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RESEARCH ARTICLE

THE 3-D Pictorial Spirochetal Pathway to Alzheimer's Disease

Herbert B. Allen, MD [1]; Judith Miklossy, MD, PhD [2]

[1] Department of Dermatology, Drexel University College of Medicine, Philadelphia, PA, USA Dermatology, Eastern Virginia Medical School, Norfolk, VA, USA
Rowan School of Osteopathic Medicine Geriatrics and Gerontology, Stratford, NJ, USA
[2] International Alzheimer Research Centre, Prevention Alzheimer International Foundation Martigny-Croix, Switzerland

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ABSTRACT

This perspective article features a visual depiction supporting a potential link between spirochetal infection and Alzheimer's disease (AD). Two-dimensional (2D) images, alongside innovative three-dimensional (3D) imaging derived from 2D photomicrographs, provide the basis for a pathway through which spirochetes travel to the brain, with the hippocampus identified as their initial target. Upon arrival at this specific region, spirochetes can be found both extracellularly and intracellularly. Despite their slow growth, spirochetes eventually create a biofilm. Biofilm formation requires 10 cells in every direction, which can take two or more years for a significant biofilm to develop. To establish the biofilm, the spirochetes produce a slime coating that shields them from antibiotics, the immune system, and harmful irritants. Simultaneously with biofilm formation, spirochetes may induce beta-amyloid precursor protein (AβPP) and beta-amyloid (Aβ) production. In the extracellular space, biofilms can be covered with Aβ to be part of senile plaques. Intracellularly, during biofilm formation, spirochetes also generate amyloid precursors. It can also be hypothesized that spirochetes may induce tau hyperphosphorylation (p-tau), perhaps through a mechanism involving phosphatase inhibition. Accumulation of p-tau prevents the stabilization of microtubules within dendrites, leading to the disintegration of tubules and dendrites. Overall, neurofibrillary tangles are formed that, together with amyloid plaques, contribute to neuronal death. As more dendrites and neurons are destroyed, impulse transmission is impaired, resulting in cognitive deficits.

Introduction

The scope and purpose of this is perspective article is to present the many different precepts present. The most important is the presentation of 3-D vs 2-D images of the documented pathology, immunopathology and microbiology photomicrographs, Bright field microscopy enlarges the images 1000X vs 100,000X in 3D images. Also, the spirochetes are presented as in a darkfield examination. Another precept is the pathology of AD and tertiary syphilis with dementia are similar: the same senile plaques, same tau tangles, spirochetes, etc in each.[1] The background information includes those pathology changes and a discussion of the microbes involved. The methods in the original article included observation and categorization of the changes noted.

There are three different spirochetes documented to cause dementia: Treponema pallidum (TP) that causes syphilis and general paresis (GP) or syphilitic dementia; Borrelia burgdorferi (BB) that causes Lyme disease, neuroborreliosis, and Alzheimer's disease (AD); and oral spirochetes, represented by Treponema denticola (TD), that cause dental plaque and AD.[1-4] The evidence supporting BB and TD in AD is strong: they have been cultivated from AD brains, BB directly and TD as Spirochaetales. Further, both BB and TD have not only been cultured from AD brains but also have been characterized by immunopathology, fluorescent in situ hybridization (FISH) analysis, atomic force microscopy, and electron microscopy.[4] BB has been further characterized by 16s rRNA and taxonomical analysis by electron microscopy.[5]

TP was the first to be noted because it was seen decades ago on silver pathology stains of the brain and was recognized by the number of coils (up to 14) it contained.[5] TD, in its 4 multiple iterations (T. socranskii, T. pectinovorum, T. medium T. amylovorum, T. maltophilum, and T. denticola) was the last to be noted, but it was found on species-specific polymerase chain reaction (PCR).[2] GP forms up to 40% of tertiary neurosyphilis and neurosyphilis forms up to 30% of tertiary syphilis.[6,7] Thus, syphilitic dementia is seen in a maximum of 12% of patients with syphilis. The same is likely to be true for BB and neuroborreliosis as well.

