Emerging Microbial and Viral Infections of the Central Nervous System

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Emerging viral and bacterial infections of the central nervous system

Abstract: This review focuses on emerging viral and bacterial infections in the human central nervous system (CNS) that are responsible for significant global morbidity and mortality. These infections include those responsible for acute neurological disease such as meningitis and encephalitis as well those associated with chronic neurodegenerative conditions. Recent changes in climate conditions and pollution have been precipitating factors leading to the emergence of many of these pathogenic organisms. In addition, increased urbanization, global travel, life span, and exposure to new vectors have promoted the organisms’ spread across the globe. Categorization of many of these organisms includes identification of new species, recognition of new tropism to the CNS, spread into naïve demographic areas, increased human contact with zoonotic repositories including insect vectors, and reemergence of well-known organisms. These mechanisms are highlighted for the different organisms included in this review. Other mechanisms for CNS emergence such as genetic mutation of the organisms and immunosuppression and/or immunosenescence of the host are addressed. Viral and bacterial infections in chronic neurodegenerative diseases traditionally not thought to be infectious are considered. Although this review cannot be all-inclusive, the organisms included represent a sampling of extremely important microbes and their role in CNS pathogenesis in the twenty-first century.

Keywords: viruses, bacteria, central nervous system, emergence

Global emergence of central nervous system (CNS) associated infectious disease is currently being recognized. Pathogenic viruses, bacteria, fungi, and protozoa are infecting the human CNS resulting in widespread disease. Global variances including climate changes and pollution have led to changes in these pathogenic organisms. Increased human urbanization, global travel, and life span have led to increased exposure to drug-resistant viral and bacterial strains, as well as to new strains, often through increased zoonotic and vector contact. This review focuses on viral and bacterial infections in the CNS that are causing and/or associated with significant morbidity and mortality in acute neurological disease and chronic neurodegenerative conditions. As research is uncovering associations of viral and bacterial infections with major CNS diseases traditionally not considered caused or exacerbated by infectious entities, we have included these as emerging infections. In this way, this review extends our awareness and understanding of the involvement of infection in the concomitant pathogenesis of CNS disease.

Viruses

Prior studies and reviews by others have highlighted many viruses (see Table 1) contributing to the new emergence of infection in the human CNS. Categorization
of these viruses includes identification of new viral species, recognition of new viral tropism to the CNS, viral spread into naïve demographic areas, increased human contact with zoonotic repositories including insect vectors, and reemergence of well-known viral species. Other mechanisms for CNS emergence include genetic mutation of existing viruses and immunosuppression and/or immunosenescence of the host. Some of these viruses may be associated with specific disease states such as John Cunningham virus (JC virus) and progressive multifocal leukoencephalopathy, while others, like West Nile virus, appear to play a role in meningitis, encephalitis, or meningoencephalitis.

Identification of new viral species

Henipaviruses (Hendra and Nipah) in the family Paramyxoviridae were first identified in the mid to late 1990s. Hendra infection was first identified in the aseptic meningitis and frank encephalitis deaths of a few Australian individuals who had been in close contact with horses. Hendra was originally thought to be an equine Morbillivirus but was subsequently reclassified with Nipah virus into the Henipaviruses. Nipah virus is the more frequently encountered virus of the Henipaviruses, and most cases of emergence have resulted from this infection. Nipah was identified originally in pig farmers in Malaysia in 1998 and resulted in acute encephalitis that proved fatal in >30% of cases. Common neurological symptoms include fever, headache, segmental myoclonus, reduced tendon reflexes, nuchal rigidity, and seizures. Interestingly, with Nipah infection, 3% of individuals developed late-onset encephalitis that did not initially have neurological symptoms, and 8% of acute encephalitic patients had recurrent or relapsing encephalitis on an average of 8 months following acute disease. Of the fatal cases of Nipah virus infection, analysis of brain tissues at autopsy suggested the virus spreads to the CNS from the bloodstream. Following this spread, there is subsequent multifocal vasculitis, multicentric thrombosis, and direct neuronal infection. Outbreaks of Nipah virus encephalitis also have appeared in India and Bangladesh with high mortality; however, these are thought to be mitigated by a different source of infection, secretions from the fruit bat. Newer studies suggest that transmission now can occur from person to person. Regardless of the mode of transmission, infection with this family of viruses exacts a large toll on the human population, thus keeping these viruses near the top of emerging CNS infectious threats. There is no effective treatment for these viruses other than supportive care.

