peptidoglycan are highly resistant to degradation by mammalian enzymes and thus may provide a persisting inflammatory stimulus [71]. It has been shown that human intestinal bowel contains soluble bacterial cell wall components that are arthropathic in an animal model [97]. In these models it was the bacterial cell wall peptidoglycan component which was found to be the arthritogenic factor [20].

SPIROCHETES

Spirochetes are Gram negative free-living or host-associated helical bacteria possessing periplasmic fibrils which are unique for these microorganisms. They are the causative agents e.g. of syphilis, Lyme disease, periodontitis, necrotizing ulcerative gingivitis, and leptospirosis. *Treponema pallidum* is the pathogenic agent of syphilis. Many other Treponema species are found in the human mouth, genital mucosa and gastrointestinal tract. Their pathogenic role is not yet fully established. *Borrelias* include *Borrelia burgdorferi*, the causative agent of Lyme disease; *Borrelia recurrentis* and *Borrelia vincentii* the causative agents of relapsing fever and Vincent's angina, respectively.

Treponema pallidum, which causes syphilis is transmitted by sexual contact. *Treponema pallidum* has not yet been grown in synthetic media alone, although it has long been propagated in the testes of rabbits and cell monolayer systems [16]. *Borrelia burgdorferi*, which can be cultivated in a synthetic medium, is transmitted by tick bites to humans and causes Lyme disease [11]. The similarity of the clinical and pathological manifestations of syphilis and Lyme disease is striking [18]. *Borrelia burgdorferi* in analogy to *Treponema pallidum* can also persist in infected host tissues and play a role in chronic neuropsychiatric disorders. Dementia, including subacute presenile dementia, has been reported to occur not only in syphilis but also in Lyme disease [17].

ALZHEIMER'S DISEASE AND CHRONIC NEUROSPIROCHETOSIS

Nearly a century ago, Fischer has suggested that senile plaques may correspond to colonies of microorganisms [19]. Alzheimer cited Fischer's view in his discussion on the origin of senile plaques in AD [3].

Recent observations, using dark field microscopy analysis showed helically shaped microorganisms in the CSF, blood and cerebral cortex in 14 AD cases that were absent in 13 controls which were without any AD-type changes [59,60]. Further taxonomic analyses have shown that these microorganisms possess axial filaments (endoflagellae) indicating that taxonomically they belong to the order Spirochaetales [61,62]. The amyloidogenic bacterial cell wall peptidoglycan was co-localized with Aβ in senile plaques in 17 AD cases analyzed and were absent in controls without any plaques or tangles [63,64]. These results indicated that several types of spirochetes may be involved in AD including *Borrelia burgdorferi* and several types of oral and intestinal spirochetes [59–64].

It was MacDonald and Miranda (1987) [47] who first cultivated *Borrelia burgdorferi* spirochetes from the brain of two AD patients and proposed a possible link between AD and *Borrelia burgdorferi* [47,48]. Miklossy [59] cultivated spirochetes in medium selective for *Borrelia burgdorferi* from the brains of 3 other AD patients where 16S rRNA gene sequence analysis identified the spirochetes as *Borrelia burgdorferi sensu stricto* (s. s.) [59,65]. The post mortem serological analysis of blood and cerebrospinal fluid (CSF) and the detection of *Borrelia burgdorferi* antigens and genes in the brains of these AD patients were further confirmations that these patients suffered from chronic Lyme neuroborreliosis. Borrelia antigens and genes were co-localized with cortical Aβ deposits. The pathological findings were similar to those of the atrophic form

of general paresis [37,38,75]. Consistent with these findings, the genospecies *Borrelia garinii* and *Borrelia burgdorferi s. s.* have been reported to be predominantly involved in neuroborreliosis [111]. Lyme disease is geographically confined and the incidence is low when compared to AD [12] which suggests that *Borrelia burgdorferi* is involved only in a low percentage of AD cases. The low number of cases investigated and the lack of a positive serology for *Borrelia burgdorferi* may explain why some previous investigators have failed to detect an involvement of *Borrelia burgdorferi* and AD [32,49,57]. In order to study the particular involvement of *Borrelia burgdorferi* in AD, it is important to analyze AD patients with a positive serology for *Borrelia burgdorferi*.

