

Alzheimer's Disease: Possible Mechanisms for Worsening of the Disease

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Abstract

Stroke, diabetes, nicotine, haloperidol, diet soft drinks, and others have all been shown to cause worsening of Alzheimer's disease (AD). In the following, we outline a possible mechanism for each of these entities to cause worsening by impacting a pathway to AD that we have developed based on our observations and those of others. That pathway includes microbes that make biofilms which activate the innate immune system; this ultimately leads to tissue destruction. The leading candidates for the microbes are pathogenic periodontal spirochetes and Lyme spirochetes which we believe are the driving forces in the formation of biofilms. We show how diabetes and its inherent hyperosmolality causes worsening of AD because the microbes make more biofilms in the presence of the hyperosmolar stress. More biofilms lead to more activation of the innate immune system (biofilms have receptor sites for Toll-like receptor 2 [TLR2]). Also outlined is how the dispersal of biofilms via nicotine and other commonly ingested/inhaled chemicals and medications leads to more severe disease.

Consequently, either "making" them as with diabetes, or "breaking" them as with nicotine, results in more biofilms and more activation of TLR2. Low serum levels of vitamins K2 or D3 lead to upregulation of TLR2 again causing worsening of the disease from increased innate immune system activation. Involvement of the adaptive arm of the immune system, in conjunction with biofilms, also leads to neurologic sequelae. Cerebrovascular accident (CVA), stroke, is the most disastrous malefactor of all because it is accompanied by activation of the adaptive immune system (lymphocytes and IgG) after disruption of the blood brain barrier. This creates massive tissue damage very rapidly. There are many fewer things that make Alzheimer's disease better when compared to worsening it. These are briefly mentioned.

Introduction

Previous work by Macdonald, Riviere, and Miklossy has shown Alzheimer's disease (AD) to be microbial in nature [1,2,3]. Macdonald, in fact, was able to culture *Borrelia burgdorferi* spirochetes from an AD brain [1]. This finding was completely disregarded. Subsequently, Riviere and Miklossy by polymerase chain reaction (PCR) were able to identify *Borrelia burgdorferi* spirochetes (25%) and dental spirochetes (75%) in AD brains. Further, Miklossy has been able to cultivate *Borrelia burgdorferi* from AD brains [4]. This has substantiated Macdonald's observations [1].

In an extensive and comprehensive work, Miklossy has recently shown AD to be similar pathologically when compared to general paresis (GP) [5]. GP, tertiary neurosyphilis, is also caused by a spirochete (*T. pallidum*) and is the classic disease associated with dementia [5]. In GP and AD, both the clinical features (dementia, in particular) and the pathological features (neurofibrillary tangles and plaques) are the same [5].

Spirochetes are clearly visible in the brains of both AD and syphilitic dementia [5].

Allen has recently shown that senile plaques (that are a signature pathologic finding of AD) are composed of biofilms made by the spirochetes [6]. This confirms the work of Macdonald [7]. Biofilm formation is a predictable occurrence because bacteria prefer to live in communities rather than in the planktonic state [8]. In fact, biofilm living is the way most organisms exist in nature [8,9]. The biofilms are a protective barrier for the microbes against environmental changes and against the immune system and/or antibiotics. Biofilms made by one organism contain attachment sites for other organisms [10]; this is clearly demonstrated in the biofilms causing dental plaque [11]. In dental plaque, streptococcus mutans is the organism generally responsible for attachment of the biofilm; it is then joined by porphyromonas and pathogenic spirochetes to form the community [12]. This finding may account for various organisms such as *C. Pneumoniae* [13] and Herpes simplex in the brains of AD patients [14].

The microbes (spirochetes) in the affected brains make the biofilms, most likely through quorum sensing, a population sensing mechanism they possess, rather than by formation due to environmental stress [15]. The spirochetes divide so slowly that it takes considerable time (up to two years) to develop sufficient numbers to form a single plaque [15]. In addition to making the biofilms, the spirochetes create beta amyloid precursor protein (BAPP) as well as beta amyloid (A β) itself [4].

Further, the presence of biofilms causes activation of the innate immune system in the form of Toll-like receptor 2 (TLR2) because there are receptor sites on biofilms for that molecule [16].