Viruses emerging in new demographic areas

Numerous viruses have emerged recently in new demographic areas around the world. Some of the most notable are Enterovirus 71, West Nile virus, Japanese encephalitis virus, and Chikungunya virus. Interestingly, other than for Enterovirus 71, one commonality of these viruses is that they are insect vector borne.

Enterovirus 71

Enterovirus 71 (EV71) is a member of the family Picornaviridae and is one of the most important regarding widespread demographic emergence and involvement with CNS disease. This is particularly the case in children in which hand-foot-mouth disease is manifest most often following this infection. Brainstem encephalitis, acute flaccid paralysis, and aseptic meningitis have been recognized as sequelae in these children, although this may vary with different outbreaks. EV71 was first isolated in California in the late 1960s, but since then there have been numerous outbreaks worldwide with some of the most severe occurring in Southeast Asia and the Pacific Rim nations. During hand-foot-mouth disease epidemics, CNS disease is frequently encountered, and symptoms may include systemic features such as fever, mouth ulcers, cough, vomiting, and irritability. Treatment for EV71 infections is principally supportive. EV71 and mutated EV71 viruses appear to be one of our greatest threats with emerging Picornaviridae.

Table 1 Proposed viruses emerging in central nervous system disease

<table>
<thead>
<tr>
<th>Virus</th>
<th>Condition/disease association</th>
<th>Viral family</th>
</tr>
</thead>
<tbody>
<tr>
<td>Henipah virus (Hendra and Nipah)</td>
<td>Encephalitis/meningitis</td>
<td>Paramyxoviridae</td>
</tr>
<tr>
<td>Enterovirus 71</td>
<td>Encephalitis/meningitis/ flaccid paralysis</td>
<td>Picornaviridae</td>
</tr>
<tr>
<td>West Nile virus</td>
<td>Encephalitis/meningitis</td>
<td>Flaviviridae</td>
</tr>
<tr>
<td>Japanese encephalitis virus</td>
<td>Encephalitis</td>
<td>Togaviridae</td>
</tr>
<tr>
<td>Chikungunya virus</td>
<td>Encephalitis/meningitis</td>
<td>Orthomyxoviridae</td>
</tr>
<tr>
<td>Influenza virus</td>
<td>Encephalitis/meningitis/ schizophreria</td>
<td>Polyomaviridae</td>
</tr>
<tr>
<td>JC virus</td>
<td>Progressive Multifocal Leukoencephalopathy (PML)</td>
<td>Herpesviridae</td>
</tr>
<tr>
<td>Human</td>
<td>Encephalitis/epilepsy/multiple sclerosis</td>
<td>Herpesviridae</td>
</tr>
<tr>
<td>Herpesvirus 6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Herpes simplex virus 1</td>
<td>Encephalitis/Alzheimer’s disease</td>
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and thus, there is an increasing need for effective and specific vaccines.15

