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RESEARCH ARTICLE

The Historical Development of the Pathological Changes in Alzheimer's Disease Based on Microbiology, Anatomy, and Physiology

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ABSTRACT
The major pathological changes in Alzheimer's disease were found in hippocampal specimens from Alzheimer disease patients. We contend that spirochetal bacteria that make biofilms cause these changes. The spirochetal/biofilm complexes induce the changes of note including neurofibrillary tangles, senile plaques, beta amyloid, and atrophy. It has been shown previously that when spirochetes make biofilms, they create beta amyloid simultaneously. When the biofilm is made intracellularly (in the neuron), the beta amyloid that is also produced, interacts with tau protein and converts it to hyperphosphorylated tau. This leads directly to neurofibrillary tangles. Produced extracellularly (outside the neuron), the biofilms, which are coated by beta amyloid, form the senile plaques. The interaction of the biofilm in the senile plaques with the innate immune system molecule Toll-like receptor 2 produces beta amyloid by known pathways. The atrophy, both total and regional, is produced when the neurons disintegrate. All these pathological findings take considerable time that fits with the clinical course of the disease. For instance, it takes up to two years for spirochetes to make a single biofilm. This differs from other microbes such as Chlamydia pneumoniae, Porphyromonas gingivalis, and Herpes simplex that make biofilms in minutes. The long time for development therefore fits better with spirochetes compared to other organisms.

Introduction

The notable pathological changes in Alzheimer's disease (ALZ) are senile plaques, neurofibrillary tangles (NFT), beta amyloid (Aβ), and atrophy. (Fig.1) These are present in all ALZ pathology specimens, yet their origins have remained unexplained since the disease was first categorized. Incidentally, even though Fischer wrote about 12 dementia patients while Alzheimer described one, the disease was identified as ALZ. This was because Kraepelin, a prominent German neurologist favored Alzheimer.

Figure 1. Senile plaques, NFT in ALZ hippocampus

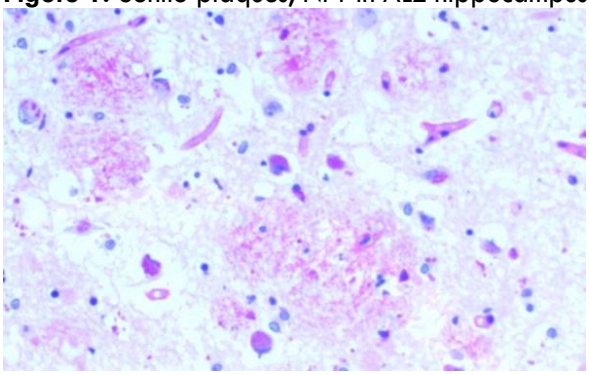

Fig. 1 Large senile plaques stain positively with PAS stain indicating the presence of biofilm. The triangular shaped NFT (right of center) also stains positively. Intracellular biofilms are also present. PAS stain 10X

The most cogent observations as to the origins of the changes have been made first by Macdonald and then by Riviere, and Miklossy.[2-4] Macdonald cultured *Borrelia burgdorferi* (Lyme spirochetes, [BB]) from ALZ brains, but this achievement has been overlooked for the past 5 decades. This occurred even though Fischer thought the disease could be of microbiologic origin because the plaques reminded him pathologically of sulfur granules in Actinomycosis.[1]

Riviere next demonstrated the presence of dental spirochetes in ALZ brains by polymerase chain reaction (PCR).[2] These included many different treponemal subspecies including *T. denticola*, *T. sochranskii*, *T. pectinovorum* and others. All these will be referred to as *T. denticola* (TD) and were alluded to by Miklossy in her salient paper documenting ALZ as an infection by the Koch/Hill criteria[5].