Antibodies to various "commensal", spirochetes, particularly spirochetes of the oral cavity are highly prevalent in the population at large [59]. Intestinal spirochetes were also cultivated from the blood of humans [21]. Riviere et al. [83] using species-specific PCR and monoclonal antibodies, detected two oral Treponema spirochetes, both are known periodontal pathogens in 14/16 AD cases and in 4/18 controls. The invasive property of these oral Treponemas was previously demonstrated [82].

Previous observations showed that in an analogous way to *Treponema pallidum*, *Borrelia burgdorferi* persist in the brain in chronic Lyme neuroborreliosis and following a long latent stage may lead to dementia, cortical atrophy and amyloid deposition [47,48,59,60,65, 66]. The presence of oral Treponemes in the brain in more than 90% of the AD cases analyzed [83] further suggest that these spirochetes may also persist in the brain and cause dementia and brain atrophy. Taken together these observations strongly suggest that several types of spirochetes may sustain persisting inflammation and induce amyloid deposition in AD.

BACTERIA INDUCED Aβ DEPOSITION AND TAU PHOSPHORYLATION

Previous observations suggested that amyloidogenic protein may be an integral part of spirochetes and may play a role in amyloidogenesis in AD [59,60,66]. The more recent investigations made by Ohnishi et al. [72, 73] revealed that the outer surface protein (OspA) of *Borrelia burgdorferi* is amyloidogenic and forms amyloid fibrils *in vitro*, similar to human amyloid deposits. Recently, Aβ deposits were induced in rat primary neuronal and astrocytic cell cultures exposed to *Borrelia burgdorferi* spirochetes [66]. Using the reference strain B31 of *Borrelia burgdorferi* or strains ADB1 and ADB2 which were cultivated from the brain of AD patients had the same effect. Exposure of cultured mammalian neuronal and glial cells to these Borrelia spirochetes induced the defining pathological hallmarks of AD, including Aβ deposition, increased AβPP levels, and hyperphosphorylation of tau. Thioflavin S positive and Aβ-immunoreactive "plaques", as well as tangle- and granulovacuolar-like formations, were all observed in cell cultures exposed to spirochetes. Western blot analysis detected a 4kDa Aβ immunoreactive band in the infected cultures, which was more pronounced in microglia-enriched astrocytic cultures, suggesting that microglia may enhance Aβ formation. Using Synchrotron InfraRed MicroSpectroscopy (SIRMS) β-sheet protein structure was detected in the *in vitro*-induced Aβ deposits identical to that observed in senile plaques [66].

Increased AβPP levels were also detected in Borrelia-infected cultures, which may indicate the importance of host-derived AβPP in amyloidogenesis in AD. AβPP was shown to be a proteoglycan core protein [87, 112]. A role for proteoglycans in the Major Histocompatibility Complex (MHC)-mediated infections is well established. The *in vitro* and *in vivo* synthesis of proteoglycans by host cells in response to bacterial infections, including spirochetal infections, has been repeatedly reported [101]. Proteoglycans are present in early stages of all types of amyloid formation [94] but their exact role in amyloidogenesis has yet to be determined. Increased tau phosphorylation detected in cell cultures exposed to Borrelia spirochetes represented further experimental evidence, which together with Aβ deposition and increased AβPP levels supported the role of bacteria mediating amyloidogenesis in AD [66]. These observations suggest that spirochetes may play a role in amyloid formation and participate in the development of the defining morphological changes of AD.

Infusion of LPS for 37 days into the 4th ventricle of rats can reproduce many of the inflammatory, neurochemical, and behavioral changes seen in AD [33]. Aβ accumulation and increased AβPP mRNA in the basal forebrain and hippocampus was observed in response to LPS infusion [33,34]. The Aβ deposition and microglia activation induced by LPS infusion were alleviated by ibuprofen [81]. LPS induced acceleration of amyloid deposition in LPS-treated APPV717F transgenic mice was also reported [80]. LPS-induced-neuroinflammation increases intracellular accumulation of AβPP and Aβ in APPswe transgenic mice [91].

