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Alzheimer's neuroborreliosis with *trans-synaptic spread of infection and neurofibrillary tangles derived from intraneuronal spirochetes*

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Summary

In the realm of dementia, it is astonishing to note that neurofibrillary tangles (NFT) are microscopically identical in a childhood illness (SSPE) and in a dementia of late adult life (Alzheimer's disease). The words "Alzheimer-type" NFT in peer reviewed scientific articles written by acknowledged experts underscore the striking similarities in "tangles" in two different diseases. Subacute Sclerosing Panencephalitis (SSPE) is caused by infection with atypical measles virus. Alzheimer's disease has no known cause.

There is little controversy in suggesting that all of the Tangles in SSPE infected neurons are produced by slow viral type variant of Measles infection. But the mere suggestion that infection might be a cause of Alzheimer's disease confounds the establishment. If a good case is to be made for infection in Alzheimer's disease, an excellent nerve cell infection model is needed. Monkeys have provided a very reasonable model. Recently, a primate neuroborreliosis brain infection model demonstrated that *Borrelia* injected into the skin of monkeys resulted in the appearance of *Borrelia* transcriptomes in brain neurons. If *Borrelia* can travel from skin to brain in the monkey, then why not look at human Alzheimer's tissues to see if the DNA of *Borrelia* is present in the human brain? The molecular detection tools

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perfected in animal neuroborreliosis studies have been applied to human Alzheimer's disease brain tissues. Seven of ten cases of Alzheimer's disease from McLean Hospital Brain Bank of Harvard University yielded positive signals for infectious DNA in a small pilot study. Alzheimer's diseased neurons analyzed with DNA probes, produced little "dots" of positive staining. Granulovacuolar bodies in Alzheimer's diseased neurons (little dots in a bubble), are one of the expected microscopic profiles of Alzheimer's disease. "Little dots" inside nerve cells are also signatures of viral infectious agents inside of nerve cells. So with the assistance of the microscope and the tools of molecular biology, a new model of infection emerges as a cause of "Alzheimer's-type" neurofibrillary tangles. Here I hypothesize that it is chronic infection of human neurons in Alzheimer's disease that produces neurofibrillary tangles by a pathway similar to the chronic SSPE infection tangle pathway. In addition, transmission of infection from nerve to nerve is proposed to explain the evolution of Alzheimer's disease. Herein is offered a new view for the origins and for the progression of diseased nerves with tangle formations in Alzheimer's disease based on infection.

Article Outline

[Introduction](#)
[Hypothesis](#)
[Evaluation of the hypothesis](#)
[Consequences of the hypothesis](#)
[Acknowledgements](#)
[References](#)

Introduction

Too many neurofibrillary tangles in too many neurons in demented persons in the 7th, 8th and 9th decades of life are, on a statistical basis, Alzheimer's disease until proven otherwise. Such a provocative declaration is offered to call attention to the necessity of "tangles" in Alzheimer's disease Ref. [1], [2] and [3]. If the root cause for the overabundance of tangle bearing neurons could be known, then opportunities for early diagnosis, treatment, and possibly eradication of Alzheimer's disease would exist. The arena of "tangles" is cluttered with enigmas and paradoxes. There is the paradoxical observation that a few tangles in the elderly brain do not produce dementia. We do not know what the upper "healthy limit" of tangle number might be. We do know that normal pediatric brains never have any tangles in neurons. Therefore, the opportunity to study a pediatric dementia with neurofibrillary tangles (SSPE) Ref. [4], [5] and [6] is a perfect occasion to observe an "assembly line" for pure neurofibrillary tangles, without any of the other contributions from the "Elderly brain". This concept might be restated by imagining two different assembly lines to tangle formation. In the pediatric patients and in young adults with SSPE infection where tangles are present the pathology findings are similar Ref. [7], [8] and [9]. In the Elderly Alzheimer brain, two possible assembly lines to tangle formation might be present. The first is the "old age" assembly line. This functions in all senior citizens to produce just a few tangles, but not so many tangles as to produce dementia. These are the "background benign tangles" of senior citizens who are not demented Ref. [10]. Elderly persons with Alzheimer's disease, however,

have “too many tangles”. The excess of tangles is herein postulated to come from the extra contribution of an second assembly line pathway namely the nerve infection pathway to tangle formation.

Two possible pathways to tangle formation establish a rationale for two clinical outcomes in the senior citizen. To paraphrase the poet Robert Frost, “The road less travelled by ..makes all the difference”. Two roads to tangles eliminate the confusion and the *Paradox of a few tangles with no dementia*. In healthy elderly patients without dementia the infection pathway is absent. Total “tangle burden” in the brain is a manageable condition.

The next issue for discussion in tangle development is the variable the duration of time that neuron infection is present in any individual. Short-term versus long-term infection are two choices on this menu. Again, there are lessons in the examples of SSPE in childhood. The “short duration” SSPE cases proceed to death in less than one year from the onset of symptoms. “Long duration” SSPE cases demonstrate chronic illnesses with dementia and survivals in excess of one year to many years.

What pathology evidence exists to prove that infection is indeed persistent? Chronic SSPE brain infection is caused by a variant paramyxovirus (Atypical measles) Ref. [11], [12], [13] and [14]. There is also an example of another virus (JC virus) which may cause tangles. This virus, like SSPE persists inside of infected neurons as tangles are produced. The electron microscope photographs prove that the viral agent (JC virus) persists in tangle infested brain neurons right up to the death of the patient Ref. [15]. Photographs of virus inside diseased cells early and late in SSPE conclusively prove persistent chronic long term residence of an intracellular pathogen Ref. [16] and [17].

