Can Infections Cause Alzheimer’s Disease?

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Late-onset Alzheimer’s disease (AD) is the most prevalent cause of dementia among older adults, yet more than a century of research has not determined why this disease develops. One prevailing hypothesis is that late-onset AD is caused by infectious pathogens, an idea widely studied in both humans and experimental animal models. This review examines the infectious AD etiology hypothesis and summarizes existing evidence associating infectious agents with AD in humans. The various mechanisms through which different clinical and subclinical infections could cause or promote the progression of AD are considered, as is the concordance between putative infectious agents and the epidemiology of AD. We searched the PubMed, Web of Science, and EBSCO databases for research articles pertaining to infections and AD and systematically reviewed the evidence linking specific infectious pathogens to AD. The evidence compiled from the literature linking AD to an infectious cause is inconclusive, but the amount of evidence suggestive of an association is too substantial to ignore. Epidemiologic, clinical, and basic science studies that could improve on current understanding of the associations between AD and infections and possibly uncover ways to control this highly prevalent and debilitating disease are suggested.

Alzheimer disease; bacteria; dementia; infection; neurodegenerative diseases; prions; sepsis; viruses

Abbreviations: Aβ, β-amyloid; AD, Alzheimer’s disease; ApoE4, apolipoprotein ε4; APP, amyloid precursor protein; CNS, central nervous system; CSF, cerebral spinal fluid; HSV-1, herpes simplex virus type 1; PCR, polymerase chain reaction.

INTRODUCTION

Alzheimer’s disease (AD) is a chronic neurodegenerative disorder and the leading cause of dementia among individuals aged 65 years or older. Clinically, AD manifests as progressively deteriorating cognitive function, and a diagnosis is made according to the criteria of the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (1) and the National Institute of Neurological Disorders and Stroke–Alzheimer Disease and Related Disorders working group (2); this diagnosis is also applied for research purposes. Definitive diagnosis, however, necessitates the histopathologic examination of either biopsy or postmortem brain tissue. In most cases, gradually degenerating memory is the earliest and predominant cognitive deficit (2, 3), but other cognitive deficits as well behavioral disorders, personality changes, and motor and sensory deficits can become manifest, especially in advanced stages of the disease (4). Typically, symptoms gradually worsen; ultimately, the ability to communicate and perform the activities of daily living is severely impaired, resulting in the loss of independence (4).

AD is categorized into early- and late-onset subtypes depending on whether the onset of clinical symptoms occurs before or after the age of 65 years, respectively. Early-onset AD is uncommon, accounting for less than 1% of all AD cases, and is caused primarily by autosomal dominant mutations in either the amyloid precursor protein (APP) or the presenilin (presenilin-1 or presenilin-2) genes (5–9). In contrast, the exact cause of late-onset AD remains largely unknown. Some risk factors for late-onset AD have been identified and include increasing age (10, 11), lesser educational attainment (12, 13), head trauma (14–16), cardiometabolic disorders such as midlife hypertension (17, 18) and diabetes mellitus (19, 20), and certain genetic variants, most prominently, the apolipoprotein ε4 (ApoE4) allele (21–28). Few other environmental factors have been consistently associated with AD in humans (29, 30).

Infectious agents have been known to cause chronic progressive central nervous system (CNS) diseases and
syndromes for well over a century. Several of these agents, such as herpes simplex virus type 1 (HSV-1), *Helicobacter pylori*, *Chlamydia pneumoniae*, and *Borrelia burgdorferi*, are associated with neurocognitive decrements either in humans or in experimental animal models and have been implicated as possible causes of AD in humans (31–38). These pathogens might induce AD directly through CNS infection and resulting neuroinflammation or indirectly via the various effects of systemic inflammation on the brain. Alternatively, infectious pathogens might induce an autoimmune response that targets the brain, resulting in neuroinflammation and possibly AD (39). Although such possibilities have been suggested, no specific pathogen has been linked conclusively to the causation of late-onset AD in humans.

The present review examines the existing evidence for infections as possible causes of AD. Specifically, our review intended to 1) examine whether AD neuropathology is compatible with an infectious cause; 2) systematically review the evidence associating certain infectious agents with AD in humans; 3) consider evidence suggesting that various clinical and subclinical infections indirectly promote AD progression, including the possibility that patients with AD could be prone to infectious diseases; 4) search for correlations between putative infectious agents and the epidemiology of AD; and 5) suggest epidemiologic and basic science studies that might improve on current understanding of the associations between infections and AD and possibly uncover ways to control this prevalent and debilitating disease.

**MATERIALS AND METHODS**

We searched the PubMed, Web of Science, and EBSCO databases for research articles pertaining to infection and AD using the following key words: "Alzheimer’s disease" AND "infection", "Alzheimer’s disease" AND "bacteria", "Alzheimer’s disease" AND "virus", "Alzheimer’s disease" AND "Herpes simplex", "Alzheimer’s disease" AND "Chlamydia", "Alzheimer’s disease" AND "Chlamydia pneumoniae", "Alzheimer’s disease" AND *Helicobacter pylori*, "Alzheimer’s disease" AND *Borrelia burgdorferi*, "Alzheimer’s disease" AND "varicella zoster", "Alzheimer’s disease" AND "cytomegalovirus", "Alzheimer’s disease" AND *Treponema*, "Alzheimer’s disease" AND "prions", and "amyloid-beta" AND "infection". We limited our search to original research articles, previous reviews, and research letters and excluded publications in languages other than English for which an English translation was not readily available online. The initial database search yielded 6,017 articles, of which 2,960 were duplicates; these were excluded, leaving 3,057 articles. We reviewed some of these abstracts and selected key, representative papers to include in the review. For the systematic review of the 4 major pathogens associated with AD, the initial database search yielded 664 articles; these were categorized by pathogen and arranged according to author and title, and duplicates and irrelevant articles were excluded (Figure 1). All the relevant publications were included in the systematic review.

**COMPATIBILITY OF CENTRAL NERVOUS SYSTEM ALZHEIMER’S DISEASE PATHOLOGY WITH INFECTIONS**

AD neurohistopathology is characterized by the simultaneous presence of neuronal degeneration, intraneuronal neurofibrillary tangles and neuritop hil threads, and extracellular β-amyloid (Aβ) plaques within particular regions of the brain. Neurofibrillary tangles and neuritop hil threads reside inside nerve cell bodies and dendritic processes, respectively, and arise as the result of tau hyperphosphorylation, which causes tau to accumulate and aggregate into insoluble fibrils (40–43). Aβ plaques, on the other hand, accumulate in extracellular spaces as the result of gradual deposition and accumulation of specific Aβ peptides (44). Plaque-forming Aβ peptides are derived from the stepwise cleavage of APP, an integral membrane glycoprotein. APP is first cleaved by α- and β-secretase into N- and carboxyl terminal fragments (44, 45). Next, the carboxyl terminal fragments are cleaved by γ-secretase into 39 to 42 amino acid residue long Aβ peptides, of which the 42 (Aβ$_{42}$) and 40 (Aβ$_{40}$) amino acid residue long peptides primarily constitute the AD Aβ plaques (44).

