BJMP 2009:2(4) 20-28

Review Article

Role of Chronic Bacterial and Viral Infections in Neurodegenerative, Neurobehavioral, Psychiatric, Autoimmune and Fatiguing Illnesses: Part 1

Garth L. Nicolson and Jörg Haier

Abstract

Chronically ill patients with neurodegenerative, neurobehavioral and psychiatric diseases commonly have systemic and central nervous system bacterial and viral infections. In addition, other chronic illnesses where neurological manifestations are routinely found, such as fatiguing and autoimmune diseases, Lyme disease and Gulf War illnesses, also show systemic bacterial and viral infections that could be important in disease inception and progression or in increasing the number and severity of signs and symptoms. Evidence of Mycoplasma species, Chlamydia pneumoniae, Borrelia burgdorferi, human herpesvirus-1, -6 and -7 and other bacterial and viral infections revealed high infection rates in the above illnesses that were not found in controls. Although the specific roles of chronic infections in various diseases and their pathogeneses have not been carefully determined, the data suggest that chronic bacterial and/or viral infections are common features of progressive chronic diseases

Abbreviations: Ab beta amyloid; AD Alzheimer's disease; ADHD attention-deficit/hyperactivity disorder; ALS amyotrophic lateral sclerosis; ASD autism spectrum disorders; EBV Epstein-Barr virus; CFS chronic fatigue syndrome; CFS/ME chronic fatigue syndrome/myalgic encephalomyopathy; CI confidence interval; CMV cytomegalovirus; CSF cerebrospinal fluid; CNS central nervous system; ELISA enzyme linked immunoabsorbant assay; GWI Gulf War illnesses; HHV human herpes virus; HSV herpes simplex virus; PCR polymerase chain reaction; PD Parkinson's disease

Introduction

Chronic infections appear to be common features of various diseases, including neurodegenerative, psychiatric and neurobehavioral diseases, autoimmune diseases, fatiguing illnesses and other conditions.[1-4] Neurodegenerative diseases, chronic degenerative diseases of the central nervous system (CNS) that cause dementia, are mainly diseases of the elderly. In contrast, neurobehavioral diseases are found mainly in younger patients and include autism spectrum disorders (ASD), such as autism, attention deficit disorder, Asperger's syndrome and other disorders.[5] For the most part, the causes of these neurological diseases remain largely unknown.[2] Neurodegenerative diseases are characterized by molecular and genetic changes in nerve cells that result in nerve cell degeneration and ultimately nerve cell dysfunction and death, resulting in neurological signs and symptoms and dementia.[2,3] On the other hand, neurobehavioral diseases are related to fetal brain development but are less well characterized at the cellular level and involve both genetic and environmental factors.[6, 7] Even less well characterized at the cellular and genetic level are the psychiatric disorders, such as schizophrenia, paranoia, bipolar disorders, depression and obsessive-compulsive disorders.

Genetic linkages have been found in neurodegenerative and neurobehavioral diseases, but the genetic changes that occur and the changes in gene expression that have been found are complex and usually not directly related to simple genetic alterations.[2, 6-8] In addition, it is thought that nutritional deficiencies, environmental toxins, heavy metals, chronic bacterial and viral infections, autoimmune immunological responses, vascular diseases, head trauma and accumulation of fluid in the brain, changes in neurotransmitter concentrations, among others, are involved in the pathogenesis of various neurodegenerative and neurobehavioral diseases.[2, 3, 5-16] One of the biochemical changes found in essentially all neurological, neurodegenerative and neurobehavioral diseases is the over-expression of oxidative free radical compounds (oxidative stress) that cause lipid, protein and genetic structural changes.[9-11] Such oxidative stress can be caused by a variety of environmental toxic insults, and when combined with genetic factors could result in pathogenic changes.[14]

Neurodegenerative diseases

Infectious agents are important factors in neurodegenerative and neurobehavioral diseases and may enter the brain within infected migratory macrophages. They may also gain access by transcytosis across the blood-brain-barrier or enter by intraneuronal transfer from peripheral nerves.[15] Cell wall-deficient bacteria, such as species of *Mycoplasma*, *Chlamydia (Chlamydophila), Borrelia* and *Brucella,* among others, and various viruses are candidate brain infectious agents that may

play important roles in neurodegenerative and neurobehavioral diseases.[16-19] Such infections are systemic and can affect the immune system and essentially any organ system, resulting in a variety of systemic signs and symptoms.[4, 15, 16, 19, 20]

Amyotrophic lateral sclerosis

Amyotrophic lateral sclerosis (ALS) is an adult-onset, idiopathic, progressive neurodegenerative disease that affects both central and peripheral motor neurons.[21] Patients show gradual progressive weakness and paralysis of muscles due to destruction of upper motor neurons in the motor cortex and lower motor neurons in the brain stem and spinal cord. This ultimately results in death, usually by respiratory failure.[21, 22] The overall clinical picture of ALS can vary, depending on the location and progression of pathological changes.[23]

The role of chronic infections has attracted attention with the finding of enterovirus sequences in a majority of ALS spinal cord samples by polymerase chain reaction (PCR).[24] However, others have failed to detect enterovirus sequences in spinal cord samples from patients with or without ALS.[25-26] In spite of the mixed findings on enterovirus, infectious agents that penetrate the CNS could play a role in the aetiology of ALS. Evidence for transmission of an infectious agent or transfer of an ALS-like disease from man-to-man or man-to-animals has not been found.[27]

Using PCR methods systemic mycoplasmal infections have been found in a high percentage of ALS patients.[28, 29] We found that 100% of Gulf War veterans from three nations diagnosed with ALS had systemic mycoplasmal infections.[28] All but one patient had *M. fermentans*, and one veteran from Australia had a systemic *M. genitalium* infection. In nonmilitary ALS patients systemic mycoplasmal infections of various species were found in approximately 80% of cases.[28] Of the mycoplasma-positive civilian patients who were further tested for various species of Mycoplasma, most were positive for *M. fermentans* (59%), but other *Mycoplasma* species, such as *M. hominis* (31%) and *M. pneumoniae* infections (9%) were also present. Some of the ALS patients had multiple infections; however, multiple mycoplasmal infections were not found in the military patients with ALS.[28] In another study 50% of ALS patients showed evidence of systemic *Mycoplasma* species by PCR analysis.[29]

ALS patients who live in certain areas often have infections of *Borrelia burgdorferi*, the principal aetiological agent in Lyme disease. For example, ALS patients who live in a Lyme-prevalent area were examined for *B. burgdorferi* infections, and over one-half were found to be seropositive for *Borrelia* compared to 10% of matched controls.[30] In addition, some patients diagnosed with ALS were subsequently diagnosed with neuroborreliosis.[31] Spirochetal forms have been observed in the brain tissue of ALS patients and in patients with other neurodegenerative diseases.[32] In general, however, the incidence of Lyme infections in ALS patients is probably much lower. In one recent study on 414 ALS patients only about 6% showed serological evidence of *Borrelia* infections.[33] Some Lyme Disease patients may progress to ALS, but this is probably only possible in patients who have the genetic susceptibility genes for ALS as well as other environmental toxic exposures.[34, 35]

Additional chronic infections have been found in ALS patients, including human herpes virus-6 (HHV-6), *Chlamydia pneumoniae* and other infections.[36, 37] There is also a suggestion that retroviruses might be involved in ALS and other motorneuron diseases.[38] McCormick et al.[39] looked for reverse transcriptase activity in serum and cerebrospinal fluid of ALS and non-ALS patients and found reverse transcriptase activity in one-half of ALS serum samples tested but in only 7% of controls. Interestingly, only 4% of ALS cerebrospinal fluid samples contained reverse transcriptase activity.[39]