West Nile virus
West Nile virus (WNV), a member of the Flaviviridae family, was first isolated in the West Nile province of Uganda in the 1930s.2 The virus has been reported in Central America, the Caribbean, Europe, the Middle East, Africa, India, Asia, and Australia.18,19 No cases of WNV encephalitis were recognized in the United States until the late 1990s yet the virus has spread rapidly; today, most states have reported cases of human disease.20,21 Culex genus mosquitoes are the principal vectors for WNV, and resident bird species are the major host reservoir thought to be responsible for spread of the virus.22 The majority of WNV infections are acute and asymptomatic, with approximately 20% resulting in West Nile Fever and approximately 1% leading to neuroinvasive disease.23 Upon neuroinvasion, encephalitis, meningitis, and acute flaccid paralysis may occur. Individuals 60 years of age or older and afflicted with other conditions, including diabetes and hypertension, are more susceptible to developing encephalitis.24 Encephalitis symptoms include mental status change, headache, fever, and Parkinsonian movement disorders. Meningitis symptoms typically consist of headache and fever, photophobia, and, at times, nerve palsies. Individuals exhibiting acute flaccid paralysis also show signs of encephalitis and Parkinsonism change with deficits in nerve conduction; although some of these patients may regain some strength over time, others may not recover.25 The clinical course is variable for WNV infections; patients convalescing from meningitis may continue to have persistent headaches and fatigue, while those with encephalitis may manifest persistent neurologic deficits.26 There is no specific treatment other than supportive care for infected individuals.

Japanese encephalitis virus
Similar to WNV, the Japanese encephalitis virus (JEV) is a member of the Flaviviridae, and is transmitted by Culex genus mosquitoes.27 Natural reservoirs for this virus are pigs, egrets, and herons. JEV was first identified in Japan in the 19th century and has spread over decades into China, Southeast Asia, India, and the Indian subcontinent, New Guinea, and Australia.27 The emergence of JEV can be attributed to increased population growth in endemic areas and occupational exposure with rice and pig farming presenting increased risk of vector-borne infection.27 JEV often is asymptomatic, but may cause severe acute encephalitis, which can be fatal.28 In this regard, 10,000 deaths or more annually have been attributed to JEV infections and their role in acute viral encephalitis.29,30 Symptoms range from nuchal rigidity, severe rigors, and hemiparesis to nausea, headache, and fever. Although there is no specific therapy for JEV, there is a live-attenuated vaccine, and new candidate vaccines are being developed.30

Chikungunya virus
Chikungunya virus (CHIKV), which belongs to the family Togaviridae, is an arbovirus transmitted by the Aedes mosquito (eg, Aedes aegypti). CHIKV was first isolated in Tanzania and subsequently in other areas of sub-Saharan Africa, India, and Southeast Asia.31 The virus is considered an encephalitic and arthritic virus. Neurological diseases attributed to CHIKV include encephalitis, meningitis, encephalomyelitis, Guillain-Barré-like syndrome, and acute flaccid paralysis.32–35 Experimental evidence from neonatal and adult mice in which the interferon α/β receptor was knocked out to prevent interferon signaling suggests that virus inoculated peripherally may enter the choroid plexus of the brain following a viremia.36 The association of this virus with CNS disease in humans is thought to arise due to increased geographical distribution by population mobility from endemic areas to naïve areas and possibly by commercial trade of materials containing water-borne mosquito larvae.37 In addition, there is evidence from an outbreak of this infection on the island of La Reunion in the Indian Ocean in 2005–2006 that the virus underwent mutation to infect a second Aedes species, Aedes albopictus.31,38–41 As Aedes albopictus mosquitoes are found in urban areas of Europe and the United States, there is increased risk for this infection to spread in these areas.31,38 No specific antiviral treatment or vaccine is currently available.