Supporting evidence for this comes from the fact that TLR2 has been shown to be present in the areas of senile plaques, as well as throughout the tissue [15]. In its main mode of response, TLR2, via the myeloid differentiation 88 pathway (MyD88), generates nuclear factor kappa b and tumor necrosis factor alpha (TNF α) in an attempt to kill the microbes inside the biofilm. TNF α cannot penetrate the biofilm, so it has been thought to attack the surrounding neural tissue instead (the “innocent bystander” concept) [6]. The pathway that characterizes this concept is as follows: microbes lead to biofilms which activate the innate immune system and cause tissue destruction. Given the lengthy time for AD to develop, this is a possible mechanism for the observed tissue destruction to occur because it not only takes an extended period of time for the biofilms to form, it also takes a long time for the TLR2 to work.

Additionally, TLR2 also leads to the production of A β , by activating the MyD88 pathway which generates NF κ B. NF κ B, acting in conjunction with beta amyloid converting enzyme (BACE), catalyzes beta and gamma secretase which cleave off the terminal portions of the BAPP to form A β [15,17]. Moreover, A β has been found to be an antimicrobial peptide [18]. A β also attempts to kill the biofilm-forming spirochetes, but it is unable to do so because it is unable to penetrate the slime. Its buildup further impairs the neurocircuitry [6]. The foregoing, based on observations, is the proposed pathogenesis of AD from spirochetes to A β (**Figure 1**). To be presented in the following are various things that are known to make AD worse. We will show how each causes worsening based on the pathogenesis outlined above.

Traumatic Brain Injury

AD is well known to occur much more rapidly and be much more devastating after a cerebrovascular accident (stroke) [19]. Ordinarily, AD takes three decades or more to develop; after a stroke, it is reduced to 1-3 years. The blood brain barrier is disrupted in the area of the stroke, and this is rapidly followed by an influx of lymphocytes followed by a massive buildup of immunoglobulin G (IgG) [19]. With this influx of lymphocytes and IgG, the adaptive immune system is in play and is armed with far greater destructive power (classical and alternate complement systems, killer T cells and cytokines)

than the innate system (NF κ B and TNF α). This allows for the rapid destruction of the neural tissue because, even with all that “killing” apparatus, the biofilms remain impenetrable. The surrounding tissue is killed instead (again the “innocent bystander” theory) [6].

Chronic traumatic encephalopathy (CTE) has many of the same pathological features as AD and GP (senile plaques, neurofibrillary tangles, A β and hyperphosphorylated tau protein) [20]. The repeated concussions and traumatic brain injury associated with CTE would cause breaks in the blood brain barrier (BBB) and allow for the adaptive immune system to work similarly to its action in stroke. Again, this would occur much more rapidly and destructively leading to the profound clinical and pathological AD-type changes. CTE has been found not only in American football players where it was first described by Omalu [20], but also in boxers, soccer players and others. Boxers have a 90% occurrence of concussions and champions have succumbed to the disease [21]. At the 2014 World Cup, 81 concussions occurred and all but three players returned to the pitch [22].

Biofilm Production

The next disorder to make AD worse is diabetes [23]. Recently, this has conceptually been shown to occur because of the increased serum osmolality that is present in diabetes (**Figure 1**). Hyper osmolality has been shown to be a strong stimulus for biofilm formation [24]. Because of this, the organisms make more biofilms more rapidly, without waiting for a “quorum” to be reached [25]. Similarly, homocysteine has been observed to encourage organisms to make biofilms; consequently, it may be compared to hyperglycemia [26] (**Figure 1**). Biofilms form more rapidly in the presence of salt and water which have recently been shown to be the provocative factors in eczema. In this disease, the biofilms form in the sweat ducts and trigger its onset [27]. Sub-therapeutic levels of antibiotics, lowered pH, and many other factors that induce stress (for the organisms) also trigger biofilm production [28].

Hyper osmolality increases biofilm production; increased biofilm production induces greater TLR2 which results in greater amounts of TNF α which results in greater tissue destruction. Also, this is possibly the pathway for diabetes to make arteriosclerosis worse: biofilms and activated TLR2 have recently been found in the arterial plaques in that disease [29]. Further, this may possibly be the pathway for many other chronic diseases including arthritis [30]. The effect of hyperosmolality, the effect of salt, water, subtherapeutic levels of antibiotics and lowered pH cause similar behavior of spirochetes in vitro, namely to form agglomerations and biofilm formation in these unfavorable conditions [31].