Although the exact cause of ALS remains to be determined, there are several hypotheses on its pathogenesis: (1) accumulation of glutamate causing excitotoxicity; (2) autoimmune reactions against motor neurons; (3) deficiency of nerve growth factor; (4) dysfunction of superoxide dismutase due to mutations; and (5) chronic infection(s).[24, 27-40] None of these hypotheses have been ruled out or are exclusive, and ALS may have a complex pathogenesis involving multiple factors. [28, 36]

It is tempting to propose that infections play an important role in the pathogenesis or progression of ALS.[28, 40] Infections could be cofactors in ALS pathogenesis, or they could simply be opportunistic, causing morbidity in ALS patients. For example, infections could cause the respiratory and rheumatic symptoms and other problems that are often found in ALS patients. Since the patients with multiple infections were usually those with more rapidly progressive disease,[28] infections likely promote disease progression. Indeed, when Corcia et al.[41] examined the cause of death in 100 ALS patients, the main causes were broncho-pneumonia and pneumonia. Finally, there are a number of patients who have ALS-like signs and symptoms but fall short of diagnostic criteria. Although a careful study has not been attempted on these patients, there is an indication that they have the same infections as those found in patients with a full diagnosis of ALS (personal communication). Thus ALS-like diseases may represent a less progressive state, in that they may lack additional changes or exposures necessary for full ALS.

Multiple sclerosis

Multiple sclerosis (MS) is the most common demyelinating neurological disease. It can occur in young or older people and is a cyclic (relapsing-remitting) or progressive disease that continues progressing without remitting.[42] Inflammation and the presence of autoimmune antibodies against myelin and other nerve cell antigens are thought to cause the myelin sheath to break down, resulting in decrease or loss of electrical impulses along the nerve fibers.[42, 43] In the progressive subset

of MS neurological damage occurs additionally by the deposition of plaques on the nerve cells to the point where nerve cell death occurs. In addition, breakdown of the blood-brain barrier in MS is associated with local inflammation caused by glial cells.[42, 43] The clinical manifestations of demyelinization, plaque damage and blood-brain barrier disruptions cause variable symptoms, but they usually include impaired vision, alterations in motor, sensory and coordination systems and cognitive dysfunction.[43]

There is strong evidence for a genetic component in MS.[44, 45] Although it has been established that there is a genetic susceptibility component to MS, epidemiological and twin studies suggest that MS is an acquired, rather than an inherited, disease.[46]

MS has been linked to chronic infection(s).[46, 47] For example, patients show immunological and cytokine elevations consistent with chronic infections.[48-50] An infectious cause for MS has been under examination for some time, and patients have been tested for various viral and bacterial infections. [44, 45,47, 48, 51] One of the most common findings in MS patients is the presence of *C. pneumoniae* antibodies and DNA in their cerebrospinal fluid.[51-53] By examining relapsing-remitting and progressive MS patients for the presence of *C. pneumoniae* in cerebrospinal fluid by culture, PCR and immunoglobulin reactivity Sriram et al.[52] were able to identify *C. pneumoniae* in 64% of MS cerebrospinal fluid versus 11% of patients with other neurological diseases. They also found high rates (97% positive) of PCR-positive MOMP gene in MS- patients versus 18% in other neurological diseases, and this correlated with 86% of MS patients being serology-positive patients by ELISA and Western blot analysis.[52] Examination of MS patients for oligoclonal antibodies against *C. pneumoniae* revealed that 82% of MS patients were positive, whereas none of the control non-MS neurological patients had antibodies that were absorbed by *C. pneumoniae* elemental body antigens.[53] Similarly, Contini et al.[54] found that the DNA and RNA transcript levels in mononuclear cells and cerebrospinal fluid of 64.2% of MS patients but in only 3 controls.

Using immunohistochemistry Sriram et al.[55] later examined formalin-fixed brain tissue from MS and non-MS neurological disease controls and found that in a subset of MS patients (35%) chlamydial antigens were localized to ependymal surfaces and periventricular regions. Staining was not found in brain tissue samples from other neurological diseases. Frozen tissues were available in some of these MS cases, and PCR amplification of *C. pneumoniae* genes was accomplished in 63% of brain tissue samples from MS patients but none in frozen brain tissues from other neurological diseases. In addition, using immuno-gold-labeled staining and electron microscopy they examined cerebrospinal fluid sediment for chlamydial antigens and found that the electron dense bodies resembling bacterial structures correlated with PCR-positive results in 91% of MS cases.[55] They also used different nested PCR methods to examine additional *C. pneumoniae* gene sequences in the cerebrospinal fluid of 72 MS patients and linked these results to MS-associated lesions seen by MRI.[56]

MRI was used by Grimaldi et al.[57] to link the presence of *C. pneumoniae* infection with abnormal MRI results and found linkage in 21% of MS patients. These turned out to be MS patients with more progressive disease.[58] In addition, higher rates of *C. pneumoniae* transcription were found by Dong-Si et al.[58] in the cerebrospinal fluid of 84 MS patients. The data above and other studies strongly support the presence of *C. pneumoniae* in the brains of MS patients,[59-61] at least in the more progressed subset of MS patients.

Other research groups have also found evidence for *C. pneumoniae* in MS patients but at lower incidence. Fainardi et al.[62] used ELISA techniques and found that high-affinity antibodies against *C. pneumoniae* were present in the cerebrospinal fluid of 17% of MS cases compared to 2% of patients with non-inflammatory neurological disorders. They found that the majority of the progressive forms of MS were positive compared to patients with remitting-relapsing MS. The presence of *C. pneumoniae* antibodies was also found in other inflammatory neurological disorders; thus it was not found to be specific for MS.[62]

In contrast to the studies above, other researchers have not found the presence of *C. pneumoniae* or other bacteria in the brains of MS patients.[63-65] For example, Hammerschlag et al.[66] used nested PCR and culture to examine frozen brain samples from MS patients but could not find any evidence for *C. pneumoniae*. However, in one study *C. pneumoniae* was found at similar incidence in MS and other neurological diseases, but only MS patients had *C. pneumoniae* in their cerebrospinal fluid.[64] Swanborg et al.[67] reviewed the evidence linking *C. pneumoniae* infection with MS and concluded that it is equivocal, and they also speculated that specific genetic changes may be necessary to fulfill the role of such infections in the aetiology of MS.

Another possible reason for the equivocal evidence linking MS with infections, such as *C. pneumoniae,* is that multiple co-infections could be involved rather than one specific infection. In addition to *C. pneumoniae* found in most studies, MS patients could also have *Mycoplasma* species, *B. burgdorferi* and other bacterial infections as well as viral infections.[68] When multiple infections are considered, it is likely that >90% of MS patients have obligate intracellular bacterial infections caused by *Chlamydia (Chlamydophila), Mycoplasma, Borrelia* or other intracellular bacterial infections. These infections were found only singly and at very low incidence in age-matched subjects.[68] In spite of these findings, others did not find evidence of *Mycoplasma* species in MS brain tissue, cerebrospinal fluid or peripheral blood.[69]

Viruses have also been found in MS. For example, HHV-6 has been found at higher frequencies in MS patients, but this virus has also been found at lower incidence in control samples.[70] Using PCR Sanders et al.[70] examined postmortem brain tissue and controls for the presence of various neurotrophic viruses. They found that 57% of MS cases and 43% of non-MS neurological disease controls were positive for HHV-6, whereas 37% and 28%, respectively, were positive for herpes simplex virus (HSV-1 and -2) and 43% and 32%, respectively, were positive for varicella zoster virus. However, these differences did not achieve statistical significance, and the authors concluded "an etiologic association to the MS disease process [is] uncertain." They also found that 32% of the MS active plaques and 17% of the inactive plaque areas were positive for HHV-6.[70] Using sequence difference analysis and PCR Challoner et al.[71] searched for pathogens in MS brain specimens. They found that >70% of the MS specimens were positive for infection-associated sequences. They also used immunocytochemistry and found staining around MS plaques more frequently than around white matter. Nuclear staining of oligodendrocytes was also seen in MS samples but not in controls.[71] Using immunofluorescent and PCR methods HHV-6 DNA has also been found in peripheral leukocytes in the systemic circulation of MS patients.[72, 73] However, using PCR methods, others did not found herpes viruses in the peripheral blood or CSF of MS patients.[74, 75] Evidence that prior infection with EBV could be related to the development of MS was proposed; however, EBV infects more than 90% of humans without evidence of health problems and 99% of MS patients.[76] The difference in MS patients could be the presence of multiple infections, including EBV. Recently Willis et al.[77] used multiple molecular techniques to examine MS tissue but failed to find EBV in any MS tissues but could find EBV in CNS lymphomas.