BB has the fewest spirals (as few as three), TD is next with 6-10 and TP has 6-14. Both TP and TD have three characteristic movements: undulation, rotation, and angulation. TP is further distinguishable by sharp angulation as opposed to TD that bends and by TP's ability to "snap back" from an angulation. The mouth, incidentally, has been a difficult location to determine whether a lesion is a syphilitic chancre because of the close similarity of TP and TD. The three different spirochetes have been fully discussed in the commentary section of this article.

The spirochetes in the mouth have the shortest distance to travel: it is but a few centimeters from the mouth to the hippocampus, the first site involved in AD. From there, they can travel to other portions of the brain. BB would have the longest distance to travel, if the tick bite that injected the organism, into the skin was on the lower extremity.

The next key occurrence is the formation of biofilms because it is very likely there is no AD without biofilms. Biofilms form when organisms divide and form a quorum which is ten organisms in every direction. To obtain a quorum of spirochetes takes up to 2 years because they divide so slowly.[8] These fits with the clinical appearance of the disease at advanced age. Fischer who studied 12 cases of dementia to Alzheimer's one, thought the disease was infectious because the senile plaques resembled the sulfur granules of actinomycosis.[9] It is interesting that both the senile plaques and sulfur granules are biofilm structures. One obvious difference is the sulfur granules are surrounded by inflammatory cells of the adaptive immune system while the senile plaques are not (those cells, neutrophils and lymphocytes, are too large to fit through the blood brain barrier). The innate immune system molecule (TLR2) is present, and it creates numerous cytokines such as TLR2/MyD88/TNFa/NF-kB. (Figs. 1,2) This is responsible for some Aβ and much of the inflammation in AD.

The final necessary observation in AD is the presence of intracellular biofilms: without them there would be no disease.[10] When the intracellular spirochetes make biofilms, they also create beta amyloid (Aβ); and, when Aβ chemically interacts with tau protein, it creates hyperphosphorylated tau (p-tau) likely via a kinase or phosphatase inhibition reaction arising from TLR2/MyD88 generating NF-kB.[11-14] P-tau no longer stabilizes the neuronal microtubules in the dendrites as does tau, and they disintegrate.[15] This ultimately leads to destruction of the neuron.

Figure1 Toll-like receptor 2

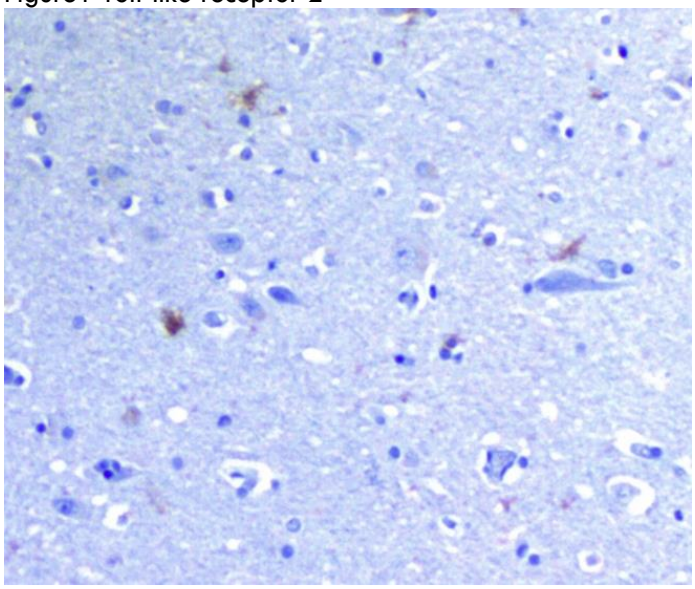

Fig.1 TLR 2 in hippocampal brain section stained with CD 282 immunostain (stains black); with the MyD88 pathway, it creates many of the cytokines noted in AD brains. NFT are noted as "tear drop" structures.