The next critical observation was made by Miklossy who showed the pathology of general paresis (GP) or syphilitic dementia was identical to the pathology of ALZ---the same Aβ, senile plaques, NFT, and atrophy.[6] Thus the syphilitic spirochete, *T. pallidum*, caused the same clinical and pathological changes as BB and TD spirochetes cause in ALZ.[6]

The making of spirochetal biofilms; the process that creates both the pathology and the chronicity of the disease.

The next major finding was that the spirochetes made biofilms; this was observed both *in vitro* and *in vivo*.[7-9] Making biofilms is not an unusual occurrence because more than 90% of organisms in nature make biofilms.[10] The critical observation with biofilms and ALZ is the extraordinary slowness with which they develop. This sluggishness fits with spirochetes and not with other microbes such as *Herpes simplex* virus, *Porphyromonas gingivalis*, or *Chlamydia pneumoniae*.[11-14] These organisms, if they made biofilms, would make them in minutes, not months. Specifically, *porphyromonas* is the only microbe of those listed that has been shown to make biofilms. The spirochete/biofilm concept fits the profile of ALZ which takes years to develop.

Next came the discovery that while BB cultured from ALZ brains made biofilms, they also made Aβ.[12] Thus, the spirochetes not only made biofilms, they also made Aβ and AβPP. Miklossy showed this *in vitro*[13]; the biofilms in ALZ occurred intracellularly in addition to extracellularly. The biofilms in both locations have been identified by pathology and immunopathology staining[13]. The Aβ produced by the spirochetes when they made biofilms is very likely the origin of most of the Aβ in ALZ.

The development of the innate system molecule Toll-like receptor 2

Next, the extracellular biofilms have been shown to interact with the innate immune system molecule Toll-like receptor2 (TLR 2) as they do in many chronic diseases. That interaction in addition to the subsequent interaction with the MyD88 pathway (which leads to NFkB and TNFα which inactivate microbes). This pathway also leads to the development of Aβ.[9] Consequently, the spirochetes make Aβ when they make biofilms, and the biofilms lead to the production of more Aβ. The adaptive immune system (immunoglobulins, complement, killer T cells and others) is prevented from interacting by the blood brain barrier (BBB);

only when the BBB is breached, is the adaptive immune system active. This is devastating as is shown in stroke.[14]

Development of neurofibrillary tangles

Next for consideration is the formation of NFT. These are formed when Aβ reacts with ordinary tau protein and, by a documented process, converts it to hyperphosphorylated tau (p-tau).[15] P-tau leads to destruction of the dendrites that leads to apoptosis.[16] The Aβ, in this instance, was produced simultaneously with the formation of the biofilms inside the neurons. This is likely the most important occurrence in ALZ. The pathway for this is as follows: intracellular spirochetes form biofilms and while making biofilms make Aβ. The Aβ interacts with tau protein and converts it to p-tau that leads to dendritic destruction and NFT formation.[16] Each of the steps in this pathway has been documented.

Development of senile plaques

Senile plaques are next for consideration. Again, they are formed by spirochetes that make biofilms. They are quite large and are coated with Aβ[9] (Fig. 2). Aβ has been shown to be antibacterial.[17] Teleologically, this is difficult to explain: the spirochetes create a molecule that leads to their destruction?