Biofilm Dispersion

Cigarette smoking is known to make AD worse, and the role of nicotine in that process has recently been outlined [32] (**Figure 1**) Nicotine is a biofilm disperser; conceptually, once

The Pathway to Alzheimer's Disease

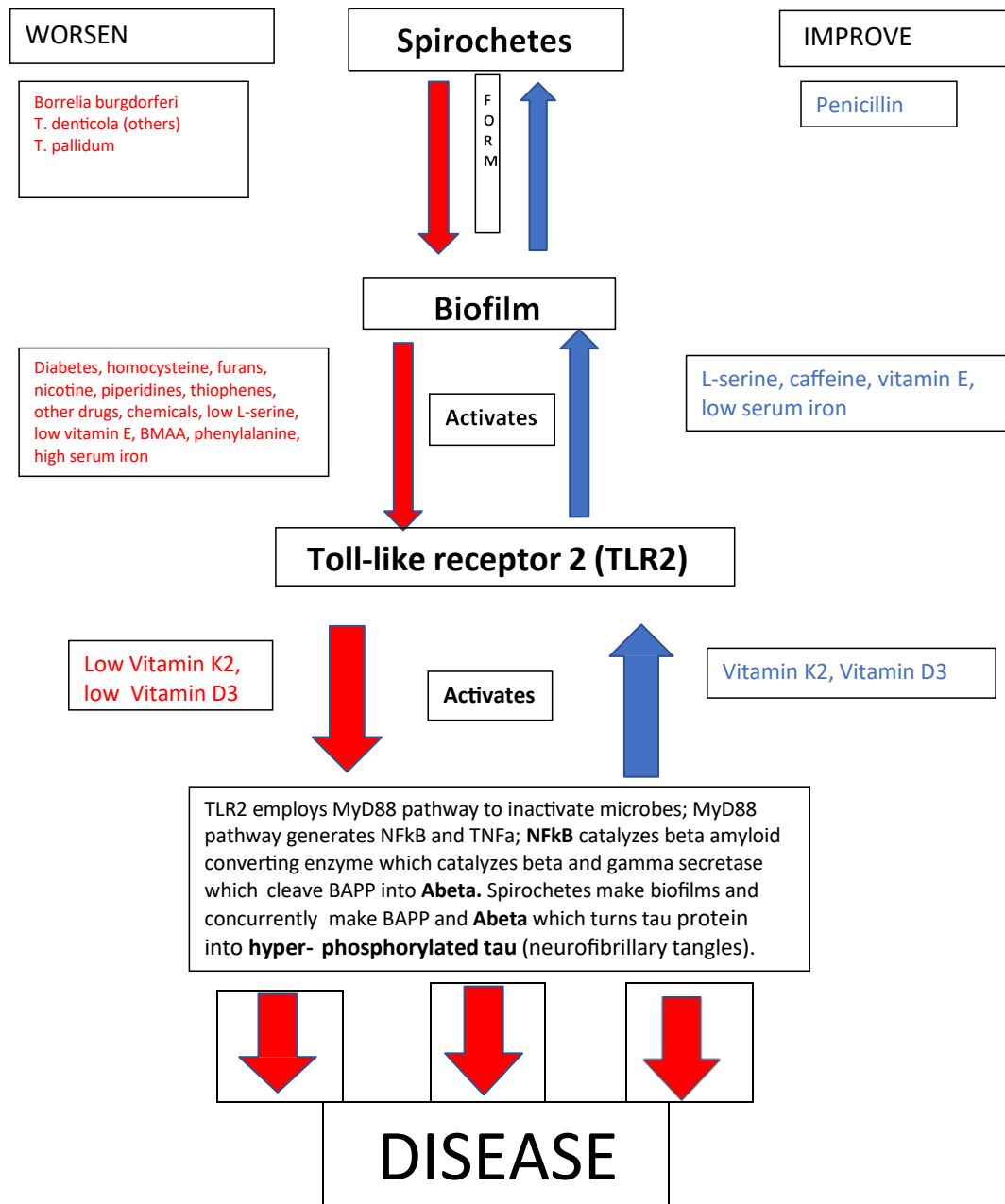


Figure 1. The Pathway to Alzheimer's Disease.

a biofilm is dispersed (in effect creating “exporter cells”) and there are no bactericidal antibiotics present, a whole crop of new biofilms gets sown, seeded by the dispersed organisms. With TLR2 activated, new levels of destruction are created, and the AD gets worse.