Despite being the histopathologic hallmarks of AD, Aβ plaques, neurofibrillary tangles, and neuritop hil threads are not unique to AD; they occur in a variety of other CNS conditions, including chronic infections. Neurofibrillary tangles and neuritop hil threads, for example, have been observed in cases of measles virus-induced subacute sclerosing pan-encephalitis (46, 47) and in general paresis of tertiary syphilis (48), whereas amyloid plaques are present in the majority of cases of some prion protein diseases such as Kuru and Creutzfeldt-Jakob disease (49–51). In addition, amyloidopathy—a condition characterized by elevated levels of serum amyloid and by amyloid deposition and aggregation in tissues—is a frequent occurrence in several acute and chronic systemic inflammatory conditions, especially chronic infections like tuberculosis and leprosy (51–58). Furthermore, emerging evidence indicates that Aβ has an antimicrobial property (59), which further supports the possibility that Aβ production and deposition in AD might be induced by infectious pathogens.

AD neuropathology characteristically starts in particular CNS sites, primarily the locus coeruleus, and gradually spreads to other subcortical and cortical sites in a specific sequence (60, 61). In addition, AD neuropathology spreads within anatomically connected CNS sites, from affected sites to only those regions that receive neuronal input from the affected sites (62), yet neurotropic infectious pathogens (e.g., varicella zoster virus and herpes simplex virus types 1 and 2) infect and spread within the nervous system via transsynaptic and intra-axonal anterograde and retrograde transport (63–66). These findings have led some to suggest that sequential spread of AD neuropathology reflects dissemination of infectious pathogens within the CNS (67–70). Still, sequentially spreading neuropathology is not limited to AD but is also observed in noninfectious pathogen-related disorders—for example, Lewy-body-associated disorders such as Parkinson’s disease and dementia with Lewy bodies (71). Moreover, transsynaptic spread of tau...
pathology in the absence of infectious organisms has been described in the transgenic mouse model (72).

AD neuropathology is accompanied by a significant inflammatory component in the form of activated microglia and reactive astrocytes within the neuritic plaques, as well as elevated levels of various CNS and systemic inflammatory cytokines such as interleukin-1, interleukin-6, and tumor necrosis factor-α (73–76). Although inflammation is not triggered only by infectious pathogens, it is typical of most infectious diseases; hence, AD neuropathology could be a manifestation of an infection. Evidence from animal models supports this hypothesis: For example, the injection of a bacterially derived endotoxin, lipopolysaccharide, into the mouse hippocampus has been found to trigger a neuroinflammatory response characterized by activation of microglia, infiltration by macrophages and T cells, and hyperphosphorylation and aggregation of tau proteins (77). Intraperitoneal injection of lipopolysaccharide in mice also resulted in significantly elevated levels of proinflammatory cytokines and Aβ1-42 (78) in the mouse hippocampus; however, interpretation of these experiments is complicated by the observation that microglia can detect and be activated by Aβ deposition and tau aggregation in the absence of infection (79). An alternative hypothesis is that neuroinflammation in AD reflects an autoimmune response, in which epitopes from an infectious pathogen trigger production of autoantibodies that attack the brain. In support of this hypothesis, autoantibodies have been found in patients with AD (80–83), and mounting evidence indicates that a significant aspect of the disease is immune deregulation (84–87). Nevertheless, no specific pathogen has been linked to the autoantibodies in AD.

**INFECTIOUS AGENTS THAT COULD BE ASSOCIATED WITH ALZHEIMER’S DISEASE**

Several researchers have posited that certain specific infectious pathogens cause AD in humans. The following section systematically reviews the evidence associating Herpes simplex virus type-1, *C. pneumoniae*, *B. burgdorferi*, *H. pylori*, prions, and other specific infectious pathogens with the pathogenesis of AD.

**Herpes simplex virus type 1**

HSV-1 is a is highly neurotropic double-stranded DNA virus that is transmitted from person to person, mainly through direct contact with discharging vesicles or infected bodily fluids such as saliva (88). Shortly after initial infection, HSV-1 infects and remains latent within neural tissues, primarily the trigeminal ganglia (89). HSV-1 infection is characterized by prolonged latent periods and episodic recrudescence. In humans, HSV-1 is mainly associated with herpes labialis, but HSV-1 is also known to
cause genital herpes and is the leading cause of sporadic encephalitis in the United States (90).

HSV-1 also has been implicated in the possible causation of AD. The seroprevalence of HSV-1 increases with age and is highest among those aged 60 years and older (88, 91). Similarly, the prevalence of AD increases with age and is highest among those aged 65 years and older (92). In addition, genes that influence immune responses to HSV-1 infection also influence the risk of developing AD (93), and HSV-1 proteins that regulate host cell infectivity and viral replication interact with the products of many AD susceptibility genes, such as ApoE4, presenlin 1, presenlin 2, and APP (94). Furthermore, the combination of ApoE4 genotype and HSV-1 infection is associated with an increased risk of AD: Using polymerase chain reaction (PCR), Lin et al. (95) examined postmortem brain tissue samples from 36 patients with AD and 36 age-matched normal controls and found a significantly higher frequency of the ApoE4 genotype in the HSV-1-positive AD samples. A similar study by Izhaki et al. (96) also found the combination of infection with HSV-1 and ApoE4 genotype to be associated with a significantly higher risk of AD, but neither HSV-1 infection nor ApoE4 genotype was independently associated with AD risk. Moreover, Beffert et al. (97) found no association at all between AD risk and the combination of HSV infection and ApoE4 genotype.

Serologic analysis, however, has also linked HSV-1 to increased AD risk. In a population-based cohort study, Leterme et al. (32) followed 512 initially dementia-free older individuals for 14 years and found, after controlling for age, gender, educational level, and ApoE4 status, that anti-HSV-1 immunoglobulin M antibody seropositivity was associated with a significantly increased risk of developing AD. In addition, high serum anti-HSV-1 immunoglobulin M antibody levels are associated with lower levels of plasma Aβ1–42 and Aβ1–40 (98)—a biomarker for AD.

HSV-1 also has been detected in postmortem brain tissue from AD cases (31, 99–101) (Table 1). Notably, in situ hybridization of postmortem brain tissue samples from 21 patients with AD and 19 controls detected HSV-1 DNA in a significantly higher proportion of AD samples (81%) than controls (47.4%) (99). Similarly, using PCR, Jamieson et al. (31) detected HSV-1 thymidine kinase gene sequences in a higher proportion of brain tissue samples from AD cases (14/21) than controls (9/15); in addition, among all HSV-1-positive samples, HSV-1 was detectable only at CNS sites primarily affected in AD, such as the temporal cortex and hippocampus. Furthermore, using in situ PCR to detect HSV-1 DNA and immunohistochemistry to detect amyloid plaques in AD postmortem brain tissue samples, Wozniak et al. (102) found that 90% of Aβ plaques contained HSV-1 DNA.

Evidence also directly links HSV-1 infection to abnormal APP metabolism and elevated CNS Aβ peptide production. APP is a major component of the HSV-1 viral envelope (63). Moreover, the HSV-1 viral envelope contains glycoprotein B, which possesses an internal sequence that is homologous to the carboxyl-terminal region of AD Aβ peptides and is capable of self-assembling into insoluble fibrils ultrastructurally indistinguishable from AD Aβ plaques (103). In addition, in vitro evidence indicates that HSV-1 interferes with normal intraneuronal APP transportation and distribution (104) and inhibits Aβ peptide degradation and secretion by preventing the fusion of Aβ peptide autophagosomes with lysosomes (105). Furthermore, human neuroblastoma cells inoculated with HSV-1 showed marked reduction in intracellular APP levels, elevated levels of C-terminal APP fragments, and significantly increased levels of both Aβ1–40 and Aβ1–42 peptides (63, 106, 107).

