Alzheimer's disease and spirochetes; a questionable relationship

A commentary on the Research Article by Judit Miklossy entitled "Alzheimer's disease - a spirochetosis?"

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Alzheimer's disease (AD) continues to grow in prevalence, in its cost to society and in its share of research expenditure. Few diseases have received so much attention from both the scientific community and the public, and fewer still will continue to be as extensively investigated in this decade of the brain. Until the present the puzzle has been assembled a piece at a time, with small advances gradually adding to the overall picture. There has been extensive peer review with confirmation and rejection of hypotheses. As a result the collective experience in this field is both formidable and highly critical, and although all parties hope for a significant breakthrough, the findings in the article by Judit Miklossy in this issue,[1] are so far removed from the current thrust of investigations into the pathogenesis of AD that we are certainly interested but respectfully sceptical.

Interestingly, it is not the first time (and possibly not the last) that spirochetes have been blamed for an idiopathic neurological disease.[2,3] In the previous two notable examples, the spirochetes were found to be artifact and contaminant respectively, and the etiology of multiple sclerosis remained enigmatic. If the current findings are confirmed in other laboratories, this would certainly rank among the most significant contributions in the history of medicine, but there remain several concerns regarding the present findings and several AD phenomena that are difficult to explain in light of an infectious cause.

It is surprising that with the quoted yield of spirochetes from the identified cases, no images are available of the organisms in the brains of the 14 specimens and although we do not claim to be expert in the identification of spirochetes, we do not find the photomicrographs and electron micrographs of the putative spirochetes from the AD cases to be unquestionably compelling. The immunohistochemical positivity of spirochetes for amyloid precursor protein (APP) is intriguing but APP is a ubiquitous and highly conserved protein at least in mammals. It may not be surprising that it is present in bacteria as well. Alternatively, the positive reaction may have been the result of binding to an unrelated but cross reactive bacterial protein epitope. Ultimately, the reported immunohistochemical association would at some point have to be supported by Western blot analysis and/or protein sequencing; this is not within the scope of the current paper.

It is difficult to understand the absence of round cell inflammation within parenchyma and in the CSF at all stages of the presumed infection. It is also surprising that none of the control cases had any Alzheimer type changes since these are very common in the elderly and which by the author's proposal are indicative of an early stage of infection. This is unlike the pattern observed in other spirochetal and bacterial infections of the CNS. Furthermore, we know that AD patients show no signs or symptoms specific to a chronic ongoing infection, nor do their tissues or body fluids display round cell inflammatory changes.

Other aspects of the demographics of AD would remain puzzling should it be recognized as an infectious disease. For instance, it is difficult to explain how persons in close contact with AD patients do not exhibit a greater risk for developing the disease than the population at large. It is equally difficult to account for the clear pattern of inheritance of AD in the significant number of cases that are familial. The frequent dementia and Alzheimer-like pathology of trisomy 21 is also not easily explained on the basis of an infectious agent unless it is proposed that Down's syndrome and familial AD impart some universal susceptibility to this organism, a phenomenon for which there is poor precedent.

Finally we look to Koch's postulates for the common basis and minimal criteria for the classification of a disease as infectious. Indeed, the putative organism is claimed to be present in all of the index cases and in none of the control cases. The authors also report that they have been able to culture the organism. However, it has yet to be transmitted to another animal, identified therein and recovered from the recipient animal. This missing evidence will likewise leave doubts about the reported findings and conclusions until successfully performed. Its lack of transmissibility is instead confirmed in the world's experience of the demographic pattern of this disease in man. It should be noted that the reported transmission of AD to primates has since been retracted[4] (see also authors' reference 16).

The paper remains an intriguing report that will raise the interest, if not the voices and blood pressure, of many in the neuroscience community. We remain sceptical and even incredulous at the thought that such an etiology for such an important and exhaustively studied disease could have been overlooked by so many including ourselves. This is not a condemnation but it should be emphasized that such remarkable results would have to be consistently replicated, and expanded upon by other investigators before the conclusions of this report could be endorsed by the scientific community. We look forward to the widespread attention this report will undoubtedly receive and the judgments that will follow.

REFERENCES

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