Current reviews and the information above points to an infectious process in MS.[47, 48, 75, 76, 78-80] Although a few studies did not come to this conclusion,[74, 75] most studies have found infections in MS patients. It is interesting that it is the progressive rather than relapsing-remitting forms of MS which have been associated with chronic infections; therefore, infections might be more important in MS progression than in its inception. Various infections may also nonspecifically stimulate the immune system.[47, 48] Infections may also invade immune cells and alter immune cell function in a way that promotes inflammation and autoimmune activity.[78] If infections like *C. pneumoniae* and *Mycoplasma* species are important in MS, then antibiotics effective against these infections should improve clinical status. Although preliminary, that is in fact what has been seen, but not in all patients.[81] As in other neurodegenerative diseases, multiple factors appear to be involved in the pathogenesis of MS.

Alzheimer's disease

Alzheimer's Disease (AD) is a family of brain disorders usually found in elderly patients and is the most common cause of dementia. AD is characterized by slow, progressive loss of brain function, notable lapses in memory, disorientation, confusion, mood swings, changes in personality, language problems, such as difficulty in finding the right words for everyday objects, loss of behavioral inhibitions and motivation and paranoia. The course of AD varies widely, and the duration of illness can range from a few years to over 20 years. During this period the parts of the brain that control memory and thinking are among the first affected, followed by other brain changes that ultimately result in brain cell death.[82]

AD is characterized by distinct neuropathological changes in brain tissues and cells. Among the most notable are the appearance of plaques and tangles of neurofibrils within brain nerve cells that affect synapses and nerve-nerve cell communication. These structural alterations involve the deposition of altered amyloid proteins.[83, 84] Although the cause of AD is not known, the formation of the amyloid plaques and neurofibrillary tangles may be due to genetic defects and resulting changes in the structure of beta amyloid proteins. This in turn may be caused by chemicals or other toxic events, inflammatory responses, excess oxidative stress and increases in reactive oxygen species, loss of nerve trophic factors and reductions in nerve cell transmission.[83-87]

Recently AD brain infections have become important.[88-90] For example, one pathogen that has attracted considerable attention is *C. pneumoniae*.[91, 92] As mentioned above, this intracellular bacterium has a tropism for neural tissue, and it has been found at high incidence in the brains of AD patients by PCR and immunohistochemistry.[92] *C. pneumoniae* has also been found in nerve cells in close proximity to neurofibrillary tangles.[92, 93] Similarly to *Mycoplasma* species, *C. pneumoniae* can invade endothelial cells and promote the transmigration of monocytes through human brain endothelial cells into the brain parenchyma.[94] *C. pneumoniae* has been found in the brains of most AD patients,[91] and it has been cultured from AD brain tissue.[95] Injection of *C. pneumoniae* into mice stimulates beta amyloid plaque formation.[96] Although the data are compelling, some investigators have not found *C. pneumoniae* infections in AD.[97, 98]

AD patients also have other bacterial infections, such as *B. burgdorferi*.[99] Using serology, culture, Western blot and immunofluorenscence methods this Lyme Disease infection has been examined in AD.[100, 101] Not all researchers, however, have found evidence of *B. burgdorferi* in AD patients.[102, 103] The presence of intracellular infections like *B. burgdorferi* in AD patients has been proposed to be a primary event in the formation of AD beta amyloid plaques. This is thought to occur by the formation of "congophilic cores" that attract beta amyloid materials.[104] Multiple reports indicate that AD nerve cells are often positive for *B. burgdorferi,* indicating that this

intracellular bacteria could be important in the pathogenesis of AD.[99, 100, 104, 105]

The hypothesis in AD that intracellular microorganisms could provide "cores" for the attraction of beta amyloid materials is appealing, but other factors, including the induction of reactive oxygen species, lipid peroxidation and the breakdown of the lysosomal membranes releasing lysosomal hydrolases, are also thought to be important in beta amyloid deposition.[105] That infections may be important in AD pathogenesis is attractive; however, some negative reports have not confirmed the presence of infections like *B. burgdorferi* in AD patients.[99-101] This suggests that the infection theory, although compelling, remains controversial.[102, 105]

Herpes virus infections have also been found in AD, especially HSV-1.[106, 107] Previously it was determined that HSV-1 but not a related neurotrophic virus (varicella zoster virus) is present more often in AD brains, and this could be linked to AD patients who have the risk factor ApoE e4 allele.[108, 109] HSV-1 is thought to be involved in the abnormal aggregation of beta amyloid fragments within the AD brain by reducing the amount of full-length beta amyloid precursor protein and increasing the amounts of their fragments.[110] HSV-1 infection of glial and neuronal cells results in a dramatic increase in the intracellular levels of beta amyloid forms, whereas the levels of native beta amyloid precursor protein are decreased.[111] This is similar to what has been found in mice infected with HSV-1, indicating that HSV-1 is probably involved directly in the development of senile-associated plaques. Another herpes virus, HHV-6, has also been found in AD patients, but it is thought that this virus is not directly involved in AD pathogenesis. HHV-6 may exacerbate the effects of HSV-1 in AD ApoE e4 carriers.[112]

Other infections have been found in AD patients, for example, *C. pneumoniae, Helicobacter pylori* amongst others.[113] It has been proposed that such infections may act as a trigger or co-factor in AD.[114] Although experimental evidence that pathogens can elicit the neuropathological changes and cognitive deficits that characterize AD is lacking, this approach may yield interesting and important results. These authors also stressed that systemic infections must be considered as potential contributors to the pathogenesis of AD.[114]

Parkinson's disease

Parkinson's disease (PD) is characterized by akinesia, muscular rigidity and resting tremor.[103] In addition, autonomic dysfunction, olfactory disturbances, depression, sensory and sleep disturbances and frequently dementia characterize this disease.[115] The pathology of PD indicates a progressive loss of the dopamine neurons of the substantia nigra together with the presence of Lewy bodies and alpha-synuclein. More extensive brain degeneration also occurs, from the medulla oblongata to the cerebral cortex.[116, 117]

Age-related inclusion bodies and protein aggregations or defects in their degradation characteristically occur in PD, but their role in PD pathogenesis remains unclear.[117, 118] Some evidence suggests a relationship between PD and specific genetic changes, such as changes in the genes affecting mitochondria, protein degradation, organelle trafficking and vesicular fusion, and in proteins involved in oxidative stress or antioxidant function.[102] Inflammation has also been associated with PD pathology.[119]