Tau pathology and neurodegeneration also have been linked directly to HSV-1 infection. Mouse neuronal cultures infected with HSV-1 displayed abnormal microtubule dynamics, tau hyperphosphorylation, and significant neurite damage ultimately resulting in apoptosis (108). Similar tauopathies were observed in HSV-1-infected human neuroblastoma cell cultures (109). Moreover, Wozniak et al. (110) found that, in vitro, HSV-1 infection induced glycosyn-thase kinase 3 beta and protein kinase A to phosphorylate tau at sites phosphorylated in AD samples (i.e., serine 202, threonine 212, serine 214, serine 396, and serine 404).

Nevertheless, the role of HSV-1 in the causation of AD remains questionable. Several studies of postmortem brain tissues found no evidence linking HSV-1 to AD (111–117). For example, Taylor et al. (112) used in situ hybridization to analyze postmortem brain samples (55 from 8 patients with AD and 57 from 9 non-neurologic control patients), as well as samples from HSV-1-infected mice; with this technique, none of the samples revealed detectable levels HSV-1 DNA. In another in situ hybridization study, Roberts et al. (113) examined postmortem brain specimens from 25 patients with AD and 32 controls, but none hybridized to HSV-1 DNA probes. Similarly, HSV-1 DNA was not detected by Southern blotting in any postmortem brain tissue samples or peripheral blood cells obtained from 5 patients with AD and 5 normal controls (116). These negative findings, however, could be due in part to differences in methodology because in situ hybridization and Southern blotting are less sensitive than PCR in detecting DNA. Consistently, the majority of studies reporting positive findings used PCR. Nevertheless, most PCR-based studies show no significant difference in the frequency of AD versus control brain tissue samples that contain HSV-1 DNA (97, 102, 118–123).

Several serology-based studies also found no evidence to link HSV-1 infection to AD (83, 124, 125). For example, Renvoize et al. (124) analyzed serum from 33 patients with a clinical diagnosis of AD and 28 controls suffering from psychiatric disorders but without evidence of comorbid dementia. They found that serum from the 2 groups did not differ significantly in the levels of antibody titers to various viral pathogens, including HSV-1, but this result is not surprising given the high prevalence of HSV-1 among older adults. Moreover, Ounanian et al. (83) found that controls, rather than patients with AD, showed higher levels of anti-HSV-1 antibody titers. Thus, lack of consistency leaves studies linking HSV-1 to the causation of AD inconclusive.

C. pneumoniae

C. pneumoniae is an obligate intracellular bacterium that is spread from person to person mainly through droplet
Table 1. Epidemiologic Studies on the Association Between Herpes Simplex Virus Type 1 and Alzheimer’s Disease

<table>
<thead>
<tr>
<th>First Author, Year (Reference No.)</th>
<th>Study Design</th>
<th>No. of Patients With Alzheimer’s Disease</th>
<th>No. of Controls</th>
<th>Specimen</th>
<th>Method</th>
<th>Herpes Simplex Virus Type 1 Positive Patients With Alzheimer’s Disease</th>
<th>Controls</th>
<th>Crude OR</th>
<th>95% CI</th>
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<tbody>
<tr>
<td>Sequiera, 1979 (100)</td>
<td>Case series</td>
<td>3</td>
<td>7</td>
<td>Postmortem brain</td>
<td>In situ hybridization</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Middleton, 1980 (111)</td>
<td>Case series</td>
<td>3</td>
<td>3</td>
<td>Postmortem brain</td>
<td>In situ hybridization</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mann, 1983 (117)</td>
<td>Case-control</td>
<td>13</td>
<td>7</td>
<td>Postmortem brain</td>
<td>Immunoperoxidase staining</td>
<td>1</td>
<td>1</td>
<td>0.5&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.03, 9.46</td>
</tr>
<tr>
<td>Taylor, 1984 (112)</td>
<td>Case-control</td>
<td>8</td>
<td>9</td>
<td>Postmortem brain</td>
<td>In situ hybridization</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
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<tr>
<td>Roberts, 1986 (113)</td>
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<td>25</td>
<td>32</td>
<td>Postmortem brain</td>
<td>Immunohistochemistry</td>
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<td>0</td>
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<td></td>
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<td>18</td>
<td>5</td>
<td>Postmortem brain</td>
<td>In situ hybridization, Southern blotting</td>
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<td>0</td>
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<td></td>
</tr>
<tr>
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<td>Case-control</td>
<td>4</td>
<td>2</td>
<td>Postmortem brain</td>
<td>In situ hybridization</td>
<td>0</td>
<td>0</td>
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</tr>
<tr>
<td>Ounanian, 1990 (83)</td>
<td>Case-control</td>
<td>19</td>
<td>21</td>
<td>Serum</td>
<td>ELISA</td>
<td>16</td>
<td>84</td>
<td>19</td>
<td>90.5</td>
</tr>
<tr>
<td>Deatly, 1990 (99)</td>
<td>Case-control</td>
<td>21</td>
<td>19</td>
<td>Postmortem brain</td>
<td>In situ hybridization</td>
<td>17</td>
<td>81</td>
<td>9</td>
<td>47.4</td>
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<td>Case-control</td>
<td>8</td>
<td>6</td>
<td>Postmortem brain</td>
<td>PCR</td>
<td>8</td>
<td>100</td>
<td>6</td>
<td>100</td>
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<td>8</td>
<td>5</td>
<td>Postmortem brain</td>
<td>PCR</td>
<td>8</td>
<td>100</td>
<td>5</td>
<td>100</td>
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<td>Jamieson, 1992 (31)</td>
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<td>15</td>
<td>Postmortem brain</td>
<td>PCR</td>
<td>14</td>
<td>67</td>
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<td>60</td>
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<td>Blood</td>
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<td>36</td>
<td>Postmortem brain</td>
<td>PCR</td>
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<td>78</td>
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<tr>
<td>Itzhaki, 1997 (96)</td>
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<td>44</td>
<td>Postmortem brain</td>
<td>PCR</td>
<td>36</td>
<td>78</td>
<td>28</td>
<td>64</td>
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<tr>
<td>Lin, 1997 (120)</td>
<td>Case-control</td>
<td>24</td>
<td>20</td>
<td>Postmortem brain</td>
<td>PCR</td>
<td>18</td>
<td>75</td>
<td>12</td>
<td>60</td>
</tr>
<tr>
<td>Itabashi, 1997 (121)</td>
<td>Case-control</td>
<td>46</td>
<td>23</td>
<td>Postmortem brain</td>
<td>PCR</td>
<td>14</td>
<td>30.4</td>
<td>5</td>
<td>21.7</td>
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<tr>
<td>Beffert, 1998 (97)</td>
<td>Case-control</td>
<td>73</td>
<td>33</td>
<td>Postmortem brain</td>
<td>PCR</td>
<td>54</td>
<td>74</td>
<td>24</td>
<td>73</td>
</tr>
<tr>
<td>Cheon, 2001 (122)</td>
<td>Case-control</td>
<td>8</td>
<td>10</td>
<td>Postmortem brain</td>
<td>PCR</td>
<td>8</td>
<td>100</td>
<td>10</td>
<td>100</td>
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<td>Lin, 1998 (123)</td>
<td>Case-control</td>
<td>15</td>
<td>4</td>
<td>Postmortem brain</td>
<td>PCR</td>
<td>9</td>
<td>60</td>
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<td>50</td>
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<td>Mori, 2004 (101)</td>
<td>Case-control</td>
<td>5</td>
<td>6</td>
<td>Postmortem brain</td>
<td>PCR</td>
<td>5</td>
<td>100</td>
<td>1</td>
<td>16.7</td>
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<td>Wozniak, 2005 (125)</td>
<td>Case-control</td>
<td>27</td>
<td>13</td>
<td>Cerebral spinal fluid</td>
<td>ELISA</td>
<td>14</td>
<td>52</td>
<td>9</td>
<td>69</td>
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<td>Wozniak, 2009 (102)</td>
<td>Case-control</td>
<td>6</td>
<td>5</td>
<td>Postmortem brain</td>
<td>PCR</td>
<td>6</td>
<td>100</td>
<td>5</td>
<td>100</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; ELISA, enzyme-linked immunosorbent assay; OR, odds ratio; PCR, polymerase chain reaction.
<sup>a</sup> Not reported.
inhalation. *C. pneumoniae* is associated primarily with lower-respiratory-tract disease such as pneumonia and bronchitis, but increasing evidence implicates *C. pneumoniae* in several other acute and chronic human diseases, such as atherosclerosis (126–128). Evidence also suggests that *C. pneumoniae* could be involved in the pathogenesis of AD.

