

Bioethical Challenges Arising from the Microbiology and Pathology of Alzheimer's Disease

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Abstract

We have presented evidence based on our work and the work of others that Alzheimer's disease is caused by spirochetes that make biofilms both inside and outside of neurons. The extracellular biofilms have been shown to cause upregulation of the innate immune system molecule Toll-like receptor 2 (TLR2). The TLR2, by known pathways, eventuates in nuclear factor kappa B (NFκB) and tumor necrosis factor alpha (TNFα) and these molecules lead to beta amyloid and tissue destruction respectively. This well-documented concept of microbial pathogenicity has been largely disregarded in favor of the beta amyloid hypothesis which has been in place for the past twenty-five years. These factors comprise the first ethical challenge. The second challenge is treatment and research efforts are being utilized at, or near, the end of the pathogenic cascade and not at the beginning of the process at which time the spirochetes are easily treatable. Last is the markedly expensive effort to develop new therapeutic agents (none of which has been curative) which are not and have not been aimed at the true pathogen. All these together could lead to a large ethical challenge in the new millennium.

Mini-Review

We have recently written about how the ethics in Lyme disease and psoriasis are challenged [1,2]. This paper will focus on the bioethics of Alzheimer's disease in terms of the microbial pathogen hypothesis. Since Lyme spirochetes (*Borrelia burgdorferi*) were cultured by Macdonald in 1986 and again in 1988 from Alzheimer's disease brains [3,4] and, more recently, by Miklossy [5] similar bioethical inferences can be drawn from the seemingly disparate diseases. In Lyme disease, the continued presence of the spirochete has been disregarded. Yet, when the Lyme spirochetes can be cultured from affected brains (tertiary Lyme disease), the denial of their presence seems spurious. Further as concerns psoriasis, the evidence for group A streptococcus as an etiology in psoriasis is not miniscule but has been considered as such [2]. The same may be said for Alzheimer's disease where the prevailing hypothesis for the past 25 years has been centered on β amyloid, while the microbial pathogenesis has received little support [6]. Additionally, Lyme organisms make up 25% while dental spirochetes make up 75% of the microbes in Alzheimer's cases [7].

We have also reported on how the organisms make biofilms and upregulate the innate immune system molecule Toll-like receptor 2 (TLR2) [8]. Nearly all bacteria make biofilms, so *Borrelia*-derived biofilms would not be unusual. Bacterial biofilms, even those biofilms associated with gram negative organisms such as spirochetes, have external receptor sites for TLR2, which ordinarily responds to gram positive organisms [9]. The TLR2 that has been identified by immunopathological staining has been observed throughout the sections examined

and did not appear to be localized to microglia or to the amyloid plaques [8]. TLR2, by known pathways, generates NFκB and TNFα in an effort to kill the offending pathogens. However, the biofilm protects the organisms and the TLR2 is unable to penetrate and kill the microbes; this process is largely responsible for the destruction of the cerebral neurocircuitry because the neural tissue is "in killed in the line of fire" as an innocent bystander [10]. Moreover, NFκB, through known pathways, generates β amyloid from β amyloid precursor protein (AβPP) by catalyzing β amyloid converting enzyme [11]. This precursor (AβPP) has definitively been shown to be made by the microbes [6]. The biofilms also have receptor sites for other organisms [12]; it has been compared to a "hotel" rather than a "single family home." This may be a possible explanation for multiple organisms (such as *C. pneumoniae* and *herpes simplex*) being found in analysis of AD brains [13,14].

Tau protein ordinarily stabilizes neuronal dendrites; however, when it is hyperphosphorylated, it loses its functionality and allows for disintegration of those dendrites into neurofibrillary tangles. The pathologic finding that these tangles contain spirochetes [15], and the recent pathologic finding of intracellular biofilms may bring the discussion of microbial pathogenesis into sharper focus [15]. The spirochetes have been noted to be widely distributed in many areas including, among others the plaques where there is a co-aggregation of biofilm and Aβ. [8,15]. In a forthcoming treatise, we will show Aβ in an intracellular location, corresponding to the biofilms already observed there [15]. With Miklossy's findings that the cultured spirochetes made Aβ along with the biofilms, and with

the findings that A β contributes to hyperphosphorylation of Tau which ultimately leads to disintegration of the dendrites, the factors influencing tangles appear to be in place [16,17,18].