Figure 2. A pathway for the production of Aβ and many cytokines

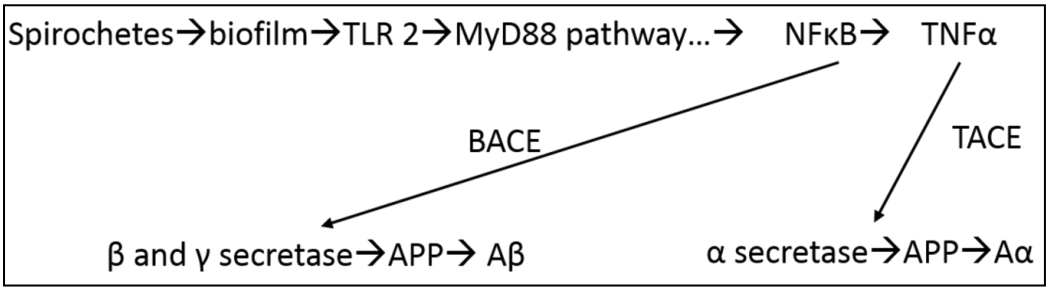

Figure 2 TLR2/MyD88/NF-kB/TNFa pathway to produce Aβ and many cytokines from NFkB and TNFa.

Commentary

In the case of the tick bite, once the (BB) is in the skin, the first lesion noted is the "bullseye" rash, Erythema migrans. The BB spirochetes cause this skin lesion, invade the dermal blood vessels, and crawl along the vessel walls until they reach the arterial system and head to the brain.[15,16] The dental spirochetes predominantly travel from the mouth, via the facial vein, to the cavernous sinus where the hippocampus sits astride the confluence of vessels that make the cavernous sinus. The spirochetes have an affinity for nerves, and they easily traverse the blood brain barrier and enter the brain. (Fig. 3) Other modes of travel for the dental microbes are via lymphatics, nerve tracts, and olfactory tissue.[3]

In the brain, the spirochetes (Fig. 4) are present intra and extracellularly. In both locations, the spirochetes make biofilms (Fig. 5A, B); these biofilms are found in the senile plaques in the extracellular space, and intracellularly in the neurons.[8] (Figs. 6A, B). Spirochetes, in both locations, create biofilms and simultaneously create Aβ.[11]. Next, the critical step inside the neuron takes place: Aβ comingled with tau chemically converts tau to hyperphosphorylated tau likely by tau kinase and/or phosphatase inhibition, possibly generated by TLR2/MyD88/NF-ÀB. (Fig. 2) P-tau causes disintegration of dendritic microtubules [15] that are stabilized by ordinary tau protein. When this occurs, the microtubules fall apart, the dendrites disintegrate and the neuron is destroyed eventuating in a neurofibrillary tangle. (Figs.8, 9, 10,) The neuron can no longer transmit impulses; when enough of these are destroyed, memory loss is sustained.

Figure 3. Syphilis and AD pathology comparison of the spirochetes in each disease.

