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 fatigue 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.

Introduction
Chronic infections appear to be common features of various diseases, including neurodegenerative, psychiatric and neurobehavioral diseases, autoimmune diseases, fatigue and other conditions. 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. For the most part, the causes of these neurological diseases remain largely unknown. 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. 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. 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. 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. 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. Such oxidative stress can be caused by a variety of environmental toxic insults, and when combined with genetic factors could result in pathogenic changes.

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. 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.\textsuperscript{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.\textsuperscript{4, 15, 16, 19, 20}

\textit{Amyotrophic lateral sclerosis}

Amyotrophic lateral sclerosis (ALS) is an adult-onset, idiopathic, progressive neurodegenerative disease that affects both central and peripheral motor neurons.\textsuperscript{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.\textsuperscript{21, 22} The overall clinical picture of ALS can vary, depending on the location and progression of pathological changes.\textsuperscript{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).\textsuperscript{24} However, others have failed to detect enterovirus sequences in spinal cord samples from patients with or without ALS.\textsuperscript{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.\textsuperscript{27}

Using PCR methods systemic mycoplasmal infections have been found in a high percentage of ALS patients.\textsuperscript{28, 29} We found that 100\% of Gulf War veterans from three nations diagnosed with ALS had systemic mycoplasmal infections.\textsuperscript{28} All but one patient had \textit{M. fermentans}, and one veteran from Australia had a systemic \textit{M. genitalium} infection. In nonmilitary ALS patients systemic mycoplasmal infections of various species were found in approximately 80\% of cases.\textsuperscript{29} Of the mycoplasma-positive civilian patients who were further tested for various species of Mycoplasma, most were positive for \textit{M. fermentans} (59\%), but other Mycoplasma species, such as \textit{M. hominis} (31\%) and \textit{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.\textsuperscript{28} In another study 50\% of ALS patients showed evidence of systemic \textit{Mycoplasma} species by PCR analysis.\textsuperscript{29}

ALS patients who live in certain areas often have infections of \textit{Borrelia burgdorferi}, the principal aetiological agent in Lyme disease. For example, ALS patients who live in a Lyme-prevalent area were examined for \textit{B. burgdorferi} infections, and over one-half were found to be seropositive for \textit{Borrelia} compared to 10\% of matched controls.\textsuperscript{30} In addition, some patients diagnosed with ALS were subsequently diagnosed with neuroborreliosis.\textsuperscript{31} Spirochetal forms have been observed in the brain tissue of ALS patients and in patients with other neurodegenerative diseases.\textsuperscript{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 \textit{Borrelia} infections.\textsuperscript{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.\textsuperscript{34, 35}

Additional chronic infections have been found in ALS patients, including human herpes virus-6 (HHV-6), \textit{Chlamydia pneumoniae} and other infections.\textsuperscript{36–37} There is also a suggestion that retroviruses might be involved in ALS and other motorneuron diseases.\textsuperscript{38} McCormick et al.\textsuperscript{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.\textsuperscript{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).\textsuperscript{24, 27–40} None of these hypotheses have been ruled out or are exclusive, and ALS may have a complex pathogenesis involving multiple factors.\textsuperscript{28, 36}

It is tempting to propose that infections play an important role in the pathogenesis or progression of ALS.\textsuperscript{26, 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,\textsuperscript{28} infections likely promote disease progression. Indeed, when Corcia et al.\textsuperscript{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.

\textit{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{52, 65} The clinical manifestations of demyelination, 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.\textsuperscript{43}

There is strong evidence for a genetic component in MS.\textsuperscript{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.\textsuperscript{46}