Seemingly, all the essential elements in AD (beta amyloid, A β PP, plaques, tangles, Tau protein, and neurodestruction) can be explained by the following: spirochetes enter the brain from the circulation or by other pathways, and these spirochetes form biofilms both intra and extracellularly. During the formation of the biofilms, A β is formed intracellularly and this induces hyperphosphorylation of Tau and leads to the formation of tangles and neuronal disintegration. The biofilms in the extracellular space upregulate the innate immune system (TLR2); by known pathways, this leads to production of extracellular A β . The surrounding tissue is subsequently destroyed. There are thus two ways for the A β to be formed: one by the microbes directly during the formation of biofilms, and the other by the action of the innate immune system.

Alzheimer's disease has been compared to general paresis of the insane (tertiary syphilis), and the neuropathology has been found to be exactly the same in both diseases [15]. Tertiary syphilis has been eradicated by treatment in the early stages of syphilis [19]. One would expect similar results with treatment of Alzheimer's disease rendered before the organisms arrive at the brain or before they do damage. The spirochetes are all sensitive to penicillin (no resistance has been noted to date); and, if this antibiotic is given before dental procedures and for early Lyme disease, similar results as in syphilis should be achievable [7]. Why not treat early in the cycle rather than later? Treating early in the cycle would also include aggressive treatment for periodontal disease [20]. It seems apparent that spirochetes have the leading role in the production of Alzheimer's disease; why not kill them?

In the comparison of bioethics of Lyme disease, psoriasis, and AD, different parameters are invoked. In Lyme disease, the current treatment at all stages of the disease is ineffective. In psoriasis, the current treatments are effective but are not aimed at events early in the pathogenesis of the disease. Consequently, they must be continued perpetually. In AD, there are no effective treatments, but the current clinical trials and research (based mostly on combatting beta amyloid) are all aimed at events occurring late in the pathogenic cascade. This has cost the pharmaceutical industry and society billions without a single effective agent being developed. This raises the ethical challenge of ignoring the microbial "pathogen" theory of this disease.

By overlooking or disregarding the evidence that has been marshalled over the past three decades, an opportunity to prevent Alzheimer's disease has been lost. In syphilis which serves as a prototype, one can administer the effective antibiotics in the primary, secondary, and latent stages of the disease and predictably achieve the expected response (cure/prevention). This spirochetal disease (syphilis) responds to penicillin at all stages except for tertiary. All that is necessary for consideration of this treatment in Alzheimer's disease, and, indeed this

concept, is epistemic humility [21]. This is very similar to the situation in psoriasis where Evidence Based Medicine (EBM) carries a "stipulative definition" because there is no reason to justify limiting the evidence for use of antibiotics for psoriasis while giving much more credence to "mainstream research" that focuses on symptomatic therapeutic options and not on causative therapies [2]. "Stipulative" in Alzheimer's disease would then refer to the evidence for microbial pathogenicity being "stipulated" as non-contributory to the disease. The word 'evidence' reveals its ambiguous nature in the context of research and the precarious position for patients when that "evidence" is used to justify this approach to clinical practice [22,23].

While recognizing costs to the pharmaceutical industry and society, the other ethical challenge is the continued research aimed at limiting or preventing beta amyloid accumulation with treatment without considering alternatives. The costs have been staggering to the healthcare system with the cost to bring one of these new drugs to market of 2.6 billion (or more) dollars [24]. Continuation of this (?misdirected?) research results in a sort of "rational inconsistency" which overlooks the problems because of the single focus on β amyloid [25]. Treatment in the other diseases in which biologics are employed may be shown (in the future) to have similar ethical challenges. This would be true if those other diseases also had microbial pathogens as their source. Alzheimer's disease is one such disease where monoclonal antibody trials are being undertaken; where the source likely is a microbe [25]. Limiting the body's reaction to that microbe, without treating the offending agent, not only seems unethical but senseless [21].

Given all the above and considering that millions of patients have been/and are involved, ignoring the likely microbial pathogenesis in AD could possibly become one of history's greatest ethical calamities. The original observation of Borrelia in the brains of AD patients by Macdonald [3] might be discounted, but the PCR observations of spirochetes by Riviere [26] subsequently confirmed by Miklossy [7] cannot be ignored. This could dwarf the ethical situation in Tuskegee and Oslo (both of which involved untreated syphilis) with numbers of patients, the impact on families, and the colossal expenditures made in pursuing a faulty theory [27,28].

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