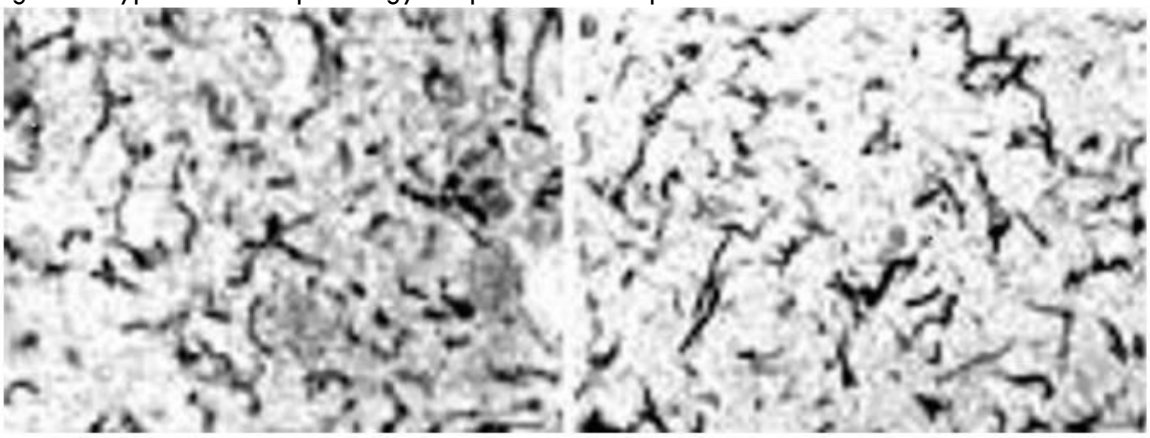

Fig. 3 The pathology sample of syphilis is on the left, and AD is on the right. They are similar in that both are helical in nature. They are demonstrated with silver stains. BB and TD spirochetes from the brains of AD patients have been cultured; to date TP has not. X100.

Figure 4. 3-D images of spirochetes.

Fig.4. 3-D representation of TD spirochetes as if they were imaged in a 3-D darkfield examination. The spirochetes undulate, rotate and bend as do TP. However, they do not make the sharp angles, nor do they "snap back" as do TP. BB mostly undulates. X100,000.

Figure 5A. Cultured BB from AD brains, immediately post-mortem, forms biofilms.
Figure 5B. A BB biofilm cut in half.

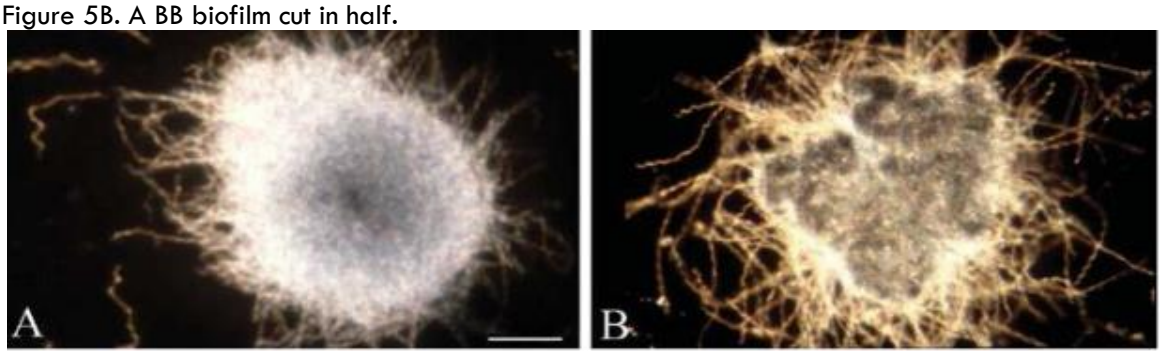

Fig.5A. Shows the external appearance in vitro of the biofilm; spirochetes are present around it.
Fig.5B. Shows water channels in the biofilm (gray areas); again, organisms surround the central biofilm.

Fig.6A. Senile plaques stained with Periodic Schiff (PAS) for demonstration of biofilms.
Fig.6B. Senile plaque stained for biofilm with PAS and for Aβ with Aβ immunostaining.