MS has been linked to chronic infection(s).\textsuperscript{46, 67} For example, patients show immunological and cytokine elevations consistent with chronic infections.\textsuperscript{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.\textsuperscript{44, 45, 47, 48, 51} One of the most common findings in MS patients is the presence of \textit{C. pneumoniae} antibodies and DNA in their cerebrospinal fluid.\textsuperscript{51-53} By examining relapsing-remitting and progressive MS patients for the presence of \textit{C. pneumoniae} in cerebrospinal fluid by culture, PCR and immunoglobulin reactivity Sriram et al.\textsuperscript{52} were able to identify \textit{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.\textsuperscript{52} Examination of MS patients for oligoclonal antibodies against \textit{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 \textit{C. pneumoniae} elemental body antigens.\textsuperscript{53} Similarly, Contini et al.\textsuperscript{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.\textsuperscript{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 \textit{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.\textsuperscript{59} They also used different nested PCR methods to examine additional \textit{C. pneumoniae} gene sequences in the cerebrospinal fluid of 72 MS patients and linked these results to MS-associated lesions seen by MRI.\textsuperscript{56}

MRI was used by Grimaldi et al.\textsuperscript{57} to link the presence of \textit{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.\textsuperscript{58} In addition, higher rates of \textit{C. pneumoniae} transcription were found by Dong-Si et al.\textsuperscript{58} in the cerebrospinal fluid of 84 MS patients. The data above and other studies strongly support the presence of \textit{C. pneumoniae} in the brains of MS patients,\textsuperscript{59-64} at least in the more progressed subset of MS patients.

Other research groups have also found evidence for \textit{C. pneumoniae} in MS patients but at lower incidence. Fainardi et al.\textsuperscript{62} used ELISA techniques and found that high-affinity antibodies against \textit{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 \textit{C. pneumoniae} antibodies was also found in other inflammatory neurological disorders; thus it was not found to be specific for MS.\textsuperscript{62}

In contrast to the studies above, other researchers have not found the presence of \textit{C. pneumoniae} or other bacteria in the brains of MS patients.\textsuperscript{65-67} For example, Hammerschlag et al.\textsuperscript{66} used nested PCR and culture to examine frozen brain samples from MS patients but could not find any evidence for \textit{C. pneumoniae}. However, in one study \textit{C. pneumoniae} was found at similar incidence in MS and other neurological diseases, but only MS patients had \textit{C. pneumoniae} in their cerebrospinal fluid.\textsuperscript{64} Swanborg et al.\textsuperscript{67} reviewed the evidence linking \textit{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 \textit{C. pneumoniae}, is that multiple co-infections could be involved rather than one specific infection. In addition to \textit{C. pneumoniae} found in most studies, MS patients could also have \textit{Mycoplasma} species, \textit{B. burgdorferi} and other bacterial infections as well as viral infections.\textsuperscript{68} When multiple infections are considered, it is likely that >90% of MS patients have obligate intracellular bacterial infections caused by \textit{Chlamydia} (\textit{Chlamydiophila}), \textit{Mycoplasma}, \textit{Barrelia} or other intracellular bacterial infections. These infections were found only singly and at very low incidence in age-matched subjects.\textsuperscript{68} In spite of these findings, others did not find evidence of \textit{Mycoplasma} species in MS brain tissue, cerebrospinal fluid or peripheral blood.\textsuperscript{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. Using PCR Sanders et al. 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. Using sequence difference analysis and PCR Challoner et al. 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. Using immunofluorescent and PCR methods HHV-6 DNA has also been found in peripheral leukocytes in the systemic circulation of MS patients. However, using PCR methods, others did not find herpes viruses in the peripheral blood or CSF of MS patients. 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. The difference in MS patients could be the presence of multiple infections, including EBV. Recently Willis et al. 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. Although a few studies did not come to this conclusion, 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. Infections may also invade immune cells and alter immune cell function in a way that promotes inflammation and autoimmune activity. 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. As in other neurodegenerative diseases, multiple factors appear to be involved in the pathogenesis of MS.

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.

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. 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.

Recently AD brain infections have become important. For example, one pathogen that has attracted considerable attention is C. pneumoniae. 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. C. pneumoniae has also been found in nerve cells in close proximity to neurofibrillary tangles.

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. C. pneumoniae has been found in the brains of most AD patients, and it has been cultured from AD brain tissue. Injection of C. pneumoniae into mice stimulates beta amyloid plaque formation. Although the data are compelling, some investigators have not found C. pneumoniae infections in AD.