*C. pneumoniae* has been detected, both directly and indirectly, in postmortem AD brain tissue (Table 2). For example, Balin et al. (33) used various methods, including PCR, electron and immunoelectron microscopy, culture, reverse-transcription PCR, and immunohistochemistry, to test postmortem brain tissue samples from 19 cases with AD and 19 controls without AD for *C. pneumoniae*. Evidence of *C. pneumoniae* was found in 17 of 19 AD samples but only 1 of 19 control samples. In addition, among the positive AD samples, *C. pneumoniae* was detected only within areas affected by AD neuropathology. A case-control study by Gerard et al. (34) reported similar findings: With PCR alone, postmortem brain tissue samples from 27 AD cases and 27 non-AD controls were analyzed for evidence of *C. pneumoniae* DNA. *C. pneumoniae Cpn1046* and *Cpn0695* genes were present in 20 of 27 AD specimens, compared with only 3 of the 27 controls. Moreover, *C. pneumoniae* DNA in the AD brain tissue samples was detected only within the astrocytes, microglia, and neurons in close proximity to Aβ plaques and neurofibrillary tangles.

Similarly, Paradowski et al. (35) used PCR to analyze cerebral spinal fluid (CSF) samples from 57 patients with AD, 21 patients with vascular dementia, and 47 normal controls. They detected *C. pneumoniae* DNA in a significantly higher proportion of patients with AD (43.9%) than controls (10.6%). The presence of *C. pneumoniae* DNA in CSF also was associated strongly with the risk of AD (odds ratio = 7.21), but there was no association between *C. pneumoniae* in CSF and CSF levels of either hyperphosphorylated tau protein or Aβ peptides.

A serology-based study by Hammond et al. (129) also reported positive findings. With immunohistochemistry, 5 AD and 5 non-AD postmortem brain tissue samples were tested for evidence of *C. pneumoniae*. *C. pneumoniae* antigens were detected intracellularly, within neurons, neuroglia, endothelial cells, and peri-endothelial cells, and in extracellular spaces in the frontal and temporal cortices in all 5 AD samples but only 2 of the non-AD samples. Furthermore, immunoreactivity was confined to CNS regions with Aβ deposition.

Studies in animals as well as in vitro also allude to a possible association between AD and *C. pneumoniae*. *C. pneumoniae* expresses a kinase that phosphorylates secreted structural proteins in vitro, specifically at motifs similar to those hyperphosphorylated in AD (130). In addition, mice intranasally infected with *C. pneumoniae* isolated from a postmortem AD brain developed amyloid deposits similar to AD Aβ plaques (131). Moreover, the density, size, and number of these deposits increased significantly as the infection progressed. Similarly, Boelen et al. (132) found extracellular Aβ immunoreactivity in mouse brains at 1 and 3 months after intranasal infection with *C. pneumoniae*. These findings, however, were inconclusive because Aβ immunoreactivity also was detected in brains of mock-infected mice, as well as in brains of mice that were neither *C. pneumoniae* nor mock infected. Still, these studies merit particular attention in light of Koch’s postulates, which suggest, as one of the criteria for establishing a causal association, that putative microorganisms isolated from affected tissue should cause the disease when inoculated into a susceptible host (133).

Furthermore, eradication of *C. pneumoniae* in infected patients with AD results in significant clinical improvement. In a randomized clinical trial, Loeb et al. (134) randomly assigned 101 patients with probable or mild to moderate AD to receive either placebo or daily doses of oral doxycycline (200 mg) plus rifampin (300 mg). Although the treatment and control groups showed similar rates of *C. pneumoniae* infection, after 3 months of therapy, the rates of cognitive decline and dysfunctional behavior in the treatment group were significantly less than in the placebo group.

Again, however, several studies found no evidence to suggest an association between *C. pneumoniae* infection and AD pathogenesis (135–143). For example, Nochlin et al. (135) examined paraffin-embedded tissue sections of autopsy brain samples from 12 patients with AD and 13 controls without AD but failed to detect *C. pneumoniae* DNA in any of the AD or control samples using both immunocytochemistry and PCR. Similarly, Gieffers et al. (136) analyzed paraffin-embedded AD brain tissue samples using nested PCR as well immunocytochemistry but detected neither *C. pneumoniae* DNA nor antigens in either case or control samples. Ring and Lyons (137) also used nested PCR and, in addition, attempted to culture *C. pneumoniae* from postmortem samples of various regions of the brain, including those typically affected by AD, from 15 patients with AD and 15 normal controls. All cultures, however, tested negative for growth, and *C. pneumoniae* DNA was not detected in any AD or control samples. Wozniak et al. (138) also found no evidence of *C. pneumoniae* DNA in any of 4 AD, 19 vascular dementia, or 16 control brain specimens tested, and Taylor et al. (139) found no evidence of *C. pneumoniae* in any of 19 AD or 2 control brain specimens tested with PCR.

Finally, Bruunsgaard et al. (140) found no association of serum anti-*C. pneumoniae* antibody titers with either dementia or cardiovascular disease. Again, ambiguous study findings leave the exact role of *C. pneumoniae* in the pathogenesis of AD unclear.