Biofilm dispersion may also be caused by many drugs: [Figure] one of these is rifampin which “pokes holes” in biofilms [33]. This drug has recently been shown to have been the key element in one of the greatest advances in medicine, namely the disappearance of leprosy [34]. With the addition of

rifampin to the regimen, Dapsone was now able to penetrate the biofilms (which were in the skin and internal organs) and kill the mycobacteria inside. The incidence of leprosy worldwide plummeted from 12 million in 1985 to less than a million in 2015 [35]. However, the addition of rifampin to any regimen in AD would very likely make the disease worse because the spirochetes within the biofilm need to be killed. And, in AD, even if they are killed by penicillin, as *M. leprae* have been killed by Dapsone, the resulting debris (dispersed biofilm, spirochetes, Abeta, and more) in the brain is likely to overwhelm the microglia; and, they would likely be unable to clear the

considerable detritus. The blood brain barrier helps keep things out of the brain, but it works both ways when it does not allow large amounts of debris to be removed from inside the brain [15].

Many other medications are biofilm dispersers, and these also are capable of worsening AD. They belong to several different categories of chemical compounds such as piperidines, pyrroles, thiophenes, and furans [36]. For discussion, haloperidol, a piperidine will be considered [37]. Use of this medication has been shown not only to cause worsening in AD, but also cause a 200% increase in mortality of AD patients given the drug [38]. As stated, haloperidol is a piperidine and those compounds cause biofilm dispersion creating many new foci of biofilms and “exporter” cells capable of forming new biofilms. Each new focus of biofilm attracts TLR2 which creates TNF α and greater tissue destruction ensues. Consequently, if biofilms are “made” as in diabetes, [23] or “broken”, as with haloperidol, the result is the same: more biofilms, more activation of TLR2 and more tissue destruction (**Figure 1**).

Another chemical impacts AD unfavorably: Beta methyl amino alanine (BMAA) [39]. This substance has been shown epidemiologically to create many neurofibrillary tangle diseases (multiple sclerosis, Parkinson's disease, and Alzheimer's disease and others) on Guam, and this has been further documented in primates (vervet monkeys) [39]. BMAA is a biofilm disperser, thus it behaves in the same way as the piperidines and furans and creates catastrophic worsening of the diseases [38,39]. AD has a signature pathologic finding of neurofibrillary tangles; and these tangles have been associated with *T. pallidum* in syphilis. The neurofibrillary tangles in AD have been shown to contain spirochetes [5].

Recently, diet soft drinks have been shown to triple the incidence of AD and stroke [40]. Phenylalanine, a constituent of aspartame (the major sweetener in those drinks) is a congener of BMAA. It has been shown both to be a biofilm disperser and a biofilm growth (size) limiter [41,42]. Thus, biofilms that arise in this setting would be more numerous because of the “dispersion” and, also, more numerous because fewer organisms would be required to fill the mature biofilm. This, consequently, would give many more targets for activation of TLR2 which then would directly lead to increased tissue destruction. The increase in arteriosclerotic stroke is related to the same mechanism: as stated previously, biofilms are present in the plaques of carotid artery endarterectomy specimens [43]. Disruption of these and similar plaques would be (and has been shown to be) disastrous [44,45].

Innate Immune System

The presence of low amounts of vitamin K2 adversely affects AD: a low concentration of K2 upregulates TLR2[46] leading to increased TNF α and greater tissue destruction (**Figure 1**). Adequate amounts of K2 lead to downregulation of TLR2 giving the opposite effect. Moreover, similar effects are noted with inadequate vitamin D3 [47]. Vitamin A and magnesium

might also have similar effects via similar mechanisms [48]. All four of these compounds (vitamin K2, vitamin D3, magnesium, vitamin A) appear to work in tandem.

Genetic Factors

The above are known factors that lead to worsening of AD. The disease itself appears to be a “double hit” phenomenon with the “environmental” hit being the microbes and their biofilms which has been the major thrust of this commentary. The “genetic” hit seems apparent from twin studies (80% concordance in monozygotic twins) [49,50] and from other treatises [51]. As with other “double hit” chronic diseases such as atopic dermatitis and psoriasis where filaggrin and PSORS2 appear to be the major genes involved [52], there are many more genes that have a role in AD. In atopic dermatitis, representative other genes include steroid sulfatase and transglutaminase-1 among others; and, in psoriasis, it is PSORS1,3,4 that are potentially involved [52].

In AD, the APO ϵ 4 gene appears to be the equivalent to filaggrin in atopic dermatitis, inasmuch as it is the most commonly found gene in the most common presentation of the disease [53]. The genes in early onset AD patients could be considered in the light of “making AD worse”, and they are the gene for BAPP, and the gene at the AD3 locus [53]. The latter (AD3) is responsible for 70% of early onset (age 30-60) AD. Although aggressive, early onset AD represents only 5% of the total AD population [53].