The pathogenesis of PD has been proposed to be due to multiple genetic and neurotoxic events that produce oxidative damage and cell death. In the case of PD the relevant targets of toxic events are neuromelanin-containing dopaminergic neurons of the substantia nigra.[118, 120] A case-control study indicated that multiple environmental factors and genetic background were statistically related risk factors for PD.[121] Prominent among these were long-term toxic exposures and trauma early in life.[122] For example, early life exposure to brain injury, chemicals and/or infections may initiate a cyclic inflammatory process involving oxidative damage, excitotoxicity, mitochondrial dysfunction and altered proteolysis that later in life results in substantia nigra neuron death.[123, 124]

A role for chronic infections in PD pathogenesis has been proposed.[123, 124] One infection found in PD that has aroused considerable interest is the presence of chronic gastrointestinal *Helicobacter pylori*.[125] Indeed, treatment of this infection offers relief to late stage cachexia in PD patients receiving L-dopa.[126] *Helicobacter pylori*-infected PD patients showed reduced L-dopa absorption and increased clinical disability,[127] whereas treatment of this infection increased L-dopa absorption and decreased clinical disability.[128] *H. pylori* may not be directly involved in the pathogenesis of PD, but its systemic presence could affect the progression and treatment of PD, probably by stimulating inflammation and autoimmunity.[128]

Chronic infections in PD have been linked to inflammation and autoimmune responses.[129-131] Experimental models of PD have been developed using neurological viral or bacterial infections to initiate the pathogenic process.[132, 133] Spirochetes have also been found in Lewy bodies of PD patients.[30] Other infections, such as viral encephalitis,[134] AIDS-associated opportunistic infections of the basal ganglia,[135] coronavirus,[136] among other infections,[68, 137, 138] have been found in PD and could be important in stimulating inflammation and autoimmune responses. It has been stressed that additional research will be necessary to establish whether a causal link exists between PD and chronic infections.[139]

Neurobehavioral diseases

Autism spectrum disorders

ASD, such as autism, Asperger's syndrome, etc., are neurobehavioral diseases of primarily the young where patients

generally suffer from an inability to communicate properly, form relationships with others and respond appropriately to their environment. Such patients do not all share the same signs and symptoms but tend to share certain social, communication, motor and sensory problems that affect their behavior in predictable ways. These patients often display repetitive actions and develop troublesome fixations with specific objects, and they are often painfully sensitive to certain sounds, tastes and smells.[140, 141]

ASD cases are likely to be caused by multiple factors, including genetic defects, heavy metal, chemical and biological exposures, among other important events, which are probably different in each patient. ASD patients appear to have similarities in genetic defects and environmental exposures that are important in patient morbidity or in illness progression.[5-8, 140-142]

Chronic infections appear to be an important element in the development of ASD.[6, 16, 143, 144] In ASD patients more than 50 different bacterial, viral and fungal infections have been found,[6] some apparently more important than others in causing symptoms. It has been known for some time that ASD patients have a number of nonspecific chronic signs and symptoms, such as fatigue, headaches, gastrointestinal, vision problems, occasional intermittent low-grade fevers and other signs and symptoms that are generally excluded in the diagnosis of ASD but are consistent with the presence of infections.[143] Indeed, increased titres to various viruses as well as bacterial and fungal infections have been commonly seen in ASD patients.[6, 16, 19, 143-145] Not withstanding these reports, epidemiological evidence for an association of childhood infections in the first two years of life and ASD has been mixed.[146]

Environmental exposures to chemicals and heavy metals also appear to be important in the development of ASD.[140, 141, 147, 148] The relationship between ASD and heavy metals may involve the role of multiple vaccines in ASD pathogenesis.[130, 141] ASD patients often show their first signs and symptoms after multiple childhood immunizations, and the sharp increase in Autism rates occurred only after the multiple MMR vaccine came into widespread use.[141] In some states in the U.S. children receive as many as 33 vaccines before they can enroll in school.[140] Such vaccines can contain mercury and other toxic preservatives, and some may also contain contaminating bacteria, as found in veterinary vaccines.[149]

There are very few studies that have followed the transmission of infections and subsequent autism. Previously we found that veterans of the Gulf War with chronic fatiguing illnesses (Gulf War illnesses, GWI) exhibited multiple nonspecific signs and symptoms similar to chronic fatigue syndrome/myalgic encephalomyopathy (CFS/ME).[150, 151] After returning to the home with GWI, their children subsequently became symptomatic, and these children were often diagnosed with ASD.[152, 153] Symptomatic children (mostly diagnosed with ASD) were infected with the same *Mycoplasma* species, *M. fermentans*, that was found in the veterans and their symptomatic family members, and this was not seen in aged-matched control subjects or in military families without GWI. In the GWI families some non-symptomatic family members did have mycoplasmal infections (~10%), but this was not significantly different from the incidence of mycoplasmal infections in healthy control subjects.[152, 153]

Subsequently ASD patients who were not in military families were examined for systemic mycoplasmal infections.[153] The majority (~54%) were positive for mycoplasmal infections. However, in contrast to the children of GWI patients who for the most part had only *M. fermentans*, the civilian children tested positive for a variety of *Mycoplasma* species. We also tested a few siblings without apparent signs and symptoms, and for the most part few had these infections.[153] In another study we examined the blood of ASD patients from Central and Southern California and found that a large subset (>58%) of patients showed evidence of *Mycoplasma* infections compared to age-matched control subjects (Odds Ratio=13.8, $p<0.001$).[19] ASD patients were also examined for *C. pneumoniae* (8.3% positive, Odds Ratio=5.6, $p<0.01$) and HHV-6 (29.2% positive, Odds Ratio=4.5, $p<0.01$). The results indicated that a large subset of ASD patients display evidence of bacterial and/or viral infections (Odds Ratio=16.5, $p<0.001$).[19]

ASD patients have been examined for *B. burgdorferi* infections.[154] Various studies revealed that 22-30% of ASD patients (N=76) have *Borrelia* infections.[6, 154] The incidence of *Borrelia* infections in ASD patients may be related to Lyme disease distribution, with some Lyme-intense areas having high prevalence, and other areas having a low prevalence. Other infections, such as Lyme-associated *Bartonella, Babesia, Ehrlichia* and non-Lyme-associated CMV, *Plasmodium* species, *Toxoplasma* species and *Treponema* species may also be associated with ASD.[6]

Final comments to part 1

When neurological symptoms are present, infections of the CNS must be considered. Brain infections can stimulate glial responses, and the presence of viral and bacterial infections in nerve cells, can stimulate autoimmune responses against nerve cell antigens as well as the infections within them.[155] For example, in MS some 20 different bacterial and viral infections have been found, but the link between these infections and the pathogenesis of MS is still being debated.[16, 47, 75] One or even a few types of infections cannot be causally linked to MS, and the reason for this is that there may be too many possibilities. No one infection or a group of infections needs to be the trigger in MS to be important in the pathogenesis of MS. In time combinations of certain infections may eventually be identified at least in a subset of MS patients, and this will allow the development of new therapeutic approaches for many MS patients that are not recognized today.

One problem that is rarely discussed is the apparent disparity between the laboratory results from different laboratories. Often different laboratories cannot agree on types of infections found in various chronic diseases.[47] There are a number of reasons for this, including differences in the source of materials, qualities of reagents and techniques used.[16] Some procedures, such as PCR, have specific challenges that must be overcome in the handling of specimens, their stability, presence of interfering substances, contamination, sensitivity and specificity of the tests and interpretation of the results. Variability in results from different laboratories will remain a problem unless research groups work closely together to solve these problems. One example of how this has been overcome is a multi-centre research study on the presence of *C. pneumoniae* in the cerebrospinal fluid of clinically defined, mono-symptomatic MS patients.[156] Sriram et al.[156] conducted this diagnostic trial with good concordance of results between different laboratories. Cooperative studies such as this should eventually alleviate discrepancies in the types of infections found by different research groups.