Genetic mutation of existing viruses and immunosuppression
Influenza viruses
Influenza viruses typically are thought of as respiratory disease–causing agents. However, their ability to undergo genetic mutation, antigenic drift, and affect host development as well as causing neurological symptoms suggests that they will continue to emerge as infections in the CNS. Influenza viruses are members of the family Orthomyxoviridae and typically are associated with symptoms of the flu.42 However, there can be neurological involvement as demonstrated during epidemics, and potential involvement in neuropsychiatric disorders following prenatal exposure. There have been
reports of increasing incidence of influenza-associated encephalitis/encephalopathy, especially in children infected with influenza A (H1N1). Other clinical manifestations also may be observed during or following influenza A infections, including Reye’s syndrome, myelitis, Guillain-Barré syndrome, and acute necrotizing encephalopathy. Prenatal influenza exposure also has been linked to the development of schizophrenia through analysis of a birth cohort of the Child Health and Development Study. Brown and colleagues used a case-control study based on this particular cohort to determine that there was a threefold elevation in risk for schizophrenia if there was exposure to influenza in the first half of gestation. Interestingly, the elevation of risk for schizophrenia was increased sevenfold when exposure occurred within the first trimester, whereas no increase was observed when influenza exposure occurred beyond the second half of gestation. Thus, the vulnerable stage for risk appears to be very early in gestation. What is not known at this time is the specific mechanism accounting for this risk. Investigations on influenza virus-infected pregnant mice have analyzed specific cellular populations in the brains of the offspring that appear to correlate in later life to decreased exploratory and social behavior, decreased contact with new objects in their environment, and an altered startle response to noise. Of the cellular changes in the offspring, there was a reduction in Cajal-Retzius cells in the cortex and hippocampus that were reelin-positive. Reelin is involved in regulating neuronal migration and positioning of cells in the developing brain. In the same mice, there was a decrease in the cortical and hippocampal area but an increase in overall cortical pyramidal cell density. These studies suggest that influenza virus infection prenatally can have a dramatic result on fetal brain development that may manifest as psychiatric disease at later ages, although causality has yet to be proven conclusively for this involvement. Furthermore, there appears to be an increasing number of reported cases of neurologic sequelae following influenza epidemics. Often there is no specific treatment for infected individuals, although a number of drugs could be used to help treat and prevent the flu such as oseltamivir (Tamiflu®; Hoffman-La Roche, Basel, Switzerland) and zanamivir (Relenza®; GlaxoSmithKline, London, UK).

JC virus
JC virus is a member of the Polyomaviridae family and causes progressive multifocal leukoencephalopathy (PML), a fatal neurological disease. This disease is observed principally in immunosuppressed or immunocompromised individuals who have low levels of cell-mediated immunity. In this regard, other infections such as those with human immunodeficiency virus (HIV) that result in an immunocompromised state as well as drug therapy for autoimmune diseases such as Crohn’s, multiple sclerosis, and rheumatoid arthritis promote an increased incidence of PML. As high percentages of the human population carry antibodies reactive to the JC virus, the virus is thought to reside latently in the body, systemically and in the CNS. Upon immunosuppression, reactivation of the virus is thought to occur leading to death of oligodendrocytes and destruction of myelin sheaths in the CNS. Neurological symptoms include weakness, paralysis, vision loss, impaired speech, and cognitive deterioration. Thus, serious consideration must be made for individuals electing to be treated with many of the newer monoclonal antibody treatments such as natalizumab for Crohn’s disease resulting in variable degrees of immunosuppression.

Herpes viruses
Herpes virus associated with immunocompetent individuals is human herpesvirus 6 (HHV6), a member of the Herpesviridae family. There are two variants (HHV6A and HHV6B). HHV6A is thought to be overall more virulent and neurotropic, although HHV6B is found significantly in CNS disease. For example, HHV6B is commonly found in childhood and has been associated with exanthem subitum (roseola infantum) and meningoencephalitis. HHV6B also has been associated with infantile febrile illness with documented seizures. Interestingly, HHV6B has been associated more recently with fatal encephalitis in a number of cases following hematopoietic stem cell transplantation. Further, studies have found evidence of HHV6B in mesial temporal lobe epilepsy and multiple sclerosis. However, conclusive disease association with this virus in these diseases awaits further investigation as there is evidence of HHV6 variants in infection in normal human brain tissues. Commonly, the limbic areas of the brain were affected, including the amygdala, entorhinal cortex, and hippocampus, leading to a designation of posttransplant acute limbic encephalitis. Ongoing research is investigating the roles of excitatory amino acids and inflammation in the pathological processes associated with HHV6 infection in the CNS. There is no specific treatment for HHV6 infections, but drugs used to treat other herpes infections (eg, ganciclovir) have been tried in severe infections.