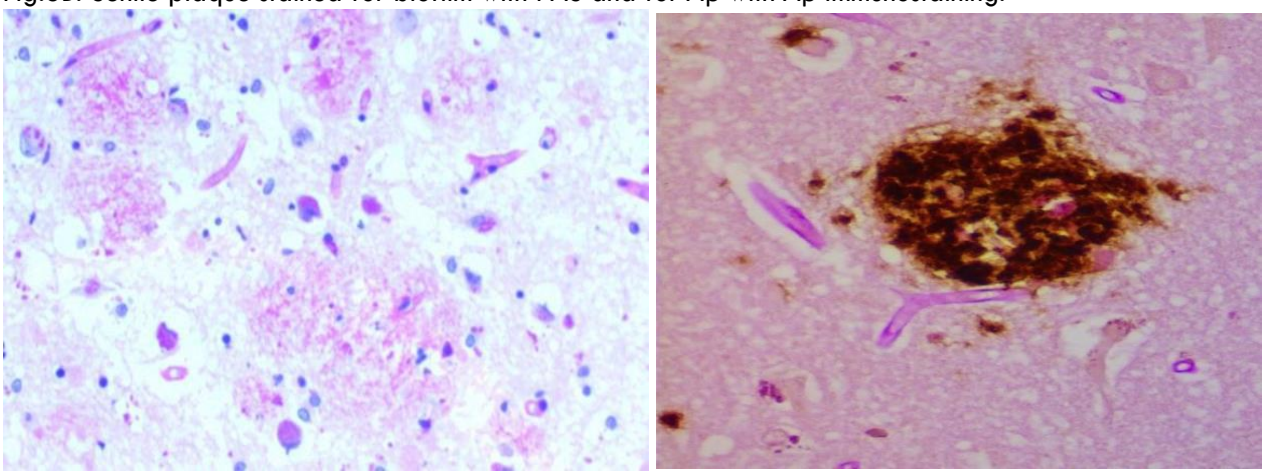

Fig.6A. Large pink (senile) plaques are noted in this pathology section. These represent biofilms, as are the intracellular pink areas. A triangular shaped neurofibrillary tangle is also present.
Fig.6B.Pink staining of the biofilm can be seen in focal areas in the center and edge of the plaque. Aβ coats the biofilm but not completely. Intracellular Aβ is noted in the surrounding tissue where biofilms were noted with PAS staining in Fig.6

Figure 7. 3-D photo image of senile plaque as seen in Fig. 7B (cut in half)

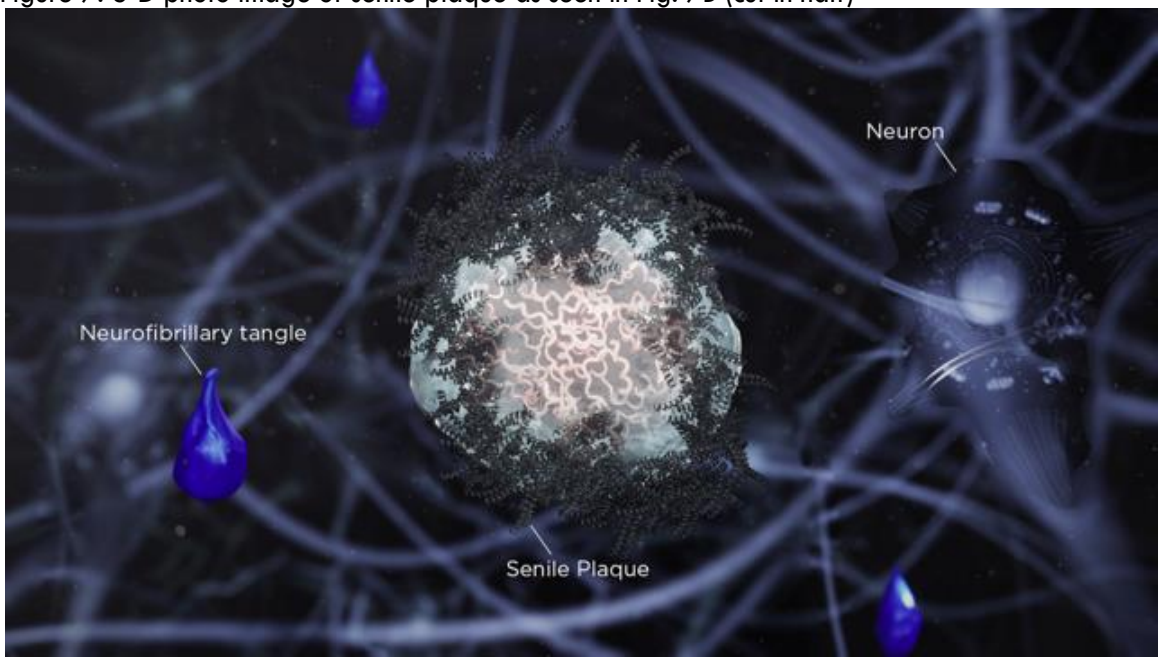

Fig.7 Pink spirochetes are noted in the center of the plaque; they are embedded in the light gray biofilm which is also seen extruding from the darker gray Aβ. A "tear-drop" NFT is also noted alongside the senile plaque.