This review continues in Part 2 with psychiatric diseases, autoimmune diseases, fatiguing illnesses, and other infectious diseases with neurological aspects and an overall discussion of the topic. [157]

COMPETING INTERESTS
None Declared

AUTHOR DETAILS
GARTH L. NICOLSON, Department of Molecular Pathology, The Institute for Molecular Medicine, Huntington Beach, California 92647, USA
JORG HAIER, Department of General and Visceral Surgery, University Hospital, Münster 48149, Germany
CORRESSPONDENCE: Prof. Garth L. Nicolson, Office of the President, The Institute for Molecular Medicine, P.O. Box 9355, S. Laguna Beach, California, 92652 USA
Email: gnicolson@immed.org

REFERENCES

1.Nicolson GL, Nasralla M, Haier J, et al. Mycoplasmal infections in chronic illnesses: Fibromyalgia and Chronic Fatigue Syndromes, Gulf War Illness, HIV-AIDS and Rheumatoid Arthritis. Med Sentinel1999; 4: 172-176.
2.Bertram L, Tanzi RE. The genetic epidemiology of neurodegenerative disease. J ClinInvestig 2005; 115: 1449-1457.
3.Griffin WS. Inflammation and neurodegenerative diseases. Am J Clin Nutrit 2006; 83: 470S-74S.
4.Nicolson GL, Haier J, Nasralla M, et al. Mycoplasmal infections in Chronic Fatigue Syndrome, Fibromyalgia Syndrome and Gulf War Illness. J Chronic Fatigue Syndr 2000; 6(3): 23-39.
5.Keen D, Ward S. Autistic Spectrum Disorder. Autism 2004; 8: 39-58.
6.Bransfield RC. Preventable cases of autism: relationship between chronic infectious diseases and neurological outcome. Pediat Health 2009; 3(2): 125-140.
7.Fatemi SH, Reutiman TJ, Folsom TD, Sidwell RW. The role of cerebellar genes in pathology of autism and schizophrenia. Cerebellum 2008; 99: 56-70.
8.Muhle R, Trentacoste SV, Rapin I. The genetics of autism. Pediatr2004; 113: 72-86.
9.Muravchick S, Levy RJ. Clinical implications of mitochondrial dysfunction. Anesthesiol 2006; 105: 819-837.
10.Ischiropoulos H, Beckman JS. Oxidative stress and nitration in neurodegeneration: cause, effect or association? J Clin Investig2003; 111: 163-169.
11.Kern JK, Jones AM. Evidence of toxicity, oxidative stress and neuronal insult in autism. J Tox Environ Health B Crit Rev 2005; 9: 485-499.
12.Larsson HJ, Eaton WW, Madsen KM, et al. Risk factors for autism: perinatal factors, parental psychiatric history and socioeconomic status. Am J Epidemiol 2005; 101: 916-925.
13.James SJ, Cutler P, Melnyk S, et al. Metabolic markers of increased oxidative stress and methylation capacity in children with autism. Am J Clin Nutrit 2004; 80: 1611-1617.
14.Deth R, Muratore C, Benzercry J, Power-Charnitsky VA, Waly M. How environmental and genetic factors combine to cause autism: a redox/methylation hypothesis. Neurotoxicol 2008; 29: 190-201.
15.Mattson MP. Infectious agents and age-related neurodegenerative disorders. Ageing Res Rev 2004; 3: 105-120.
16.Nicolson GL. Chronic infections in neurodegenerative and neurobehavioral diseases. Lab Med 2008; 39(5): 291-299.
17.Bazala E, Renda J. Latent Chlamydial infections: the probably cause of a wide spectrum of human diseases. Med Hypotheses 2005; 65: 578-584.
18.Koch AL. Cell wall-deficient (CWD) bacterial pathogens: could amyotrophic lateral sclerosis (ALS) be due to one? Crit Rev Microbiol 2003; 29: 215-221.
19.Nicolson GL, Gan R, Nicolson NL, Haier J. Evidence for *Mycoplasma, Chlamydia pneunomiae* and HHV-6 co-infections in the blood of patients with Autism Spectrum Disorders. J Neurosci Res 2007; 85: 1143-1148.
20.Nicolson GL, Nasralla M, Gan R, et al. Evidence for bacterial (*Mycoplasma, Chlamydia*) and viral (HHV-6) co-infections in chronic fatigue syndrome patients. J Chronic Fatigue Syndr 2003; 11(2): 7-20.
21.Williams DB, Windebank AJ. Motor neuron disease (Amyotrophic Lateral Sclerosis). Mayo Clinic Proc1991; 66: 54-82.
22.Swash M, Schwartz MS. What do we really know about Amyotrophic Lateral Sclerosis? J Neurol Sci 1992; 113: 4-16.
23.Walling AD. Amyotrophic Lateral Sclerosis: Lou Gehrig's Disease. Am Family Physician 1999; 59: 1489-1496.
24.Berger MM, Kopp N, Vital C, et al. Detection and cellular localization of enterovirus RNA sequences in spial cord of patients with ALS. Neurology 2000; 54: 20-25.
25.Walker MP, Schlaberg R, Hays AP, et al. Absence of echovirus sequences in brain and spinal cord of amyotrophic lateral sclerosis patients. Ann Neurol 2001; 49: 249-253.
26.Nix WA, Berger MM, Oberste MS, et al. Failure to detect enterovirus in the spinal cord of ALS patients using a sensitive RT-PCR method. Neurology 2004; 62: 1372-1377.
27.Bibbs CJ Jr, Gajdusek DC. Amyotrophic lateral sclerosis, Parkinson's disease and the amyotrophic lateral sclerosis-Parkinsonism-dementia complex on Guam: a review and summary of attempts to demonstrate infection as the aetiology. J Clin Pathol 1972; 6(suppl): 132-140.
28.Nicolson GL, Berns P, Nasralla M, et al. High frequency of systemic mycoplasmal infections in Gulf War veterans and civilians with Amyotrophic Lateral Sclerosis (ALS). J Clin Neurosci 2002; 9: 525-429.
29.Flores-Rio de la Loza LJ, Ordonez-Lozano G, Pineda-Olvera B. Determination of systemic infections due to *Mycoplasma* in patients with clinically defined amyotrophic lateral sclerosis. Rev Neurol 2005; 41: 262-267.
30.Halperin JJ, Kaplan GP, Brazinsky S, et al. Immunologic reactivity against *Borrelia burgdorferi* in patients with motor neuron disease. Arch Neurol 1990; 47: 586-594.
31.Hansel Y, Ackerl M, Stanek G. ALS-like sequelae in chronic neuroborreliosis. Wien Med Wochensch 1995; 147: 186-188.
32.MacDonald AB. Spirochetal cyst forms in neurodegenerative disorders, hiding in plain site. Med Hypotheses2006; 67: 819-832.
33.M. Qureshi M, Bedlack RS, Cudkowicz ME. Lyme serology in amyotrophic lateral sclerosis. Muscle Nerve 2009; in press.
34.Rosen DR, Siddique T, Patterson D, et al. Mutations in Cu/Zn superoxide dismutase gene are associated with familial amyotrophic lateral sclerosis. Nature 1993; 362: 59-62.
35.Rothstein JD, Martin LJ, Kuncl RW. Decreased glutamate transport by the brain and spinal cord in Amyotrophic Lateral Sclerosis. N Eng J Med 1992; 326: 1464-1468.
36.Hugan J. ALS therapy: targets for the future. Neurol 1996; 47(suppl 4): S251-S254.
37.Ince PG, Codd GA. Return of the cycad hypothesis—does the amyotrophic lateral sclerosis/parkinsonism dementia complex (ALS/PDC) of Guam have new implications for global health? Neuropathol Appl Neurobiol 2005; 31: 345-353.
38.Andrews WD, Tuke PW, Al-Chalabi A, et al. Detection of reverse transcriptase activity in the serum of patients with motorneurone disease. J Med Virol 2000; 61: 527-532.
39.A. L. McCormick AL, Brown RH Jr, Cudkowicz ME, et al. Quantification of reverse transcriptase in ALS and elimination of a novel retroviral candidate. Neurol 2008; 70: 278-283.
40.Stipa G, Taiuti R, de Scisciolo G, et al. Sporadic amyotrophic lateral sclerosis as an infectious disease a possible role of cyanobacteria? Med Hypotheses 2006; 67: 1363-1371.
41.Corcia P, Prodat PF, Salachas F, et al. Causes of death in a post-mortem series of ALS patients. Amyotrophic Lateral Sclerosis 2008; 9: 59-62.
42.Sobel RA. The pathology of multiple sclerosis. Neurol Clinic 1995; 13: 1-21.