**B. burgdorferi**

Another infectious pathogen that has been evaluated extensively for a possible etiologic link to AD is *B. burgdorferi*. *B. burgdorferi* is a spirochete bacterium that is transmitted from vertebrate hosts to humans through the bite of an infected tick of the *Ixodes* family, mainly *I. scapularis* and *I. pacificus* in the United States (144). Although the primary host reservoir is the white-footed mouse (*Peromyscus leucopus*), *B. burgdorferi* has been isolated from several other vertebrate species (144). *B. burgdorferi* is the etiologic agent of Lyme borreliosis, a disease characterized
<table>
<thead>
<tr>
<th>First Author, Year (Reference No.)</th>
<th>Study Design</th>
<th>Total</th>
<th>Method</th>
<th>Specimen</th>
<th>Crude OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Balin, 1998 (33)</td>
<td>Case-control</td>
<td>19</td>
<td>19</td>
<td>PCR</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Electronmicroscopy</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Immunohistochemistry</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Culture</td>
<td>Postmortem brain</td>
<td>17</td>
</tr>
<tr>
<td>Nochlin, 1999 (135)</td>
<td>Case-control</td>
<td>12</td>
<td>13</td>
<td>PCR</td>
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<td>Immunohistochemistry</td>
<td></td>
<td></td>
</tr>
<tr>
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<td></td>
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<td></td>
<td>Culture</td>
<td>Postmortem brain</td>
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</tr>
<tr>
<td>Gieffers, 2000 (136)</td>
<td>Case series</td>
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<td>PCR</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Immunohistochemistry</td>
<td></td>
<td></td>
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<tr>
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<td></td>
<td>Culture</td>
<td>Postmortem brain</td>
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<td>PCR</td>
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<td></td>
<td>Immunohistochemistry</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Culture</td>
<td>Postmortem brain</td>
<td>0</td>
</tr>
<tr>
<td>Taylor, 2002 (139)</td>
<td>Case-control</td>
<td>9</td>
<td>2</td>
<td>PCR</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Immunohistochemistry</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Culture</td>
<td>Postmortem brain</td>
<td>0</td>
</tr>
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<td>Wozniak, 2003 (138)</td>
<td>Case-control</td>
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<td>16</td>
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<td></td>
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<td>Yamamoto, 2005 (141)</td>
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<td>61</td>
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<td>ELISA</td>
<td>Serum</td>
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<tr>
<td>Gerard, 2006 (34)</td>
<td>Case-control</td>
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<td>PCR</td>
<td>Postmortem brain</td>
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<td></td>
<td></td>
<td>In situ hybridization</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>Culture</td>
<td>Postmortem brain</td>
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<tr>
<td>Paradowski, 2007 (35)</td>
<td>Case-control</td>
<td>57</td>
<td>47</td>
<td>PCR</td>
<td>Cerebral spinal fluid</td>
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<td>Dreses-Werringloer, 2009 (142)</td>
<td>Case series</td>
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<td>Culture</td>
<td>Postmortem brain</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>PCR</td>
<td>Postmortem brain</td>
<td>2</td>
</tr>
<tr>
<td>Ecemiş, 2010 (143)</td>
<td>Case-control</td>
<td>54</td>
<td>50</td>
<td>EIA</td>
<td>Serum</td>
<td>25</td>
</tr>
<tr>
<td>Hammond, 2010 (129)</td>
<td>Case-control</td>
<td>5</td>
<td>5</td>
<td>Immunohistochemistry</td>
<td>Postmortem brain</td>
<td>5</td>
</tr>
</tbody>
</table>

**Abbreviations:** CI, confidence interval; EIA, enzyme immunoassay; ELISA, enzyme-linked immunosorbent assay; OR, odds ratio; PCR, polymerase chain reaction.

<sup>a</sup> Not reported.
by erythema chronicum migrans at the site of the tick bite immediately after initial infection, as well as by various neurologic and cardiac symptoms and by monoarticular large-joint arthritis in advanced stages (145). B. burgdorferi also has been directly detected and isolated from postmortem AD brain tissue samples, which suggests a possible etiologic association.

MacDonald (146) was the first to report direct visualization and culture of B. burgdorferi spirochetes from the postmortem brain tissue of 2 AD cases. Subsequently, MacDonald found 2 more AD cases in which B. burgdorferi spirochetes were directly visualized as well as cultured from postmortem brain tissue samples (147, 148). Several other researchers have reported similar findings (Table 3.). For example, Meer-Scherrer et al. (149) detected B. burgdorferi DNA in association with AD neuropathology in the postmortem brain tissue of an 83-year-old female patient who had been treated unsuccessfully for Lyme disease and who later developed progressive dementia. In addition, in a case-control study, Miklossy (38) detected B. burgdorferi spirochetes in blood, CSF, and brain tissue of all 14 histopathologically confirmed AD cases but in none of the 13 age-matched controls. A subsequent follow-up study involving 3 of the B. burgdorferi-positive AD cases found that B. burgdorferi antigens and genes were localized within AB deposits (150). Furthermore, a pooled analysis of studies investigating the association between B. burgdorferi and AD found that B. burgdorferi was 13 times more frequent in the brains of patients with AD than in brains of controls (151).

B. burgdorferi also has been found to induce AD-like neuropathology in vitro. Mammalian glial and neuronal cells exposed to B. burgdorferi and lipopolysaccharide showed morphologic changes analogous to AB deposits and also demonstrated increased levels of APP and hyperphosphorylated tau protein 2–8 weeks after exposure (152).

Nevertheless, several rigorous studies found no evidence to suggest that B. burgdorferi is causally linked to AD (153–158). For example, Pappolla et al. (153) tested postmortem brain tissue samples from 6 histopathologically confirmed AD cases and 4 non-AD controls by culturing samples for B. burgdorferi, but all were negative for growth. Despite electron microscopy of the culture supernatant, direct immunofluorescence and acidine orange fluorescence, indirect immunofluorescence and enzyme-linked immunosorbent assay of CSF, as well as direct immunofluorescence of imprint preparations of brain tissues, none of the AD or control samples showed evidence of B. burgdorferi. In a similar, multipronged approach, Gutacker et al. (154) found no evidence of B. burgdorferi in any of 10 postmortem AD brain tissue samples tested with both standard and nested PCR, as well as enzyme-linked immunosorbent assay and Western blotting for anti-B. burgdorferi antibodies. Marques et al. (155) also used PCR but found no evidence of B. burgdorferi in any of the postmortem brain tissue samples from 15 patients with AD and 15 age- and sex-matched controls, and McLaughlin et al. (156) tested for B. burgdorferi spirochetes in peripheral blood and fresh postmortem brain specimens of 22 patients with AD and 6 controls, but only 1 tested positive. Another large case-control study by Galbussera et al. (157) found no conclusive evidence of B. burgdorferi in any of the serum samples from 50 patients with AD, 23 controls without AD, or 25 healthy caregivers of the patients with AD using enzyme-linked fluorescent assay. Because of these mixed findings, the role of B. burgdorferi in the etiology of AD remains unresolved.

H. pylori

H. pylori are spiral-shaped, Gram-negative bacteria associated mainly with upper gastrointestinal disorders such as chronic gastritis, peptic ulcer disease, and gastric cancer. Recently, H. pylori was implicated in the pathogenesis of several extra-digestive diseases, including atherosclerosis (159, 160), chronic respiratory disease (161), and idiopathic thrombocytopenic purpura (162–164). Evidence implicating H. pylori in AD pathogenesis also has emerged (Table 4). For example, Kountouras et al. (36) used enzyme-linked immunosorbent assay to analyze serum and CSF of 27 patients with AD and 27 age-matched cognitively normal controls and found significantly higher mean concentrations of anti-H. pylori immunoglobulin G antibodies in patients with AD. Malaguirnera et al. reported similar findings (37); they analyzed serum levels of anti-H. pylori antibodies in 30 patients with AD, 30 patients with vascular dementia, and 30 nondemented controls matched by age, educational level, and nutritional and socioeconomic status and found significantly higher levels of both anti-H. pylori immunoglobulin G and immunoglobulin A antibodies in patients with AD than in controls. Furthermore, using histology, Kountouras et al. (165) found the prevalence of H. pylori in gastric mucosal biopsies to be significantly higher among patients with AD than among control patients without AD who had iron deficiency anemia.

H. pylori is also linked to increased severity of cognitive impairments in AD. Patients with AD and with H. pylori infection performed significantly worse than noninfected patients on the Mini-Mental State Examination (36, 166). In addition, autoantibodies against H. pylori immunoglobulin G antibody concentrations in CSF correlated with the severity of cognitive impairments among patients with AD (36), and CSF tau levels were significantly elevated among H. pylori-infected patients with AD (166). Moreover, successful eradication of H. pylori in patients with AD with the use of triple therapy led to significant improvements in both cognitive and functional status symptoms even 2 years after treatment (167) and resulted in a significantly higher 5-year survival rate (168).