Figure 8. Neurons with intact and damaged dendrites.

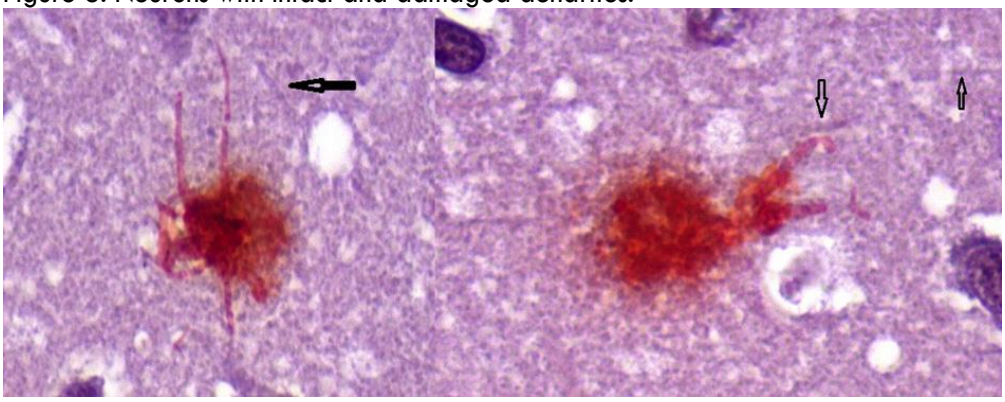

Fig.8. In the left image. The dendrites are elongated on Congo red stain; and, on the right, they are blunted and misshaped. In both images, the arrows point to intact gray dendrites.

Figure 9 Schematic uf dendrite microtubule disruption.

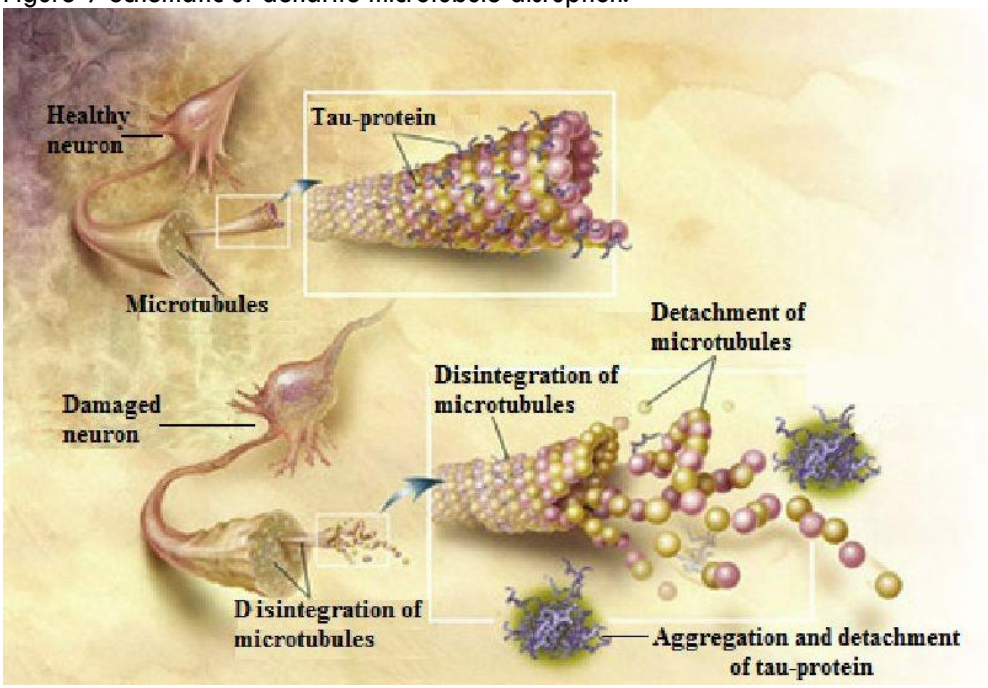

Fig.9. This schematic shows how the dendrite disintegrates. It does not show the chemical reaction causing the change in tau protein evoked by the interaction with Aβ (produced by the spirochetes). P-tau is produced by this chemical reaction, and the microtubules are destabilized. (from ADEAR/Wikimedia Commons)