43.Bruck W. Clinical implications of neuropathological findings in multiple sclerosis. J Neurol 2005; 252(suppl 3): 10-14.
44.Herrera BM, Cader MZ, Dyment DA, et al. Multiple sclerosis susceptibility and the X chromosome. Multiple Sclerosis 2007; 13: 856-864.
45.Barcellos LF, Oksenberg JR, Green AJ, et al. Genetic basis for clinical expression in multiple sclerosis. Brain 2002; 125: 150-158.
46.Currier RD, Eldridge R. Possible risk factors in multiple sclerosis as found in a national twin study. Arch Neurol 1982; 39: 140-44.
47.Greenlee JE, Rose JW. Controversies in neurological infectious diseases. Semin Neurol 2000; 20: 375-386.
48.Gilden DH. Infectious causes of multiple sclerosis. Lancet Neurol 2005;4: 195-202.
49.Malmone D, Gregory S, Arnason BG, et al. Cytokine levels in the cerebrospinal fluid and serum of patients with multiple sclerosis. J Neuroimmunol 1991; 32: 87-74.
50.Woodroofe MN. Cytokine production in the central nervous system. Neurol 1995;45 (Suppl 6): S6-S10.
51.S. Sriram S, C. Stratton and W. Mitchell, Multiple sclerosis associated with *Chlamydia pneumoniae* infection of the CNS. Neurol 1998; 50: 571-572.
52.Sriram S, Stratton CW, Yao S, et al. *Chlamydia pneumoniae* infection of the central nervous system in multiple sclerosis. Ann Neurol 1999; 46: 6-14.
53.Yao S-Y, Stratton CW, Mitchell WM. CFS oligoclonal bands in MS include antibodies against *Chamydophila* antigens. Neurol 2001; 51: 1168-1176.
54.Contini C, Seraceni S, Castellazzi M, et al. *Chlaymdophila pneumoniae* DNA and mRNA transcript levels in peripheral blood mononuclear cells and cerebrospinal fluid of patients with multiple sclerosis, Neurosci Res 2008; 62: 58-61.
55.Sriram S, Ljunggren-Rose A, Yao S-Y, et al. Detection of chlamydial bodies and antigens in the central nervous system of patients with multiple sclerosis. J Infect Dis 2005; 192: 1219-1228.
56.Contini C, Cultrera R, Seraceni S, et al. Cerebrospinal fluid molecular demonstration of *Chlamydia pneumoniae* DNA is associated to clinical and brain magnetic resonance imaging activity in a subset of patients with relapsing-remitting multiple sclerosis. Multiple Sclerosis 2004;10: 360-369.
57.Grimaldi LM, Pincherle A, Martinelli-Boneschi F, et al. An MRI study of *Chlamydia pneumoniae* infection in Italian multiple sclerosis patients. Multiple Sclerosis 2003; 9: 467-471.
58.Dong-Si T, Weber J, Liu YB, et al. Increased prevalence of and gene transcription by *Chlamydia pneumoniae* in cerebrospinal fluid of patients with relapsing-remitting multiple sclerosis. J Neurol 2004; 251: 542-547.
59.Stratton CW, Sriram S. Association of *Chlamydia pneumoniae* with central nervous system disease. Microbes Infect 2003; 5: 1249-1253.
60.Stratton CW, Wheldon DB. Multiple sclerosis: an infectious syndrome in ving *Chlamydophia pneumoniae*. Trends Microbiol 2006; 14: 474-479.
61.Layh-Schmitt G, Bendl C, Hildt U, et al. Evidence for infection with *Chlamydia pneumoniae* in a subgroup of patients with multiple sclerosis. Ann Neurol 2000; 47: 652-655.
62.Fainardi E, Castellazzi M, Casetta MI, et al. Intrathecal production of *Chlamydia pneumoniae*-specific high affinity antibodies is significantly associated to a subset of multiple sclerosis patients with progressive forms. J Neurol Sci 2004; 217: 181-188.
63.Boman J, Roblin PM, Sundstrom P, et al. Failure to detect *Chlamydia pneumoniae* in central nervous system of patients with MS. Neurol 2000; 11: 265.
64. Pucci E, Taus C, Cartechini E, et al. Lack of *Chlamydia* infection of the central nervous system in multiple sclerosis. Ann Neurol 2000; 48: 399-400.
65.Lindsey JW, Patel S. PCR for bacterial 16S ribosomal DNA in multiple sclerosis cerebrospinal fluid. Multiple Sclerosis 2008; 14: 147-152.
66.Hammerschlag MR, Ke Z, Lu F, et al. Is *Chlamydia pneumoniae* present in brain lesions of patients with multiple sclerosis? J Clin Microbiol 2000; 38: 4274-4276.
67.Swanborg RH, Whittum-Hudson JA, Hudson AP. Infectious agents and multiple sclerosis—Are *Chlamydia pneumoniae* and human herpes virus 6 involved? J Neuroimmunol 2003; 136: 1-8.
68.Nicolson GL. Systemic intracellular bacterial infections (*Mycoplasma, Chlamydia, Borrelia* species) in neurodegenerative (Alzheimers, MS, ALS) and behavioral diseases (Autistic Spectrum Disorders). Townsend Lett 2008; 295: 74-84.
69. Casserly G, Barry T, Tourtellotte WW, Hogan EL. Absence of Mycoplasma-specific DNA sequence in brain, blood and CFS of patients with multiple sclerosis (MS): a study by PCR and real-time PCR. J Neurol Sci 2007; 253: 48-52.
70.Sanders VJ, Felisan S, Waddell A, et al. Detection of herpesviridae in postmortem multiple sclerosis brain tissue and controls by polymerase chain reaction. J Neurovirol 1996; 2: 249-58.
71.Challoner PB, Smith KT, Parker JD, et al. Plaque-associated expression of human herpesvirus 6 in multiple sclerosis. Proc Natl Acad Sci USA 1995; 92: 7440-7444.
72.Sola P, Merelli E, Marasca R, et al. Human herpesvirus-6 and multiple sclerosis: survey of anti-HHV-6 antibodies by immunofluorescence analysis and viral sequences by polymerase chain reaction. J Neurol Neurosurg Psychiat 1993; 56: 917-919.