There is also evidence of an association between H. pylori infection and mild cognitive impairment, which now is known to precede AD in the majority of cases. H. pylori seroprevalence rates were found to be significantly higher in patients with mild cognitive impairment than in normal controls (169), and serum anti-H. pylori immunoglobulin G concentrations correlated with the level of cognitive functioning.

Still, as with the other pathogens discussed, a causal link between H. pylori and AD remains uncertain. The body of evidence is limited, and the exact mechanisms through which H. pylori might contribute to the genesis of AD

Table 3. Epidemiologic Studies on the Association Between *Borrelia burgdorferi* and Alzheimer’s Disease

<table>
<thead>
<tr>
<th>First Author, Year (Reference No.)</th>
<th>Study Design</th>
<th>Total No. of Patients With Alzheimer’s Disease</th>
<th>No. Controls</th>
<th>Method</th>
<th>Specimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>MacDonald, 1986 (146)</td>
<td>Case series</td>
<td>2</td>
<td>2</td>
<td>Microscopy</td>
<td>Postmortem brain</td>
</tr>
<tr>
<td>MacDonald, 1987 (147)</td>
<td>Case study</td>
<td>1</td>
<td>1</td>
<td>Culture</td>
<td>Postmortem brain</td>
</tr>
<tr>
<td>MacDonald, 1988 (148)</td>
<td>Case study</td>
<td>1</td>
<td>1</td>
<td>Culture</td>
<td>Postmortem brain</td>
</tr>
<tr>
<td>Pappolla, 1989 (153)</td>
<td>Case-control</td>
<td>6</td>
<td>4</td>
<td>Culture</td>
<td>Postmortem brain</td>
</tr>
<tr>
<td>Pappolla, 1989 (153)</td>
<td>Case-control</td>
<td>6</td>
<td>4</td>
<td>Immunoblotting</td>
<td>CSF</td>
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<tr>
<td>Miklossy, 1993 (38)</td>
<td>Case-control</td>
<td>14</td>
<td>13</td>
<td>Culture</td>
<td>Peripheral blood</td>
</tr>
<tr>
<td>Gutacker, 1998 (154)</td>
<td>Case series</td>
<td>10</td>
<td></td>
<td>PCR</td>
<td>Postmortem brain</td>
</tr>
<tr>
<td>McLaughlin, 1999 (156)</td>
<td>Case-control</td>
<td>22</td>
<td>6</td>
<td>Direct microscopy</td>
<td>Postmortem brain</td>
</tr>
<tr>
<td>Marques, 2000 (155)</td>
<td>Case-control</td>
<td>15</td>
<td>15</td>
<td>PCR</td>
<td>Postmortem brain</td>
</tr>
<tr>
<td>Riviere, 2002 (158)</td>
<td>Case-control</td>
<td>16</td>
<td>18</td>
<td>PCR</td>
<td>Postmortem brain</td>
</tr>
<tr>
<td>Meer-Scherrer, 2006 (149)</td>
<td>Case study</td>
<td>1</td>
<td></td>
<td>PCR</td>
<td>Postmortem brain</td>
</tr>
<tr>
<td>Galbussera, 2008 (157)</td>
<td>Case-control</td>
<td>50</td>
<td>53</td>
<td>ELFA</td>
<td>Serum</td>
</tr>
<tr>
<td>Miklossy, 2011 (151)</td>
<td>Pooled analysis</td>
<td>75</td>
<td>52</td>
<td>Postmortem brain</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Borrelia burgdorferi Positive Patients With Alzheimer’s Disease</th>
<th>Controls</th>
<th>Crude OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>No.</td>
<td>%</td>
<td>No.</td>
<td>%</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; CSF, cerebral spinal fluid; ELFA, enzyme-linked fluorescence assay; ELISA, enzyme-linked immunosorbent assay; IFA, immunofluorescence assay; OR, odds ratio; PCR, polymerase chain reaction.
remain undetermined. Because *H. pylori* is not known to be neurotropic, it is unlikely to induce neuroinflammatory effects directly. Nevertheless, *H. pylori* might cause CNS endothelial damage, neuroinflammation, neurodegeneration, and possibly AD through various systemic effects that have been observed in other *H. pylori*-associated conditions, such as enhanced platelet and platelet-leukocyte aggregation, release of inflammatory and vasoactive substances, development of cross-reactivity with host antigens, production of reactive oxygen metabolites, and increased homocysteine (170). It remains to be determined whether these mechanisms operate in AD, but evidence from a study by Ge and Sun (171) indicates that the cytoplasmic protein Hpn, produced by *H. pylori*, aggregates into amyloid-like fibrils in vitro.

To our knowledge, so far, only 1 study has reported negative findings with regard to the association between *H. pylori* and AD. Shiota et al. (172) measured urinary levels of anti-*H. pylori* antibodies in 385 patients with AD and 97 controls and found no significant difference.

Evidence linking *H. pylori* to AD is still limited, but these preliminary studies suggest that patients with AD and patients with mild cognitive impairment might benefit from rigorous *H. pylori* treatment and eradication. Given the potential implications of these findings for the prognosis and quality of life of patients with AD, further research is required to verify these findings.

Prions

The possibility that AD could be instigated through a prion-like mechanism also has been explored. Prions are implicated in the etiology of several chronic neurodegenerative disorders in humans, including Creutzfeldt-Jakob disease, variant Creutzfeldt-Jakob disease, Gerstmann-Sträussler-Scheinker syndrome, and kuru, as well bovine spongiform encephalitis in cattle and scrapie in sheep and goats (173). The infectious agent of prion diseases is an abnormally folded isoform of the prion protein, which via seeding or nucleation induces the templated misfolding of normal prion protein molecules (173, 174).

Several pathologic correlates exist between prion diseases and AD. These include the presence of misfolded protein aggregates consisting of highly ordered polymeric isoforms with cross-β-sheet-rich structures, neurodegeneration, and progressively and sequentially spreading neuropathology (175–177). In addition, as noted previously, AD-like neuropathology in the form of Aβ deposits is present in most cases of Creutzfeldt-Jakob disease and kuru. Evidence also suggests that prion-like seeding contributes to AD neuropathology. For example, several studies found inoculation of either human or mouse AD brain extracts containing aggregated Aβ peptides to induce Aβ deposition in the brains of recipient APP transgenic mice (178–181). Similarly, several studies found injection of either human or mouse AD brain extracts containing tau aggregates to trigger the formation of sequentially spreading tau aggregates in the brains of recipient transgenic mice (182, 183). Seeding studies using synthetic Aβ fibrils, however, generated mixed results: For example, whereas Stöhr et al. (184)

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**Table 4. Epidemiologic Studies of the Association Between Helicobacter pylori and Alzheimer’s Disease**