Figure 10. 3-D imaging of the schematic in Fig.10

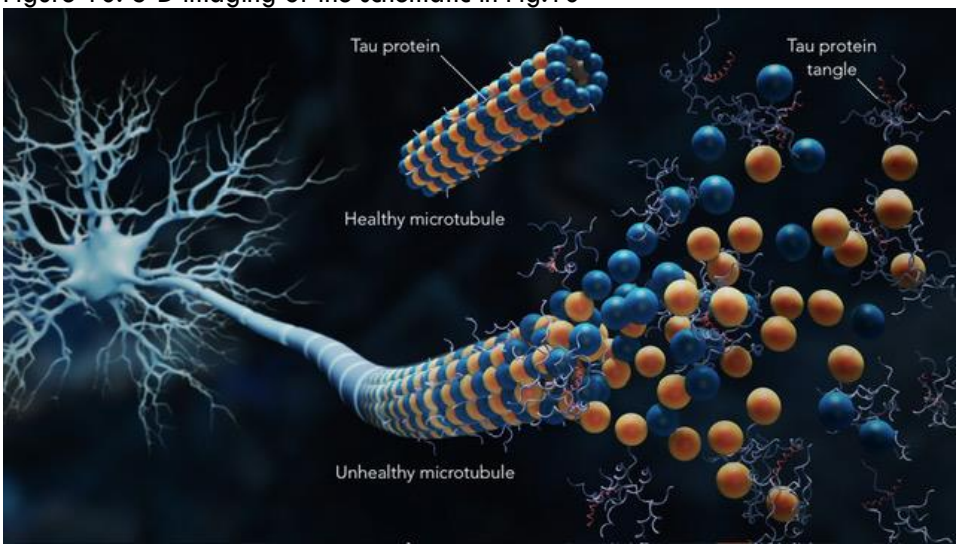

Fig.10 This shows a normal and disintegrating dendrite.

Other organisms do not fit this pattern: gram positive and gram negative bacteria, such as *Porphyromonas gingivalis* make biofilms in minutes rather than in years. Others such as *herpes simplex* virus and *Chlamydia pneumoniae* (CP) have never been shown to make biofilms.[19-21] They may join in the spirochetal biofilm[22]

because it has receptor sites for other organisms. In the case of CP, it has been shown to be nestled inside the spirochetal (BB) biofilm.[23] (Fig. 11) In that location, it is unlikely that it would play a role in any of the pathological steps that have been outlined herein. The role of other organisms in a mixed biofilm is also uncertain.[24]

Figure 11. An image of a BB biofilm with Chlamydia pneumoniae (CP) noted in its center.

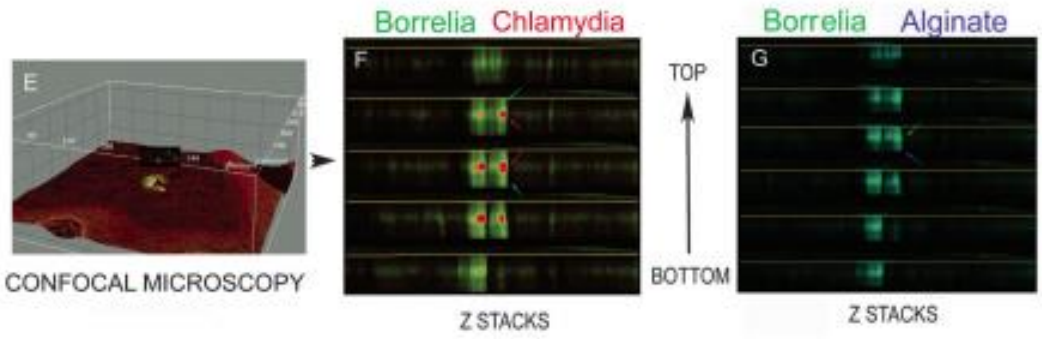

Fig.11. it is unlikely from this position that the CP is playing any role in AD.