AD patients also have other bacterial infections, such as B. burgdorferi. Using serology, culture, Western blot and immunofluorescence methods this Lyme Disease infection has been examined in AD. Not all researchers, however, have found evidence of B. burgdorferi in AD patients. 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. Multiple reports indicate that AD nerve cells are often positive for B. burgdorferi, indicating that this...
in intracellular bacteria could be important in the pathogenesis of AD.\textsuperscript{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.\textsuperscript{105} That infections may be important in AD pathogenesis is attractive; however, some negative reports have not confirmed the presence of infections like \textit{B. burgdorferi} in AD patients.\textsuperscript{99-101} This suggests that the infection theory, although compelling, remains controversial.\textsuperscript{102, 105}

Herpes virus infections have also been found in AD, especially HSV-1.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{112}

Other infections have been found in AD patients, for example, \textit{C. pneumoniae}, \textit{Helicobacter pylori} amongst others.\textsuperscript{113} It has been proposed that such infections may act as a trigger or co-factor in AD.\textsuperscript{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.\textsuperscript{114}

\textit{Parkinson’s disease}

Parkinson’s disease (PD) is characterized by akinesia, muscular rigidity and resting tremor.\textsuperscript{103} In addition, autonomic dysfunction, olfactory disturbances, depression, sensory and sleep disturbances and frequently dementia characterize this disease.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{102} Inflammation has also been associated with PD pathology.\textsuperscript{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.\textsuperscript{118, 120} A case-control study indicated that multiple environmental factors and genetic background were statistically related risk factors for PD.\textsuperscript{121} Prominent among these were long-term toxic exposures and trauma early in life.\textsuperscript{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.\textsuperscript{123, 124}

A role for chronic infections in PD pathogenesis has been proposed.\textsuperscript{125, 124} One infection found in PD that has aroused considerable interest is the presence of chronic gastrointestinal \textit{Helicobacter pylori}.\textsuperscript{125} Indeed, treatment of this infection offers relief to late stage cachexia in PD patients receiving L-dopa.\textsuperscript{126} \textit{Helicobacter pylori}-infected PD patients showed reduced L-dopa absorption and increased clinical disability,\textsuperscript{127} whereas treatment of this infection increased L-dopa absorption and decreased clinical disability.\textsuperscript{128} \textit{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.\textsuperscript{128}

Chronic infections in PD have been linked to inflammation and autoimmune responses.\textsuperscript{129-131} Experimental models of PD have been developed using neurological viral or bacterial infections to initiate the pathogenic process.\textsuperscript{132, 133} Spirochetes have also been found in Lewy bodies of PD patients.\textsuperscript{60} Other infections, such as viral encephalitis,\textsuperscript{134} AIDS-associated opportunistic infections of the basal ganglia,\textsuperscript{135} coronavirus,\textsuperscript{136} among other infections,\textsuperscript{68, 157, 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.\textsuperscript{139}

\textbf{Neurobehavioral diseases}

\textit{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, 14, 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.145 Indeed, increased titres to various viruses as well as bacterial and fungal infections have been commonly seen in ASD patients.6, 14, 18, 145-147 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.13, 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 fatigue illnesses (Gulf War illnesses, GWI) exhibited multiple nonspecific signs and symptoms similar to chronic fatigue syndrome/myalgic encephalomyopathy (CFS/ME).139, 151 After returning to the home with GWI, their children subsequently became symptomatic, and these children were often diagnosed with ASD.152, 155 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 age-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, 155

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.155 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.144 Various studies revealed that 22-30% of ASD patients (N=76) have Borrelia infections.6, 156 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, Plasmodion 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, 73 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. Oftentimes, different laboratories cannot agree on types of infections found in various chronic diseases. There are a number of reasons for this, including differences in the source of materials, qualities of reagents and techniques used. 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 *P. aeruginosa* in the cerebrospinal fluid of clinically defined, mono-symptomatic MS patients. Siriam et al. 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.

**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

CORRESPONDENCE: 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**