In addition to increased AβPP levels hyperphosphorylation of tau was also observed following exposure of primary astrocytes to LPS [66]. It was shown that LPS stimulates the secretion of AβPP via a protein kinase C mediated pathway [93]. These observations indicate that not only living bacteria, but natural or synthetic bacterial components alone may also have important biological activities in mammals. Aβ secretion by a microglial cell line was induced by Aβ-25–35 and by LPS [7] suggesting an important role of microglia in Aβ aggregation and accumulation in AD. Microglial production of Aβ may be increased by proinflammatory stimuli or by Aβ itself.

Increasing number of recent observations show that several bacteria contain amyloidogenic proteins [6,13, 15,25,40]. Analysis of the periplasmic outer membrane lipoprotein – OsmB – of Escherichia coli showed a similarity in amino acid sequences to Aβ peptide [40]. Recent biochemical, biophysical, and imaging analyses revealed that fibers produced by Escherichia coli, termed "curly" were composed of amyloid [15].

Reports of associations between infection and AD are not confined to spirochetes. The presence of Herpes virus type 1 (HSV-1) in the AD brain has been reported [35,36,39]. *Chlamydia pneumoniae* was also found to be associated with AD [4] and mice exposed to Chlamydia developed AD-like amyloid plaques [45]. Amyloid deposits resembling plaques found in AD brains were formed in the brains of non-transgenic BALB/c mice following intranasal infection with Chlamydia pneumoniae [45], indicating that several bacteria may induce Aβ deposits.

However, it is noteworthy that the clinical and pathological hallmarks of AD are similar to those of the atrophic form of general paresis caused by *Treponema pallidum* spirochetes, as illustrated by historic literature (Fig. 1) [37,38,46,74,75]. We should also consider that co-infection of spirochetes with other bacteria, including Chlamydia and Herpes viruses is frequent. The accumulation and persistence of bacteria and/or their degradation products in host tissues through their toxic component and amyloidogenic proteins may trigger a cascade of events leading to chronic inflammation and amyloid deposition.

BIOLOGICAL ACTIVITIES OF BACTERIA INDUCING AN ALZHEIMER'S TYPE HOST REACTION – A UNIFYING HYPOTHESIS?

The view that bacteria may play a role in the pathogenesis of AD would be in harmony with the majority of hypotheses proposed to play a role in the pathogenesis of AD. It does not contradict genetic defects occurring in AD. There is accumulating evidence that host responses and susceptibility to bacterial infections are genetically controlled [1,90]. The genetic mutations occurring in AD (AβPP, Presenilin1 and 2) are all related to the processing of AβPP. AβPP, a proteoglycan core protein, plays a role in cell defense mechanisms. As the production of proteoglycans aims to decrease infection, genetic defects of AβPP, PS-I and PS-II may be associated with an increased susceptibility to infection.

Mammals are constantly exposed to bacteria. Biologically active bacterial cell components are highly resistant to degradation by mammalian enzymes and thus may provide a persisting inflammatory and amyloidogenic stimulus [22,23]. The innate immune system, particularly the host complement system, plays an important role in the elimination of invading pathogens. Bacteria, similarly to Aβ, activate both the classic and the alternative complement pathways [10,84], which through the common membrane attack pathway, results in bacteriolysis. Specific acquisition of different host plasma proteins, e.g. coating their surfaces with host complement regulators, such as factor H, allows pathogens evading from host complement attack and phagocytosis, and to persist in affected host tissues. Characteristic features of *Borrelia burgdorferi sensu lato* (*s. l.*) group are their ability to invade tissues and to escape complement lysis despite elevated levels of Borrelia-specific antibodies in serum and other body fluids. *Borrelia burgdorferi* prevents complement attack by binding the complement inhibitors factor H (FH) and factor-H like protein-1 (FHL-1), the two major regulators of the alternative complement pathway, to their surfaces. Surface-attached FH and FHL-1/reconectin maintains its complement regulatory activity and promote factor I-mediated C3b cleavage to iC3b preventing bacteriolysis by the alternative complement pathway (Fig. 2). Complement resistant strains of *Borrelia burgdorferi* possess five complement regulatory acquiring surface proteins (CRASPS), that specifically bind FH and FHL-1 [43]. Bacteria evading from complement lysis will survive and proliferate in affected tissues, with consequent accumulation of persistent biologically active bacterial debris and through a vicious circle may sustain inflammation and amyloid deposition. Accordingly, both, the classic and alternative complement pathways are activated in AD and critical components of both pathways, including factor H are associated with cortical lesions and activated microglia [99,100].