Necessity of Early Treatment

The final thing that makes AD worse is perhaps the most obvious of all: namely, the disease would not even exist if Lyme spirochetes were treated effectively at the earliest stage of the disease, and if the bacteremia surrounding dental procedures and other oral manipulations was treated effectively [54]. Consequently, in the paradigm (microbes creating biofilms which activate the innate immune system and cause tissue destruction), we have outlined things that cause worsening of AD at each step. One, lack of effective treatment directed (early) at the microbes is probably the most important. Two, “making” or “breaking” biofilms have been proven injurious. Three, substances that impact the immune system, such as vitamin K2, have been shown to have a profound effect. Moreover, it is the immune system that is responsible for considerable tissue damage leading to this dreaded disorder [54].

Putative Prevention and Efficient Therapy in AD

Things that make AD better are many fewer in number. Prevention is the first and most important factor in making AD better: prevent the spirochetes from reaching the brain or prevent them from making biofilms [15]. In syphilis, treatment with penicillin in the primary, secondary, early or late latent stages prevents tertiary syphilis; penicillin should be similarly effective in other spirochetal diseases. What is lacking is a similar serologic test (to the RPR) and the will to discard the

primacy of the beta amyloid hypothesis that is now 25 years old. Recently, a microarray test tested 100% positive for early AD; perhaps this can be adjusted to find the disease before it begins [55]. Until that time, we are left with treating with penicillin for Lyme disease and for pre-dental exposures. As discussed in prior works, dental work introduces spirochetes and other microbes into the circulation leading to hematogenous and other modes of dissemination, such as via lymphatics. The patient is transiently bacteremic. Given the affinity of spirochetes for neurons, the brain will be affected. Consequently, the presence of a bactericidal antibiotic in the serum at the time of dental work would kill the microbes and prevent them from “taking up residence” in the brain [15]. Aggressive periodontal work (covered by penicillin) would lessen the spirochetal burden as well [56].

Compounds that inhibit the growth of biofilms help prevent AD. The current “best” candidate for this is L-serine [39]. It inhibits quorum sensing which is the main initiator of biofilms [57]. Microbes have genes for sensing population density and “spin out” biofilm whenever a critical density is reached [15]. Another quorum sensing inhibitor is caffeine.[58] Whether it is as effective as L-serine is debatable. Caffeine also reduces biofilm attachment which is necessary for a biofilm to be functional (in microbiologic terms). Caffeine was also shown recently to have an ameliorating impact on AD, and other chronic diseases [59]. Vitamin C, ascorbic acid, is another anti-attachment compound for biofilms [60]. Though it has not been evaluated for efficacy, vitamin C seems weaker than either L-serine or caffeine. Iron acts inversely to L-serine: low iron levels act as growth inhibitors of biofilms while high levels encourage the formation of biofilms and the subsequent immune activity [61]. Lowering serum iron seems a useful mechanism for decreasing the incidence of AD [62].

TLR2 has been shown to be inversely related to vitamin K2; low K2 results in larger amounts of TLR2 and vice versa [46]. Thus, the addition of K2 to the diet should help attenuate the immune system activity generated in AD by TLR2. Vitamin D3, vitamin A, and magnesium have similar effects towards limiting tissue destruction by the immune system [47,48].

Lastly, limiting biofilm production would also limit Abeta deposition in the extracellular space because the microbes are responsible for the production of beta amyloid precursor protein as recently demonstrated [4]. The process is nearly self-contained in that the activity of TLR2 invoking the MyD88 pathway that generates NFkB actually catalyzes the formation of both beta and gamma secretase. Thus, if there are no organisms there would be no biofilms and, most probably, no Abeta accumulation.

End Note

Recent work of Miklossy showed Lyme spirochetes cultured from AD brains could be forced *in vitro* to make biofilms [4]. In so doing, the organisms not only made biofilms,

but also made BAPP and Abeta. We have recently observed intracellular biofilms in AD brains and these showed Abeta as well [63,64]. The significance of this is intracellular Abeta leads to hyperphosphorylated tau protein and ultimately to dendritic disintegration [65]. Consequently, early treatment would help prevent not only Abeta, has been outlined, but also the development of hyperphosphorylated tau. Thus, both the major pathological findings, Abeta and tau, would be addressed.

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