73.Pietropaolo V, Floriti D, Mischitelli M, et al. Detection of human herpesviruses and polyomaviruses in a group of patients with relapsing-remitting multiple sclerosis. New Microbiol 2005; 28: 199-203.
74.Kuusisto H, Helkki H, Saara K, et al. Human herpes virus 6 and multiple sclerosis: a Finnish twin study. Multiple Sclerosis 2008; 14: 54-58.
75.Steiner I, Nisipianu P, Wirguin I. Infection and etiology and pathogenesis of multiple sclerosis. Curr Neurol Neurosci Rep 2001; 1: 271-76.
76.Bagert BA. Epstein-Bar virus in multiple sclerosis. Curr Neurol Neurosci Rep 2009; 9: 405-410.
77.Willis SN, Stadelmann C, Rodig SJ, et al. Epstein-Bar virus infection is not a characteristic feature of multiple sclerosis brain. Brain 2009; in press.
78.Beagley KW, Huston WM, Hansbro PM, Timms P. Chlamydial infection of immune cells: altered function and implications for disease. Crit Rev Immunol 2009; 29: 275-305.
79.Giraudon P, Bernard A. Chronic viral infections of the central nervous system: aspects of specific to multiple sclerosis. Rev Neurol (Paris) 2009; in press.
80.S. Haahr, M. Sommerlund, T. Christensen, et al. A putative new retrovirus associated with multiple sclerosis and the possible involvement of Epstein-Barr virus in this disease. Ann New York Acad Sci 1994; 724: 148-56.
81.Frykholm BO. On the question of infectious aetiologies for multiple sclerosis, schizophrenia and the chronic fatigue syndrome and the treatment with antibiotics. Med Hypotheses 2009; 72: 736-739.
82.Keller JN. Age-related neuropathology, cognitive decline and Alzheimer's Disease. Ageing Res Rev 2006; 5: 1-13.
83.Masters CL, Beyreuther K. Alzheimer's centennial legacy: prospects for rational therapeutic intervention targeting the Abeta amyloid pathway. Brain 2006; 129: 2823-2839.
84.Drachman DA. Aging of the brain, entropy, and Alzheimer Disease. Neurol 2006; 67: 1340-1352.
85.Markesbery WR, Lovell MA. Damage to lipids, proteins, DNA and RNA in mild cognitive impairment. Arch Neurol 2007; 64: 954-956.
86.Daly MP. Diagnosis and management of Alzheimer Disease. J Am Board Family Pract 1999; 12: 375-385.
87.Finch CE, Morgan TE. Systemic inflammation, infection, ApoE alleles and Alzheimer Disease: a position paper. Curr Alzheimers Res 2007; 4: 185-189.
88.Holmes C, El-Okl M, Williams AL, et al. Systemic infection, interleukin 1-beta and cognitive decline in Alzheimer's Disease. J Neurol Neurosurg Psychiat 2003; 74: 788-789.
89.Dobson CB, Wozniak MA, Itzhaki RF. Do infectious agents play a role in dementia? Trends Microbiol 2003; 11: 312-317.
90.Balin BJ, Appelt DM. Role of infection in Alzheimer's Disease. J Am Osteopath Assoc 2001; 101(suppl 12): S1-S6.
91.Yucesan C, Sriram S. *Chlamydia pneumoniae* infection of the central nervous system. Curr Opin Neurol 2001; 14: 355-359.
92.Balin BJ, Gerard HC, Arking EJ, et al. Identification and localization of *Chlamydia pneumoniae* in the Alzheimer's brain. Med Microbiol Immunol 1998; 187: 23-42.
93.Gerard HC, Dreses-Werringloer U, Wildt KS, et al. *Chlamydophila (Chlamydia) penumoniae* in the Alzheimer's brain. FEMS Immunol Med Microbiol 2006; 48: 355-366.
94.MacIntyre A, Abramov R, Hammond CJ, et al. *Chlamydia pneumoniae* infection promotes the transmigration of monocytes through human brain endothelial cells. J Neurosci Res 2003; 71: 740-750.
95.Dreses-Werringloer U, Bhuiyan M, Zhao Y, et al. Initial characterization of *Chlamydophila* (*Chlamydia*) *pneumoniae* cultured from the late-onset Alzheimer brain. Intern J Med Microbiol 2998; 299: 187-201.
96.Little CS, Hammond CJ, MacIntyre A, et al. *Chlamydia pneumoniae* induces Alzheimer-like amyloid plaques in brains of BALB/c mice. Neurobiol Aging 2004; 25: 419-429.
97.Ring RH, Lyons JM. Failure to detect *Chlamydia pneumoniae* in the late-onset Alzheimer's brain. J Clin Microbiol 2000; 38: 2591-2594.
98.Gieffers J, Reusche E, Solbach W, et al. Failure to detect *Chlamydia pneumoniae* in brain sections of Alzheimer's Disease patients. J Clin Microbiol 2000; 38: 881-882.
99.Meer-Scheerer L, Chang-Loa C, Adelson ME, et al. Lyme disease associated with Alzheimer's Disease. Curr Microbiol 2006; 52: 330-332.
100.Miklossy J, Khalili K, Gern L, et al. *Borrelia burgdorferi* persists in the brain in chronic Lyme neuroborreliosis and may be associated with Alzheimer's Disease. J Alzheimer's Dis 2004; 6: 639-649.
101.MacDonald AB. Alzheimer's Disease Braak Stage progressions: reexamined and redefined as *Borrelia* infection transmission through neural circuits. Med Hypotheses 2007; 68: 1059-1064.
102.Pappolla MA, Omar R, Saran B, et al. Concurent neuroborreliosis and Alzheimer's Disease: analysis of the evidence. Human Pathol 1989; 20: 753-757.
103.Marques AR, Weir SC, Fahle GA, et al. Lack of evidence of *Borrelia* involvement in Alzheimer's Disease. J Infect Dis 2000; 182: 1006-1007.
104.MacDonald AB. Plaques of Alzheimer's Disease originate from cysts of *Borrelia burgdorferi*, the Lyme Disease spirochete. Med Hypotheses 2006; 67: 592-600.
105.Glabe C. Intracellular mechanisms of amyloid accumulation and