Other authors' commentaries on comparisons between Alzheimer's disease and SSPE are excerpted from the medical literature in the following categories:

1. SSPE is the equivalent to “*Alzheimer's disease lacking amyloid plaques and granulovacuolar degeneration*” Ref. [18].
2. SSPE is a disease which is “*indistinguishable*” from Alzheimer's disease by electron microscopic findings Ref. [19].
3. SSPE is a special example of an infection in which “*..neurofibrillary tangles can occur independently of amyloid formation.*” .. and “*..this mechanism may operate in both Alzheimer's disease and virally induced disease..*” Ref. [20].
4. SSPE is an example of a disease with “*..Tau positive tangles and neuropil threads similar to Alzheimer's disease...*” Ref. [21].

Indeed, with so many parallels between SSPE Tangles and Alzheimer's disease tangles, how is it possible that the “tangled web” of interconnections has not already been unraveled? Why hasn't a credible link to infection and Alzheimer's disease been suggested up to this point in time? One reason might be that the SSPE “Infection-Tangle-Dementia Triad” requires a special type of infection. Only “inside the nerve” infections emulate the SSPE model. Such infections are extremely rare. Rabies is an intraneuronal infection which kills quickly Ref. [22]. *Rabies and other rapidly progressing infections are “ineligible” for participation in the SSPE “Infection-tangle-Dementia Triad” model.* Chronic infections evolving over years are

eligible for such consideration. At this juncture, it is restated that short duration SSPE infections never produce tangles Ref. [23]; the only SSPE infections which produce tangles are the long term infections. So it is necessary to identify a chronic and intracellular (intra-neuronal) infection candidate to link Alzheimer's disease with other slow to evolve brain infections, in the SSPE tradition.

Chronic neuroborreliosis has recently been linked to individual cases of Alzheimer's disease Ref. [24], [25] and [26]. Observations in experimental primate neuroborreliosis by Fikrig and colleagues Ref. [27] has established a category of so called "*paucibacillary*" infection in which the spirochetes are difficult to visualize in brain tissue. "Invisible" spirochetes are detectable by abundant spirochetal RNA in brain extracts. Indeed the "molecular signature" of borrelia pathogens in the primate neuroborreliosis model is so complete, that analysis of over 80 gene equivalents (Open reading frames) is possible in analysis of primate autopsy material. A bonus harvested from the monkey brain research is the ability to select out of the total 1.6 million chromosomal and plasmid nucleotides of borrelia DNA, *only the key regions* which are robustly present in Autopsy brains after experimental infection. DNA probes designed to emulate the positive findings in primate research have successfully detected specific borrelia DNA sequences inside of the neurons of the Alzheimer's disease hippocampus Ref. [28]. These in situ DNA hybridizations now provide a justification, based on the SSPE infection model, to apply the Triad of Infection-Tangle-Dementia to Alzheimer's disease. The paradoxes and enigmas of Alzheimer's disease are "untangled" by these models.

Hypothesis

Neurofibrillary tangles in Alzheimer's disease are derived from the effects of *prolonged intraneuronal infection* with Borrelia species. Infectious agents which enter the cytoplasm of nerve cells persist in the axonal space, and destabilize the microtubular systems of the neuron. Transmission of infectious DNA across synapses spreads the infection from one nerve to another nerve, in a pattern which is reminiscent of the spread of Rabies virus. Nerves which are spared from neurofibrillary tangles might be explained by the lack of synaptic connections to the nerves which are infected. The progression of Alzheimer's disease from early stages in the entorhinal cortex and hippocampal regions to late stage disease with involvement of higher cortical and neocortical brain regions might be explained by nerve to nerve transmission of infection across synapses.

A previously described mouse model for SSPE supports trans-synaptic transmission of measles virus from one nerve to another Ref. [29].

Earlier observations dating to 1996 based on the natural history of SSPE infection, have also led to published discussions by other authors of *trans*-neuronal transmission of the SSPE viral agent Ref. [16]. Once a nerve is infected, enzyme homeostasis mechanisms are corrupted by the biochemistry of the invading microbial pathogen. Hyperphosphorylation of healthy Tau protein is one consequence of intracellular infection. A toxic environment created by infection accelerates formations of paired helical filaments, which are the underlying structures of Alzheimer-type neurofibrillary tangles. Ultimately the chronically infected tangle corrupted neurons die.

Evaluation of the hypothesis

Verification of infectious DNA within the cytoplasm of tangle bearing neurons in Alzheimer's disease could be accomplished with pathogen specific DNA probes. Positive DNA hybridizations in the cytoplasmic regions of tangle laden neurons would confirm intracellular infection. Human DNA is never present in the interphase neuron in any region of the cytoplasm.

Microinjection of healthy human neurons in tissue culture with whole cell extracts of living *Borrelia* spirochetes labeled with green fluorescent protein markers (GFPs) would offer an alternate independent method for verification of the microtubule destabilization mechanism. Electron microscopy of the microtubular system of neurons after Microinjection in infectious spirochetal extracts, would provide images of destabilization of the microtubules. Microtubular collapse is a necessary condition to precede the formation of the Alzheimer-type tangles.

Consequences of the hypothesis

Ratification of the neural infection pathway to neurofibrillary tangles in Alzheimer's disease would add an essential link to connect Alzheimer's disease with occult chronic intraneuronal infections. The "infection tangles" concept explains a specific pathway to nerve cell death and the origins of large numbers for NFT laden nerve cells in Alzheimer's disease. Previous borrelia infection mechanisms to relate Alzheimer "amyloid" Plaques and the granulovacuolar bodies of Alzheimer's have been described Ref. [30] and [31]. A three part "infection explanation" encompassing the genesis of NFT, plaques, and GVB in Alzheimer's disease provides immediate justification for aggressive antispirochetal therapies in early Alzheimer's disease, with the prospect of a possible cure.

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