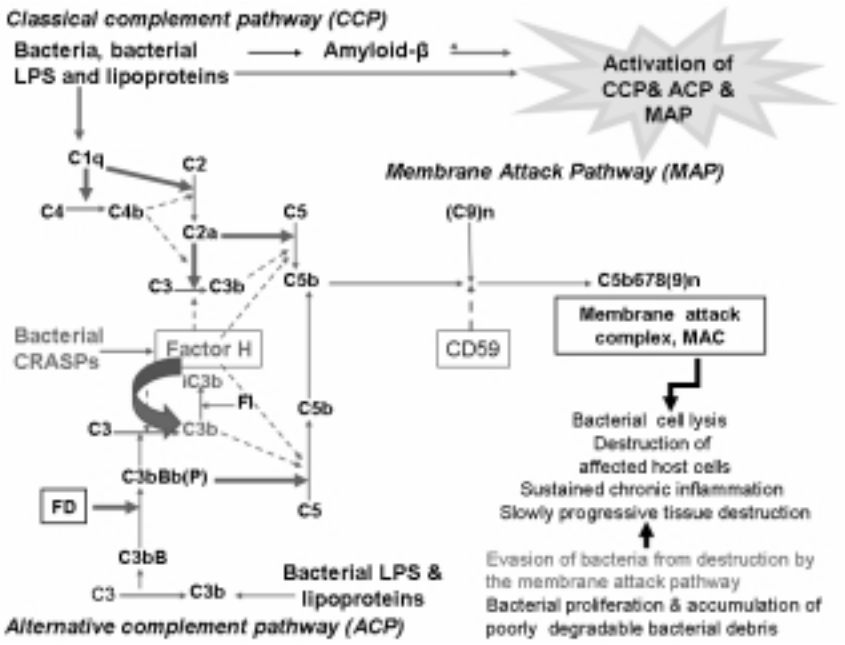

Fig. 2. Bacteria and Aβ are both able to activate the classic and the alternate complement pathways (CCP, ACP) through the common membrane attack pathway (MAP) resulting of bacteria and affected host cell lysis by the membrane attack complex (MAC or C5b-9). One way of evasion of Bacteria from complement lysis is their ability to bind the complement regulatory protein, factor H of the alternative pathway. Complement resistant *Borrelia burgdorferi* strains possess complement regulatory acquiring surface proteins (CRASPs), which specifically bind factor H, resulting in inactivation of C3b (iC3b) and in evasion of spirochetes from bacteriolysis by C5b-9 (MAC). Continuous arrows = activation, interrupted arrows = inhibition.

In addition, bacteria are powerful inflammatory cytokine stimulators, they affect vascular permeability, they generate nitric oxide, and they induce proteoglycan synthesis and apoptosis [22,23,33,34]. Exploding number of observations related to the mechanisms involved in *Treponema pallidum* and *Borrelia burgdorferi* infections indicate that exposure of host to spirochetes or to their toxic products, through a complex interaction with the host immune responses may induce persistent chronic inflammation, leading to slowly progressive tissue destruction.