From this pathway, it is obvious where treatment intervention would be effective at preventing dementia: kill the spirochetes before they travel to the brain or before thy form biofilms. This is already taking place in syphilis where a positive serologic test identifies a patient in the early or latent stages of the disease, and treatment with penicillin (or azithromycin for those allergic to penicillin) will prevent the disease from progressing to tertiary.

Lyme disease is like syphilis in that regard because it generally comes from a single tick bite. Consequently, a single treatment as in syphilis would likely be preventative. With oral spirochetes, they periodically seed the brain; and, consequently, they need periodic treatment to ensure they do not form biofilms. We currently recommend a yearly 2 or 3 week course of penicillin (or equivalent) for our patients.[25] In over 250 patients aged 60- 85 treated in this manner, there have been zero cases of dementia. "You can cheat to get a paper. You can cheat to get a grant. You can't cheat to cure a disease. Biology doesn't care."[26] This means if the treatment works, it works or if it doesn't, it doesn't. Moreover, the development of resistance to the antibiotic has not occurred. In a small number of patients who have developed AD, the penicillin plus a biofilm disperser ("buster") seems to restore cognition. This obviously requires a more extended course of penicillin and rifampin or a fluoroquinolone (is both an antibiotic and a biofilm disperser). Ciprofloxin or levofloxacin, fluroquinolones, both kill the organisms and break the biofilms.

In summary and conclusion, dental spirochetes make up the vast majority (approximately 90%) of the microbes precipitating AD; BB comprises 10% and syphilitic spirochetes have nearly been eradicated by treatment with penicillin. All these spirochetes make biofilms like almost all the microbes in nature; and they also make Aβ simultaneously when they make biofilms. When this occurs intracellularly (as has been shown), the Aβ chemically reacts with ordinary tau protein and converts it (by tau kinase inhibition) to ptau. P-tau no longer stabilizes the microtubules in the dendrites (as has been demonstrated) and they disintegrate. They no longer form synapses with other neuronal dendrites; the absence of impulse transmission in the memory center of the brain forms the basis of dementia.

We have shown TLR 2 to be present in hippocampal specimens from AD brains (and not in controls). Together with MyD88, presumably from microglia, this leads to the cytokines NFkB and TNFa and many more cytokines. This creates the inflammation necessary to create the tau kinase inhibitor. This TLR 2/MyD88 pathway also creates extracellular Aβ, as has also been shown.

The historical comparison of the clinical and pathological findings of syphilitic dementia and AD has shown them to be identical, with the only difference being caused by different spirochetes. Given this, it appears very likely that treatment before the microbes arrive at the brain, or before they make biofilms would likely prevent this scourge from happening.[27] Currently, this is exactly what has occurred in over 250 of our patients aged 60 -85 who have taken a yearly 2–3 week course of penicillin or azithromycin. (The antibiotic is given yearly because dental spirochetes in the mouth constantly seed the brain, as opposed to the single occurrence during syphilitic infection. For those patients with (mild or greater) cognitive impairment, penicillin or azithromycin plus a biofilm disperser, such as rifampin given for a longer interval has been shown in a dozen patients to clear the fog of dementia. A fluoroquinolone, such as ciprofloxacin or levofloxacin, is both an antibiotic and a biofilm disperser, may require only one medication as opposed to two. 9/12 have improved dramatically.[28] This needs considerably more study. The cost of these approaches is in the tens of dollars vs tens of thousands of dollars for the current biologic compounds under study; 200 studies to date on removal of Aβ and/or tau have been fruitless. These have been based on the Aβ theory of the disease and not what we have demonstrated herein.

Approval

All work in this paper was done under the approval of the Drexel College of Medicine institutional Review Board and nearly all the text was peer reviewed in J Alz Dis 2021; 84: 61-67

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