pathogenesis in Alzheimer's Disease. J Molec Neurosci 2001;17: 137-145.
106.Denaro FJ, Staub P, Colmer J, et al. Coexistance of Alzheimer's Disease neuropathology with Herpes Simplex encephalitis. Cell Molec Biol 2003; 49: 1233-1240.
107.Itzhaki RF, Wozniak MA. Herpes simplex virus type 1 in Alzheimers's disease: the enemy within. J Alzheimers Dis 2008; 13: 393-405.
108.Lin WR, Shang D, Itzhaki RF. Neurotrophic viruses and Alzheimer's Disease: Interaction of Herpes Simplex type-1 virus and apolipoprotein E in the etiology of the disease. Molec Chem Neuropathol 1996; 28: 135-141.
109.Itzhaki RF, Lin WR, Shang D, et al. Herpes Simplex Virus type 1 in brain and risk of Alzheimer's Disease. Lancet 1997; 349: 241-44.
110.Shipley SJ, Parkin ET, Itzhaki RF, et al. Herpes Simplex virus interferes with amyloid precursor protein processing. BMC Microbiol 2005; 5: 48.
111.Wozniak MA, Itzhaki RF, Shipley SJ, Dobson CB. Herpes simplex virus infection causes cellular beta-amyloid accumulation and secretase upregulation. Neurosci Lett 2007; 429: 95-100.
112.Itzhaki R. Herpes simplex virus type-1, aolipoprotein E and Alzheimer disease. Herpes 2004; 11(suppl 2): 77A-82A.
113.Kountouras J, Boziki JM, Gavalas E, et al. Increased cerebrospinal fluid Helicobacter pylori antibiody in Alzheimer's disease. Intern J Neurosci 2009; 119: 765-767.
114.Robinson SR, Dobson C, Lyons J. Challenges and directions for the pathogen hypothesis of Alzheimer's disease. Neurobiol Aging 2004; 25: 629-637.
116.Wolters EC, Braak H. Parkinson's disease: premotor clinico-pathological correlations. J Neural Transmiss 2006; 70(suppl 1); 309-319.
117.Klockgether T. Parkinson's disease: clinical aspects. Cell Tissue Res 2004;318: 115-120.
118.Sulzer D. Multiple hit hypothesis for dopamine neuron loss in Parkinson's disease. Trends Neurosci 2007; 30: 244-250.
119.Fahn S. Description of Parkinson's disease as a clinical syndrome. Ann New York Acad Sci 2003; 991: 1-14.
120.Olanow CW, Arendash GW. Metals and free radicals in neurodegeneration. Curr Opin Neurol 1994; 7: 548-558.
121.Zorzon M, Capus L, Pellegrino A, et al. Familial and environmental risk factors in Parkinson's disease: a case control study in north-east Italy. Acta Neurol Scand 2002; 105: 77-82.
122.Logroscino G. The role of early life environmental risk factors in Parkinson disease: what is the evidence? Environ Health Perspect 2005; 113: 1234-1238.
123.Stoessl AJ. Etiology of Parkinson's disease. Can J Nuerol Sci 1999; 26(suppl 2): S5-S12.
124.Liu B, Gao HM, Hong JS. Parkinson's disease and exposure to infectious agents and pesticides and the occurrence of brain injuries: role of neuroinflammation. Environ Health Perspect 2003; 111: 1065-1073.
125.Jenner P, Olanow CW. The pathogenesis of cell death in Parkinson's disease. Neurol 2006; 66(suppl 4): S24-S36, 2006.
126.Dobbs RJ, Dobbs SM, Bjarnason IT, et al. Role of chronic infection and inflammation in the gastroinstestinal tract in the etiology and pathogenesis of idiopathic parkinsonism. Part 1: eradication of *Helicobacter* in the cachexia of idiopathic parkinsonism. Helicobacter 2005; 10: 267-275.
127.Pierantozzi M, Piertroiusti A, Sancesario G, et al. Reduced L-dopa absorption and increased clinical fluctuations in *Helicobacter pylori*-infected Parkinson's disease patients. Neurol Sci 2001; 22: 89-91.
128.Pierantozzi M, Piertroiusti A, Brusa L, et al. *Helicobacter pylori* eradication and L-dopa absorption in patients with PD and motor fluctuations. Neurol 2006; 66: 1824-1829.
129.Barker RA, Cahn AP. Parkinson's disease: an autoimmune process. Intern J Neurosci 1988; 43: 1-7.
130.Wersinger C, Sidhu A. An inflammatory pathomechanism for Parkinson's disease. Curr Med Chem 2006; 13: 591-602.
131.Arai H, Furuya T, Mizuno Y, Mochizuki H. Inflammation and infection in Parkinson's disease. Histol Histopathol 2006; 21: 673-678.
132.Ogata A, Tashiro K, Nukuzuma S, et al. A rat model of Parkinson's disease induced by Japanese encephalitis virus. J Neurovirol 1997;3: 141-147.
133.Beaman BL, Canfield D, Anderson J, et al. Site-specific invasion of the basal ganglia by *Nocaardia asteriodes* GUH-2. Med Microbiol Immunol 2000; 188: 161-168.
134.Ickenstein GW, Klotz JM, Langohr HD. Virus encepthalitis with symptomatic Parkinson syndrome, diabetes insipidus and panhypopituitarism, Fortschr Neurol Psychiat 1999;67: 476-481.
135.Maggi P, de Mari M, Moramarco A, et al. Parkinsonism in a patient with AIDS and cerebral opportunistic granulomatous lesions. Neurol Sci 2000; 21: 173-176.
136.E. Fazzini E, Fleming J, Fahn S. Cerebrospinal fluid antibodies to coronavirus in patients with Parkinson's disease. Movment Disord 1992; 7: 153-158.
137.Alasia DD, Asekomeh GA, Unachuku CN. Parkinsonism induced by sepsis: a case report. Niger J Med 2006; 15: 333-336.
138.Fiszer U, Tomik B, Grzeslowski P, et al. The antibodies against *Bordetella pertussis* in sera of patients with Parkinson's disease and other non-neurological diseases. Acta Neurol Scand 2004; 110: 113-117.
139.Richy F, Mégraud F. *Helicobacter pylori* infection as a cause of extra-digestive diseases: myth or reality? Gastroenterol Clin Biol 2003; 27: 459-466.
140.Rimland B. The Autism epidemic, vaccinations and mercury. J Nut Environ Med 2000; 10: 261–266.
141.Downing D. Mercury again. J Nut Environ Med 2000; 10: 267–269.
142.Muhle R, Trentacoste SV, Rapin I. The genetics of autism. Pediatr 2004; 113: 472-486.
143.Takahashi H, Arai S, Tanaka-Taya K, et al. Autism and infection/immunization episodes in Japan. Jap J Infect Dis 2001; 54: 78-79.
144. Libbey JE, Sweeten TL, McMahon WM, et al. Autistic disorder and viral infections. J Neurovirol 2005; 11: 1-10.
145. Yamashita Y, Fujimoto C, Nakajima E, et al. Possible association between congenital cytomegalovirus infection and autistic disorder. J Autism Develop Disord 2003; 33: 355-359.
146.Rosen J, Yoshida CK, Croen LA. Infection in the first 2 years of life and austim spectrum disorders. Pediatr 2007; 119: 61-69.
147Colborn T. Neurodevelopment and endocrine disruption. Environ Health Perspect 2004; 112: 944-949.
148.R. F. Palmer, S. Blanchard, Z. Stein, et al., Environmental mercury release, special education rates and autism disorder: an ecological study of Texas, *Health and Place*, . 12, no. 2, 203-209, 2006.
149.Thornton D. A survey of Mycoplasma detection in veterinary vaccines. Vaccine 1986; 4: 237–240.
150.Nicolson GL, Nicolson NL. Chronic fatigue illness and Operation Desert Storm. J Occupat Environ Med 1996; 38: 14-16.
151.Nicolson GL, Nicolson NL. Diagnosis and treatment of mycoplasmal infections in Persian Gulf War Illness-CFIDS patients. Intern J Occupat Med Immunol Tox 1996; 5: 69–78.
152.Nicolson GL, Nasralla M, Nicolson NL, et al. High prevalence of mycoplasmal infections in symptomatic (Chronic Fatigue Syndrome) family members of mycoplasma-positive Gulf War Illness patients. J Chronic Fatigue Syndr 2003; 11(2): 21-36.
153.Nicolson GL, Berns P, Gan R et al. Chronic mycoplasmal infections in Gulf War veterans' children and autism patients. Med Veritas 2005; 2: 383-387.
154.Bransfield RC, Wulfman JS, Harvey WT, Usman AI. The association between tick-borne infections, Lyme borreliosis and autism spectrum disorders. Med Hypotheses 2008; 70: 967-974.
155.Sherbet G. Bacterial infections and the pathogenesis of autoimmune conditions. Br J Med Practit 2009; 2(1): 6-13.
156. Sriram S, Yao S-Y, Stratton C, et al. Comparative study of the presence of *Chlamydia pneumoniae* in cerebrospinal fluid of patients with clinically definite and monosymptomatic multiple sclerosis. Clin Diag Lab Immunol 2002; 9: 1332-1337.
157.Nicolson GL, Haier J. Role of chronic bacterial and viral Infections in neurodegenerative, neurobehavioral, psychiatric, autoimmune and fatiguing illnesses: Part 2. Br J Med Practit 2009; in press