finally ready for a treatment trial?

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Could infections really have something to do with disorders that cause dementia? Several chronic diseases, such as peptic ulcer, certain cancers, and autoimmune conditions, have established infectious etiologies, either bacterial or viral, but mainstream cognitive disorder research has not fully considered microbial involvement. Evidence is emerging,[1] but the size of the problem—millions of patients with Alzheimer disease (AD) worldwide, and increasing—compels searching for clues in the dark, and not only below the streetlight, especially if established and safe treatments are available.

Thirty years ago, on the basis of the similar topographic distribution of AD and herpes encephalitis—in the temporal and frontal lobes, but also in the hippocampus—Ball[2] speculated about a connection between dementia and herpesviridae. Thereafter, professor Ruth Itzhaki's[3] group in the United Kingdom has been stubbornly pursuing the idea: they have repeatedly argued for associations between herpes simplex virus (HSV) and AD, especially in individuals with the *APOE* ε4 genotype, known to make one more vulnerable to AD.

A plethora of studies elegantly link microbial effects to AD pathology: inflammation, formation of amyloid plaques, genetic host responses, and so forth. These pathogenetic mechanisms have been recently exhaustively reviewed.[1] There are also increasing numbers of epidemiologic reports,[1] not only of HSV, but also of other viruses, especially cytomegalovirus, which seems to play a substantial role in immunosenescence.[4]

In this issue of *Neurology*®, Katan et al.[5] present further epidemiologic evidence of an association between infectious burden and cognitive function in the multiethnic and population-based Northern Manhattan Study. Although the authors primarily used a composite serologic measure of exposure to both bacterial (*Chlamydia pneumoniae* and *Helicobacter pylori*) and viral (cytomegalovirus and HSV-1 and -2) pathogens, closer analyses implied that the association was primarily driven by viral infectious burden. These results strengthen the idea of an association between herpesviridae and cognitive decline. However, is the evidence sufficient to consider new types of prevention and treatment? Moreover, what causes damage in the brain is uncertain: a specific pathogen? a collection of pathogens? interactions among pathogens? In the study by Katan et al., the infectious burden variable assumed an additive effect and therefore does not elucidate pathogen interactions or the possibility of competitive antagonism between or among pathogens. Further research should focus on the roles of combinations of pathogens in a way that allows for testing of specific interactions in relation to cognitive outcomes.

Undoubtedly, demonstrating that old-age cognitive disorders, including AD, are slowly progressing diseases of viral etiology would revolutionize the dementia research field (and be Nobel Prize worthy). However, great challenges remain. Most studies to date have been cross-sectional and associative, which do not prove cause and effect. There may be important differences in the ability of various microbes to provoke amyloid substance aggregation, the pathognomonic feature of AD. Herpesviridae may be a more attractive candidate in this respect, given their ability to get into the brain and their potential interactions with *APOE*.[1] However, in case–control studies of brain tissue, chlamydia and spirochetes actually seemed more robustly associated with AD than herpesviridae.[1] Furthermore, during the 1990s *C pneumoniae* infection was enthusiastically greeted as a treatable, microbial cause of coronary artery disease. Failures in large antibiotic trials tempered the enthusiasm, and most now consider *C pneumoniae* infection possibly important, but only a single factor contributing to the development of atherosclerosis.[6]

As always in evidence-based medicine, a randomized controlled treatment trial would provide final proof. Interesting findings are emerging from schizophrenia research. Although valacyclovir treatment did not alleviate schizophrenia symptoms in patients seropositive for cytomegalovirus,[7] a new study seems more promising. In a small test-of-concept study in individuals with schizophrenia, a group from Pittsburgh and Harvard demonstrated a favorable effect of valacyclovir 3 g on

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cognitive domains related to executive function.[8] This finding fits well with unpublished analyses of the editorialists, suggesting that viral infections would be associated specifically with those cognitive domains related to executive function (Aiello and Strandberg, personal communication, 2013).

But even after these promising results, several more challenges remain. The mean age in the schizophrenia trial was 29 years, and the patients were without significant comorbidity.[8] In contrast, cognitive disorders and dementia in old age are more or less a geriatric syndrome[9] with multiple contributing factors. According to the current state of knowledge, an ideal trial to prove the microbe–dementia connection would involve not only antiviral but also antibacterial (e.g., spirochete or chlamydia) and anti-inflammatory therapy. The trial should be targeted to seropositive individuals possibly with the *APOE* ε4 genotype and possibly with signs of inflammation (such as elevated C-reactive protein).[10] Comorbid factors in older patients or the advanced nature of the dementia might overwhelm any effect of the intervention.

One has to start somewhere. A first step might be a randomized controlled trial in patients with AD using valacyclovir with an adequate dose (possibly 3 g) and duration (6 months or longer) to cover reactivations of herpesviridae and with careful selection of sensitive study endpoints (such as the Alzheimer Disease Assessment Scale–cognitive subscale). Currently, no antimicrobial studies in AD can be found in trial registries. Such a study is nevertheless worth doing, and the editorialists hope that the study by Katan et al.,[5] along with earlier pioneering work by other groups that have examined specific infectious etiologies of cognition and AD, will stimulate this endeavor.

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