One of the characteristic lesions of paretic dementia is the accumulation of iron in infected brain tissue [58]. Iron is essential for bacterial growth, and is recognized to play a vital role in infection. Iron has been shown to increase the formation of reactive oxygen intermediates leading to lipid peroxidation and subsequent oxidative damage to proteins and nucleic acids. Iron also affects the antigen-specific cellular responses by affecting T cell generation, T cell functions and proinflammatory cytokine production by macrophages [29,30,109,110]. *Borrelia burgdorferi* contains a transferrin-binding protein [14]. *Borrelia burgdorferi* also induces Matrix Metalloproteinases (MMPs) [76]. All of these processes are implicated in the pathogenesis of AD (Fig. 3).

Bacteria or their biologically active toxic components may both induce Aβ accumulation and tau phosphorylation.

CONCLUSION

The pathological hallmarks of AD consist of Aβ plaques and neurofibrillary tangles in affected brain areas. The processes which drive these host reactions are unknown. It has been known from one hundred years that chronic bacterial infection may lead to amyloid deposition not only in naturally occurring infections (e.g., syphilis, tuberculosis, leprosy, osteomyelitis) but also following injection of bacteria to experimental animals. In 1913, Noguchi and Moor showed the persistence of spirochetes in the brain of syphilitic patients suffering from dementia paralytica. This observation established a direct link between dementia and chronic bacterial infection. Today it is generally accepted that *Treponema pallidum* is responsible for dementia, brain atrophy and amyloid deposition in the atrophic form of general paresis in syphilis and also that this spirochete can cause several other neurodegenerative disorders.

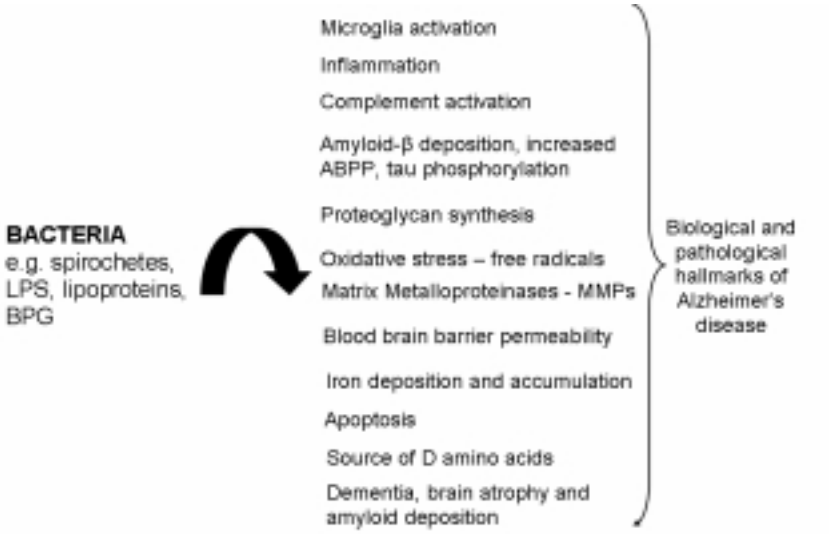

Fig. 3. Bacteria induced Alzheimer's type host reactions.

Recently observations showed that several types of spirochetes, including *Borrelia burgdorferi* and oral Treponema may be involved in the pathogenesis of AD. They may persist in the brain and following a long latent stage, in an analogous way to *Treponema pallidum* may cause dementia, cortical atrophy and amyloid deposition. Historical and recent data available indicate that to consider the view that bacteria may trigger a cascade of events leading to chronic inflammation, amyloid deposition and neurodegeneration is important as one may prevent or stop the disease with an appropriate antibiotic and anti-inflammatory therapy.

Bacteria are powerful stimulators of inflammation; they are amyloidogenic and posses biological activities which can induce the cascade of events leading to the pathological and biological hallmarks of AD. The purpose of this review was to show that the accumulated knowledge, views and hypotheses are not lying so far from each other. Each of them has its own importance and they form together a comprehensive entity when observed in the light of a persisting chronic inflammation initiated and sustained by bacteria or their persisting remnants.

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