Herpes simplex virus 1 (HSV1) is another member of the Herpesviridae family. This virus is ubiquitous and often found latent in peripheral trigeminal ganglion neurons.
HSV1 may traffic into the CNS proper where the virus may remain latent or reactivate; reactivation can result in serious acute encephalitis of the frontotemporal region of the brain in rare cases.44 Regarding neurodegenerative disease, in particular Alzheimer’s disease (AD), studies have linked CNS viral infection to AD by analyzing HSV1 DNA in the brain,69–71 and anti-HSV1 antibodies in the CSF and sera of patients with AD.71,72 Furthermore, HSV1 has been correlated to the apolipoprotein E ε4 risk for AD,73 and shown to bind to the amyloid precursor protein.74 HSV1 had been demonstrated to code for a protein kinase involved with the phosphorylation of the tau protein.75,76 More recently, the virus has been shown to impair the autophagy pathway in cells infected in vitro.77 Thus, although great strides have been made in correlating this infection to the neurodegenerative process, ongoing and future studies must continue to focus on the mechanistic underpinnings of infection leading to the emerging nature of HSV1 in AD. With regard to potential therapy in AD, a recent study found that anti-HSV1 antiviral agents reduced Aβ and phosphorylated tau accumulations in HSV1-infected cells in vitro.78 Thus, potentially, anti-HSV1 antiviral therapy could be used in HSV1-associated AD.

**Bacteria**

Emergence of bacterial infections in the CNS has been demonstrated (see Table 2). This review highlights some of the intracellular and extracellular bacteria contributing to disease in the CNS. Many of these bacteria use specific entry mechanisms into the CNS similar to those used by numerous viruses, including bloodborne entry as well as potential neuroinvasion of peripheral and cranial nerves.79,80 With the advent of improved technology such as polymerase chain reaction (PCR) and real-time PCR, microbiome sequencing, and monoclonal antibodies to very specific epitopes, unique bacteria are being identified in the human population.81 Intriguingly, many of these agents are being identified in areas of the body not thought to be initially infected such as the CNS and associated with chronic disease. Chronic disorders, more so than ever before, are being attributed to chronic infectious processes; emerging bacterial infection in the CNS may follow a similar pattern.

**Intracellular bacteria**

*Orientia tsutsugamushi*

*Orientia tsutsugamushi* is an obligate intracellular pathogen in the family *Rickettsiaceae*, and is the causative organism of scrub typhus.82 The natural vector and reservoir is the trombiculid mite.83 *O. tsutsugamushi* is a very common infection in Southeast Asia and in the western Pacific Rim countries. Because disease with this organism often presents as a febrile illness, a number of studies have investigated involvement with the CNS.80,84,85 The organism is thought to gain access to the CNS following infection of circulating monocytes and invasion of endothelial cells.80 Symptoms following entry to the CNS include nuchal rigidity, seizures, delirium, as well as meningismus and meningitis.80,84 In the endemic area of scrub typhus, *O. tsutsugamushi* should be considered a potential causative organism in mononuclear cell–involved meningitis as greater recognition has been demonstrated for the emergence of this Rickettsial organism in CNS disease.85 Treatment for infections with *O. tsutsugamushi* typically includes using the antibiotics doxycycline and/or azithromycin.

**Ehrlichia chaffeensis**

*Ehrlichia chaffeensis*, an obligate intracellular bacterium in the family *Anaplasmataceae*, causes human monocytic ehrlichiosis (HME). HME rates of infection are estimated to be 100–200 per 100,000 in endemic areas in the US, which include Mississippi, Oklahoma, Tennessee, Arkansas, and Maryland.88 Reports from other states are also being noted suggesting a continual emergence in the US.89 Importantly, as up to 66% of infections with *E. chaffeensis* are either minimally symptomatic or asymptomatic, the exact incidence of human infection may be higher.89 HME is transmitted by infection with the tick vector, *Amblyomma americanum* (Lone Star tick), which is prevalent in the southeast and south-central regions of the US.89 Neurologic manifestations occur in approximately 20% of patients infected with HME. Some patients may experience cranial nerve palsies and cognitive deficits, and in children, there may be longer-term sequelae, including foot drop, fine motor impairment, and cognitive change.92 Pathogenesis in HME infections appears to result