<table>
<thead>
<tr>
<th>First Author, Year (Reference No.)</th>
<th>Study Design</th>
<th>No. of Controls</th>
<th>Nos. % of Patients With Alzheimer’s Disease</th>
<th>Specimen Method</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malaguarnera, 2004 (37)</td>
<td>Case-control</td>
<td>30</td>
<td>30 (50)</td>
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<tr>
<td>Kountouras, 2006 (165)</td>
<td>Case-control</td>
<td>30</td>
<td>30 (40)</td>
<td>Gastric biopsy</td>
</tr>
<tr>
<td>Kountouras, 2009 (36)</td>
<td>Case-control</td>
<td>27</td>
<td>27 (40)</td>
<td>Cerebral spinal fluid ELISA</td>
</tr>
<tr>
<td>Shiota, 2011 (172)</td>
<td>Case-control</td>
<td>85</td>
<td>85 (50)</td>
<td>Serum Immunochromatography</td>
</tr>
<tr>
<td>Roubaud-Baudron, 2011 (168)</td>
<td>Case-series</td>
<td>53</td>
<td>53 (20)</td>
<td>Serum Immunoblot</td>
</tr>
</tbody>
</table>

**Abbreviations:** ELISA, enzyme-linked immunosorbent assay; OR, odds ratio; SD, standard deviation.

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found that synthetic Aβ aggregates induce Aβ deposition and propagation in mice, in a study by Meyer-Luehmann et al. (179), synthetic Aβ40 and Aβ42 aggregates, or a mixture of both, failed to induce seeding of Aβ deposition in vivo. Nevertheless, synthetic Aβ aggregates demonstrate lower specific bioactivity than that of brain-derived aggregates (184), which might explain the inconsistent results.

Studies also have suggested a link between prion disease susceptibility genes and AD, but this evidence is highly controversial. Whereas some studies claimed an association between polymorphisms of the human prion protein (PRNP) gene and AD risk, (185–189), other studies found no such evidence (190–194). Studies investigating the association between AD susceptibility genes, such as ApoE4, and the risk of prion disease also generated mixed results, with some finding an association (195, 196) and others finding no evidence of an association (197). Finally, known prion diseases are generally rare, which is not compatible with the incidence and prevalence rates of AD.

**Other infectious agents**

Several other infectious pathogens, although not widely studied, have been explored for possible associations with AD. For example, Friedland et al. (198) tested CSF and serum specimens from patients with AD, patients with Down’s syndrome (which is associated with early-onset AD), patients with non-AD dementia, and normal controls for antibodies to human immunodeficiency virus type-1, caprine arthritis encephalitis virus, and equine infectious anemia virus but failed to detect antibodies against any of these lentiviruses in any of the specimens. Studies also investigated whether herpesviruses other than HSV-1, including HSV-2, human herpesvirus 6, Epstein-Barr virus, varicella zoster virus, and cytomegalovirus, are associated with AD. Like HSV-1, these viruses are highly prevalent in the general population and cause chronic infections with prolonged latent periods and episodic recrudescence. Moreover, HSV-2 and varicella zoster virus are highly neurotropic, infecting and remaining latent in neural tissues. Nevertheless, most studies so far have found no association between any of these herpesviruses and AD. For example, using PCR, Lin et al. (95) failed to detect varicella zoster virus in any of the postmortem brain tissue samples from either patients with AD or normal controls. Using Southern blotting, Kittur et al. (116) did not detect HSV-1, HSV-2, Epstein-Barr virus, or cytomegalovirus in peripheral blood cells and postmortem brain tissue from patients with AD and normal controls. Moreover, Renvoize et al. (124) analyzed serum from 33 patients with AD and 28 controls but found no statistically significant differences in titers against the herpesviruses HSV and cytomegalovirus; against the non-herpesviruses adenovirus, influenza A, influenza B, measles; or against bacteria, including *Chlamydia* group B, *Coxiella burnetii*, or *Mycoplasma pneumoniae*. Although Strandberg et al. (199) found herpesvirus seropositivity to be associated with a significantly increased risk of cognitive impairments among older adults, their study did not ascertain whether any of the herpesviruses tested for (including cytomegalovirus, HSV-1, and HSV-2) were independently associated with the increased risk of cognitive impairment. Of the herpesviruses other than HSV-1, only human herpesvirus 6 has been remotely associated with AD. Using PCR, Lin et al. (200) detected human herpesvirus 6 DNA sequences in a higher proportion of postmortem AD brain tissue samples than samples from age-matched normal controls; however, in a similar study, Hemling et al. (201) found no significant difference in the frequency of occurrence of human herpesvirus 6, cytomegalovirus, or varicella zoster virus between AD cases and controls.

Studies also have investigated several other bacterial pathogens for possible associations with AD. As noted previously, Renvoize et al. (124) found no statistically significant correlations between serum antibody titers to *Chlamydia* group B, *Coxiella burnetii*, or *Mycoplasma pneumoniae* and AD. On the other hand, Riviere et al. (158) found oral *Treponema*, including *T. denticola*, *T. pectinovorum*, *T. vincentii*, *T. amylovorum*, *T. maltophilum*, *T. medium*, and *T. sovranski* in a significantly higher proportion of postmortem brain specimens from AD cases than controls. These results have, however, not been replicated.

**THE POSSIBLE ROLE OF SYSTEMIC INFECTIONS IN ALZHEIMER’S DISEASE AND OTHER DEMENTIAS**

In addition to the possibility that neurotropic agents might directly infect the brain and cause later-life neurologic sequelae, another mechanism by which infections could promote the genesis of AD is through the varied effects of systemic infections on the brain. Among children, for example, studies show that those with recurrent systemic infections demonstrate significant cognitive impairments in later childhood or adult life (202–204), and those surviving severe sepsis demonstrate significantly worse cognitive function than the general population (205).

Sepsis is associated with decreased brain metabolism (206), impaired microcirculation (207), and oxidative stress (208, 209), which could result in neuronal dysfunction and neurodegeneration. Sepsis also is associated with increased levels of circulating inflammatory chemokines, cytokines, and nitric oxide, all of which have neurotoxic properties (210–213). In addition, evidence shows that cytokines that are generated by inflammatory events outside the CNS reach macrophages in the brain, trigger the conversion to the microglia phenotype, and increase interleukin-Ibetta expression and axonal injury (214). Taken together, these findings suggest that severe, recurrent, or chronic systemic infections, of various types, can damage the CNS permanently, ultimately manifesting as cognitive impairments or dementia. Indeed, this hypothesis is supported by experiments in a rat model in which lipopolysaccharide-induced sepsis resulted in neurodeneration in the hippocampus and prefrontal cortex, as well as significant memory deficits up to 3 months after recovery from the sepsis (215). An example evocative of this process in humans has recently been pointed out. Iwashyna et al. (216) found that survivors of severe sepsis have a significantly higher risk of developing moderate to severe cognitive impairments even up to 8

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years after the event. Moreover, the risk of cognitive impairments increased significantly over time.

There is also evidence to suggest that individuals with AD experience significantly higher rates of various systemic infections, which further supports the hypothesis that systemic infections could play a role in the causation or promotion of AD. For example, nursing home residents with AD were found to have higher rates of hospitalization for infections, including pneumonia, gastroenteritis, and urinary tract infections (217). In addition, over a 4-year period, Perls and Herget (218) found that rates of upper respiratory infections were significantly and consistently higher in an AD special care unit than in traditional nursing home units. Similar results were found among community-dwelling persons with AD. For example, Heun et al. (219) found significantly higher rates of hospitalization for infectious diseases such as pneumonia and urinary tract infections among community-dwelling elderly patients. Natalwala et al. (220) reported similar findings, and Albert et al. (221) found the rates of pneumonia and other infectious diseases, at discharge diagnoses, to be significantly higher among patients with AD than among controls.