Figure 2. Aβ coating a senile plaque in hippocampus

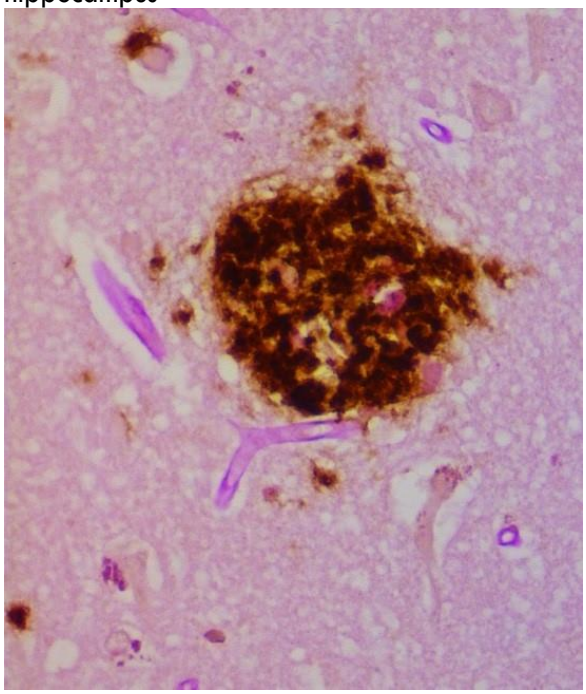

Fig.2 Aβ (brown-black) coating a senile plaque (pink material in the middle and the border of the plaque). PAS stain combined with Aβ immunostain 40X

Production of atrophy

Last of the pathological changes to consider is atrophy. It is most easily explained by the death of all the neurons caused by the spirochete/biofilm complex. The hippocampus, the site where ALZ begins, shrinks to 1/5 its size (Fig. 3). This sharply limits the transmission of impulses through this region considered the most important area for memory.

Figure 3 Atrophy of the brain and hippocampus in ALZ compared to healthy brain

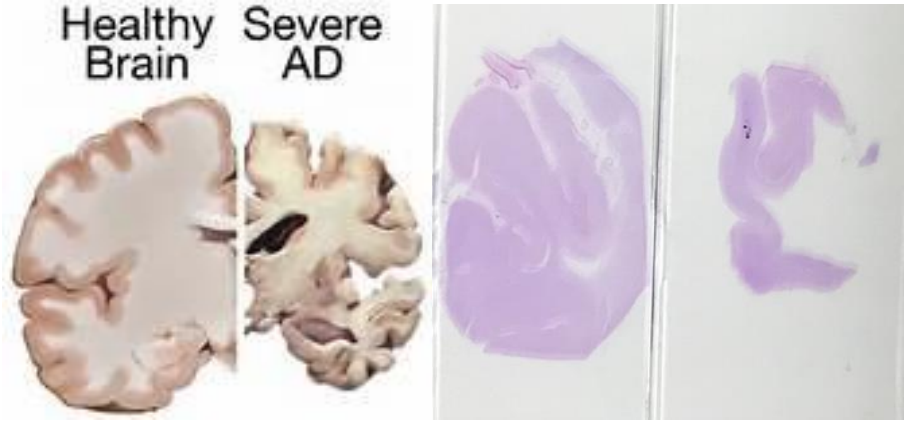

Fig.3 Total brain on left; hippocampus on right (marked atrophy noted on right vs normal age and sex matched control.) H+E stain 1.0 X

Testing the spirochetal/biofilm theory

One way to test the accuracy of all these considerations is to evaluate various molecules that cause worsening of ALZ and measure the impact of these molecules on biofilms. Haloperidol has been shown to cause such worsening in ALZ that it caused a 200% increase in death.[18] As a chemical piperidine, it is a biofilm disperser. Breaking biofilms apart (with no antibiotics around), creates the equivalent of many "exporter" cells. These can create new biofilms. Nicotine is a pyrrole chemical and is also capable of dispersing biofilms.[19] This leads to similar effects as shown with haloperidol.

Diabetes is known to exacerbate ALZ. Hyperosmolality (caused by increased blood glucose) is known to cause microbes to make biofilms. The presence of more biofilms adversely affects ALZ[19]: consequently, if biofilms are dispersed (broken) or made, the effect is deleterious to ALZ. Breaking biofilms is like making biofilms regarding worsening of ALZ.

Conclusion

The pathological changes, senile plaques, NFT, Aβ, and atrophy seen in ALZ have been shown to be induced by the spirochete/biofilm duality and have been fully documented. Osler's aphorism (re "medicine") could possibly be modified to "he who knows syphilis, knows 'pathology'."

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