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**Table 2** Proposed bacteria emerging in central nervous system disease

<table>
<thead>
<tr>
<th>Bacteria</th>
<th>Condition/disease association</th>
<th>Bacterial family</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Orientia tsutsugamushi</em></td>
<td>Meningitis</td>
<td>Rickettsiaceae</td>
</tr>
<tr>
<td><em>Ehrlichia chaffeensis</em></td>
<td>Meningoencephalitis</td>
<td>Anaplasmataceae</td>
</tr>
<tr>
<td><em>Chlamydia pneumoniae</em></td>
<td>Alzheimer’s disease/multiple sclerosis</td>
<td>Chlamydiaceae</td>
</tr>
<tr>
<td><em>Borrelia burgdorferi</em></td>
<td>Neuroborreliosis/</td>
<td>Spirochaetaceae</td>
</tr>
<tr>
<td><em>Helicobacter pylori</em></td>
<td>Parkinson’s disease</td>
<td>Helicobacteraceae</td>
</tr>
</tbody>
</table>

**Note:** Although some of these organisms have been associated with acute and/or chronic CNS disease entities, causality in numerous instances remains to be proven.
from the inability of the cell to undergo phagolysosome fusion,\textsuperscript{93} and to the immune-mediated pathology that results especially with significant expansion of cytotoxic CD8+ T cells and their production of tumor necrosis factor-alpha and interferon-gamma.\textsuperscript{94} Since 1987, HME has become a serious and prevalent tick-borne cause of human infections in the US.\textsuperscript{95} With the ever-expanding niche for ticks and animal reservoirs such as white-tailed deer, and their increasing encounters with the resident human population, HME will continue to emerge as a major cause of vector-borne meningocerephalitis. Treatment for HME typically involves a course of antibiotic therapy with doxycycline.\textsuperscript{96}

**Chlamydia pneumoniae**

*Chlamydia pneumoniae* (Cpn), an obligate intracellular bacterium in the family *Chlamydiaceae*, typically infects the human respiratory tract often resulting in a chronic cough, little sputum production, and a low-grade fever.\textsuperscript{97} The organism has been shown to enter the systemic circulation following infection of monocytes surveilling lung tissues.\textsuperscript{98} The ability to spread systemically may be one reason this bacterium has been identified in nonrespiratory conditions, including AD and multiple sclerosis (MS). Associations of Cpn with AD\textsuperscript{99} and MS\textsuperscript{100} were first reported in 1998. Over the last several years, other reports have strengthened these associations,\textsuperscript{101,102} but more evidence is required to demonstrate proof of causality. In this regard, studies have addressed and continue to address Cpn infection in vivo in diseased populations and in animal models, and in vitro in infected tissue cultures. What is becoming clearer is that Cpn can enter and remain in the CNS as a chronic/persistent infection,\textsuperscript{103,104} and may be a major stimulus for neuroinflammation.\textsuperscript{105} Furthermore, infection of the brain may involve not only monocyte delivery but also infection of the olfactory cranial nerve following exposure in the nose. Evidence for this pathway follows from analysis of olfactory tissues from patients with AD,\textsuperscript{99} as well as animal models.\textsuperscript{103} Molecular analyses following Cpn infection in cell culture are addressing specific pathways known to be disrupted or modified in AD. For example, modification of apoptosis\textsuperscript{106} and autophagy pathways as well as inflammatory pathways following infection are being studied to better understand the molecular pathogenesis of infection-mediated disease. In effect, continued correlation of CNS infection with Cpn and AD and MS may reflect the relatively newly recognized emergence of chronic infection with major neurological diseases. Treatment for community-acquired pneumonias, including those caused by Cpn, typically involves antibiotics such as doxycycline, azithromycin, and/or fluoroquinolones.\textsuperscript{107} One clinical trial with some positive results has been performed using the anti-Cpn antibiotics doxycycline and rifampin in treating patients with AD.\textsuperscript{108}