One must be cautious when interpreting these data as evidence that systemic infections cause AD and other dementia. Patients with AD might be more susceptible to infectious disease because of the cognitive and motor deficits associated with AD. Nevertheless, there is evidence to suggest that individuals with AD could be more susceptible to infections well before AD onset. For example, the ApoE4 genotype, a well-established risk factor for late-onset AD, is also strongly associated with increased susceptibility to and severity of infections in adulthood, even though it appears to exert a protective effect during early childhood (222). Evidence indicates that ApoE4 enhances the attachment and entry into host cells by various infectious pathogens, including human immunodeficiency virus type-1, HSV-1, and C. pneumoniae (223–225). ApoE4 also is associated with increased recurrence of genital herpes (226) and an enhanced immune response to infections and sepsis (227). These findings suggest the increased risk of late-onset AD that is associated with ApoE4 could result in part from a greater susceptibility to infection.

COMPATIBILITY OF AN INFECTIOUS ETIOLOGY WITH THE EPIDEMIOLOGY OF OTHER ALZHEIMER’S DISEASE RISK FACTORS

Many potential risk factors have been implicated in the complex epidemiology of AD and related dementias; not all are widely accepted. For example, claims that cigarette smoking is linked to AD remain controversial (30). Nonetheless, for any risk factor generally associated with AD, questions can be raised as to whether the factor is compatible with the infectious etiology for AD and related dementias. Although an exhaustive review of such correlates is not presented out here, a brief consideration of 2 groups of risk factors is offered. The first is a set of AD risk factors associated with infant and childhood characteristics, including lower socioeconomic status and poverty, minority status (African-American and Hispanic ethnicity in the United States), and lower educational attainment and poorer educational performance (228, 229). This set of risk factors and the economic gradient it represents are also associated with an increased risk of several categories of early-acquired infections, such as tuberculosis, sexually transmitted infections (including herpesvirus), and H. pylori (230, 231). Although this “compatibility” is noted, these childhood social and ethnic gradients also might be associated with putative noninfectious causes of AD, such as head trauma (230).

Another often-suspected group of AD risk factors is cardiometabolic disorders, such as midlife hypertension, diabetes mellitus, obesity, and their incumbent vascular diseases (230, 232). Not only might obesity directly affect metabolism in ways that affect brain function (233), but obesity also might have other connections. Like childhood infections, obesity inversely correlates with socioeconomic status (234). Also, obesity is associated with increased risk of several types of infectious outcomes in adults, including surgical-site and nosocomial infections, periodontitis, and skin infections (235), some of which could become chronic. Of interest, seroprevalence studies suggest that some infections (e.g., HSV-1, cytomegalovirus) are linked to central adiposity, which has been reported to be an AD risk factor in women but not in men (236). More generally, obesity seems to impair immune function in both humans and animal models, which likely increases the risk for several community-acquired infections, including H. pylori (237). These findings support the idea that cardiometabolic disorders are associated with AD and are also linked to infections, which supports the infectious AD-etiopathy hypothesis.

INFECTIONS AS PROMOTERS OF ALZHEIMER’S DISEASE

Another interpretation of the data associating infections with AD might be that infections are not the primary cause of AD, but rather, they exacerbate nascent CNS pathology already present at the time of infection. The fact that various infectious pathogens have been detected in the postmortem AD brain, particularly in areas showing AD neuropathology, might suggest that neuropathologic changes in the AD brain render affected areas susceptible to infections. To support this hypothesis, Wojtowicz et al. (238) found evidence that synthetic Aβ fibrils promoted the infection of target cells by enveloped viruses such as HSV-1. In addition, there is evidence to suggest that AD neuropathology impairs blood-brain barrier function, which could potentially increase the risk of CNS infections. Studies on this question however, yielded controversial results; some found evidence of blood-brain barrier disruption in AD (239–242), whereas others did not (243–245).

DISCUSSION AND CONCLUSIONS

Our review of the literature suggests that infections possibly play a role in the pathogenesis of AD. Multiple studies directly and indirectly detected various infectious pathogens in AD brain tissues; moreover, pathogens were detected primarily in or near brain areas showing AD.
neuropathology. Additionally, studies have shown that certain infectious agents, such as HSV-1 and C. pneumoniae, can induce AD neuropathologic changes in vitro and in vivo. Finally, it is important to note that the infectious AD hypothesis is compatible with the epidemiology of some of the well-established risk factors for AD and with other suggested hypotheses, such as oxidative stress and neuroinflammation.

Still, the evidence linking AD to an infectious cause is incomplete. To date, no single infectious agent has been consistently and conclusively associated with the etiology of AD. Studies investigating specific viral, bacterial, or prion-like pathogens produced mixed results, whereas associations between other pathogens such as human herpesvirus 6, cytomegalovirus, and H. pylori have not yet been exhaustively studied. Additionally, none of the human studies provided evidence that primary CNS infection or secondary spread of infection to the CNS preceded the onset of AD neuropathologic changes. Notably, most studies examined only small sample sizes, precluding any meaningful statistical analysis. Moreover, in some studies, pathogen detection relied on indirect methods such as serology, which does not demonstrate conclusive evidence of the presence or absence of an infectious pathogen or, by implication, an association with AD. Furthermore, the majority of the important work on the association between AD and particular infectious pathogens has been conducted by a few investigative groups. Also, from an epidemiologic perspective, publication bias is a strong potential limitation. It is possible that some of the studies with negative findings have not been published. In fact, some of the negative studies we found were published only as research letters. Nevertheless, we included these studies in our review.

Previous reviews on the issue have drawn differing conclusions. For example, whereas Miklossy et al. (141) identified B. burgdorferi as the most probable cause of AD on the basis of both Koch’s postulates and Bradford Hill criteria for causation, Honjo et al. (246) identified C. pneumoniae as the most likely cause of AD on the basis of the Bradford Hill criteria. Nevertheless, evidence shows that HSV-1, B. burgdorferi, and C. pneumoniae each fulfill many but not all of both the revised Koch’s postulates (247) and the Bradford Hill criteria (248). For example, although nucleic acids belonging to each of these organisms have been detected in the AD brain, particularly in areas affected by AD neuropathology, these nucleic acids also have been detected in normal brain tissue samples.

Although no single infectious agent has been linked conclusively to the causation of AD, several different infectious pathogens have been detected directly in AD brain tissue, which raises other possibilities for interpretation. For instance, various neurotropic agents might have a causal or promoting role, depending on the circumstances of exposure and possibly host factors (e.g., genetic constitution). Alternatively, viral and bacterial pathogens might be found more often in AD brain tissue because AD neuropathology increases the susceptibility of affected areas to infections. Moreover, systemic infections might play a role in AD pathogenesis, but issues surrounding any role for systemic infections are complex. Indeed, research addressing whether late-life cognitive decline can be linked to adulthood chronic infections, bacterial or otherwise, is limited. This is an important direction for future epidemiologic inquiry.

Regardless of whether certain infectious agents play a role in the genesis of AD, further work should examine the empirical findings that suggest antibiotic therapy can control AD symptoms or disease progression. For example, more research is needed to determine whether the impact of antibiotics on AD is due to effects on CNS pathogens, other systemic infections, or other AD-related pathologies. Indeed, patients with AD might benefit from prompt diagnosis and treatment of infections.

In conclusion, the particular role infections play in the pathogenesis of AD remains undetermined, but substantial evidence suggests an association. Further research is needed to 1) establish whether CNS infection precedes onset of AD neuropathology or vice versa, 2) determine whether systemic infections put patients at greater risk for AD, 3) define the role of infections in AD progression and prognosis, and 4) examine whether treating patients with AD for various systemic and CNS infections improves their quality of life and survival rate.

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