**Extracellular bacteria**

* Borrelia burgdorferi

*Borrelia burgdorferi* organisms are spirochetes in the family of *Spirochaetaceae* that cause borreliosis or Lyme disease, a zoonotic, vector-borne disease transmitted primarily by ticks such as *Ixodes scapularis* in North America. Typically, a localized infection occurs following the tick bite, and evasion of the immune system ensues once in the host.\textsuperscript{109} *B. burgdorferi* infects monocytes that are thought to disseminate the organism into the CNS through the blood-brain barrier.\textsuperscript{109} Once the organism is in the brain, a chronic infection may ensue in which neuroborreliosis and/or Alzheimer's disease may become manifest.\textsuperscript{111} Symptoms of nervous system involvement may include meningoradiculitis, cranial nerve abnormalities, and altered mental status.\textsuperscript{109} Evidence for involvement in AD comes from analysis of postmortem AD brain tissues in which *Borrelia* was identified.\textsuperscript{111} Further studies in vitro have supported these findings by demonstrating that infection of neurons, astrocytes, and microglial cells led to the production and aggregation of amyloid as well as tangle-like structures within nerve cells.\textsuperscript{112} In this regard, bacterial products from the organism such as lipopolysaccharide have been shown to initiate a strong response by neuronal and glial cells implicating *Borrelia* with AD.\textsuperscript{112} At this time, causality has not been determined regarding this infection and AD pathogenesis; however, the infection induction of beta amyloid processing and tau hyperphosphorylation comparable to what is observed in AD makes *B. burgdorferi* a candidate infection as a stimulus for CNS damage.\textsuperscript{112} Neuroborreliosis is typically treated with intravenous antibiotics that cross the blood-brain barrier such as ceftriaxone and doxycycline.\textsuperscript{113}

**Helicobacter pylori**

*Helicobacter pylori* are members of the *Helicobacteraceae* family. Infection with this organism in the stomach is considered the major cause of peptic and gastric ulcers.\textsuperscript{114} *H. pylori* infection has been postulated to play a role in idiopathic Parkinson's (IP) disease.\textsuperscript{115} This follows from analysis of common immunological manifestations, epidemiological similarities of familial aggregation and linkage with a common source of drinking water, and the demonstration that the infection can be passed between siblings in childhood.
and between spouses.115 Probands with IP and siblings share a threefold increase in odds of seropositivity for antibodies against *H. pylori* urease.116 Furthermore, a discriminant index for the presence/absence of diagnosed Parkinsonism has been derived from Western blot serum *H. pylori* antibody profiles in subjects with and without IP that contained known pathogenicity markers.117 The persistence of antibody against cytoxin-associated antigen (CagA) increased the predicted probability of Parkinsonism by 80 years of age fivefold.117 More recently, a population-based study of patients with Parkinson’s in Denmark suggested chronic *H. pylori* infection and/or gastritis either contributed to Parkinson’s disease (PD) or that these are PD-related pathologies that precede motor dysfunction.118 Mechanistically, chronic inflammation and autoimmune modulation have been proposed as contributors to IP with *H. pylori* infection.115 Some evidence for immune modulation has been demonstrated in vitro as *H. pylori* has been shown to suppress T-cell proliferation,119 and in infected individuals, *H. pylori*-specific T-reg are known to be shown to suppress T-cell responses.120 Extraintestinal influence in IP may be more prominent with CagA-positive strains of *H. pylori* regarding autoimmune mechanisms.121 The exact relationship between *H. pylori* infection and IP has yet to be determined. What is becoming clearer is that treatments for PD are not effective in Parkinson’s disease researchers must be aware of acute and chronic processes of infectious origin that may be insulting the nervous system. Neurological diseases not typically thought to be infectious must be examined fully for microbial involvement and analyzed for direct and indirect associations. We are challenged to develop methodology that will clearly detect and identify infectious agents in the CNS. Finally, understanding the relationships between systemic infection and neurologic disease is vital, and may provide clues leading to better predictability, treatment, and prevention of CNS diseases.

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**Disclosure**

The authors report no conflict of interest in this work.

**References**


