Recent Research on the Neuropsychiatric Aspects of Infectious Diseases

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Since the beginning of the twentieth century, with the discovery of the spirochetal cause of syphilis, there has been evidence for the role of infectious agents in neuropsychiatric disorders. Organisms known to cause neuropsychiatric symptoms include the spirochetes *Borrelia, Treponema and Leptospira*, which can invade a patient's central nervous system. The role of *Treponema pallidum* in neurosyphilis was first documented in the early 1900's, while the neuropsychiatric aspects of Lyme disease (caused by *Borrelia burgdorferi*) were not discovered until much later, in the early 1960's and 1970's. Other organisms known to cause neurologic and psychiatric complications are viral, such as the human immunodeficiency virus (HIV, the causative agent of AIDS) and certain strains of influenza. In addition, there is evidence that numerous other viruses, such as rabies, rubella, Epstein-Barr virus, and other herpes viruses play a role in these types of disorders. This paper examines several infectious agents that are believed to cause neurologic or psychiatric problems and the current research that is being done in these areas. It also reviews some of the current research on chronic fatigue syndrome, a neuropsychiatric disorder for which the causative agent is yet unclear, and examines the possibility of an infectious etiology.

Infectious Agents Implicated in Neuropsychiatric Disorders

Group A β-hemolytic streptococcus

Several neuropsychiatric and movement disorders have been described in children following infection with group A β-hemolytic streptococcus. Among these are Sydenham's chorea and PANDAS, or pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections. Both of these disorders tend to affect children mostly, as streptococcal infections are quite common in childhood. Sydenham's chorea is a disorder characterized by uncoordinated motor movements, hypotonia, gait disturbance, loss of fine motor control, slurred speech, and in some cases personality changes (Aron *et al.*, 1965). PANDAS is a collection of syndromes characterized by sudden onset of tics, Tourette syndrome, or obsessive-compulsive disorder following group A β-hemolytic streptococcus infection (Pavone *et al.*, 2006).

A recent community-based, longitudinal study followed 693 children for eight months to determine the prevalence of group A β-hemolytic streptococcal infections and the association with tics, behavior disorders and movement disorders (Murphy *et al.*, 2007). The researchers found that children with repeated streptococcal infection had a significantly higher rate of behavioral symptoms and distal choreiform movements. They also demonstrated a higher rate of streptococcal infection during the fall months, along with a significantly higher rate of tics, behavioral problems and choreiform movements during these same months.

In children with obsessive-compulsive symptoms, it has been hypothesized that a brain autoimmune disorder may develop after streptococcal infection. Recently Dale *et al.* (2005) examined children with obsessive-compulsive disorder (OCD) for anti-basal

ganglia antibodies (ABGA) using enzyme-linked immunosorbent assay (ELISA) and Western blotting. They found that AGBA binding on ELISA was significantly higher in children with OCD than in controls with non-neurologic autoimmune disorders, controls with other neurologic or movement disorders, and controls with uncomplicated streptococcal infections. Children with OCD also had a significantly higher rate of positive antibody binding on Western blot. These findings strengthen previous research in this area, but more studies are needed to determine the characteristics of children at risk for developing long-term neurologic sequelae after streptococcal infection, and to determine effective treatment therapies.

West Nile Virus

West Nile virus is an arthropod-borne flavivirus that was first introduced to the United States in 1999 with a disease outbreak in New York City. The virus is usually spread by infected mosquitoes, although some bird species and ticks are believed to be carriers. Infected persons are usually asymptomatic, but mild symptoms can include headache, rash, and low-grade fever. Patients with severe symptoms can have neurological problems, such as meningitis, encephalitis, and poliomyelitis. Although central nervous system (CNS) invasion by West Nile virus has not been definitively demonstrated yet in humans, it has been shown to occur in other animals, such as mice (Hunsperger and Roehrig, 2006).

A recent study by Carson *et al*. (2006) reported a number of neuropsychiatric symptoms among 49 patients with confirmed West Nile virus infection. Patients complained of difficulty with memory and word-finding, as well as fatigue, extremity

weakness and headache. Twenty percent of patients also reported a new-onset tremor. Neuropsychological testing in these patients demonstrated abnormalities in motor skills, attention and executive functions. Schafernak and Bigio (2006) reported neuronal loss and other abnormalities in the substantia nigra of a patient with a history of encephalomyelitis and poliomyelitis-like paralysis due to West Nile virus infection, suggesting direct CNS invasion. Another study by Murray *et al*. (2007) noted that 31% of patients had a new-onset depression following infection by West Nile virus. Patients also experienced personality changes, including an increase in irritability and aggression and decreased socialization.

The evidence for neuropsychiatric problems following West Nile virus infection appears to be strong, but there are still very few cases in North America and it is unclear why some patients develop such troubling symptoms, while the majority of infected persons are asymptomatic.

Mycoplasma pneumoniae

Mycoplasma pneumoniae is a small bacterium that can cause pharyngitis, bronchitis and pneumonia via respiratory droplet transmission. Campbell *et al*. first associated neurological illness with *M. pneumoniae* in 1943. Later, it was shown to be able to invade the CNS (Abramovitz *et al*., 1987), but its role in central nervous system disease has still been somewhat controversial.

In the past few years, more evidence has emerged regarding the association of *M. pneumoniae* infection with neurological and psychiatric problems. A case review by Smith and Eviatar (2000) found a wide range of neurologic symptoms, involving both the

central and peripheral nervous systems, in six patients with *M. pneumoniae* infection. These symptoms ranged from mild to severe, and most commonly included meningoencephalitis, encephalopathy and seizures. A recent letter in the European Journal of Neurology (Rajabally, 2007) reported a case of chronic inflammatory demyelinating polyneuropathy following *M. pneumoniae infection*. Matsuo *et al.* (2004) reported three cases of children with restless leg syndrome and positive anti-*Mycoplasma* antibody titers. Other pediatric case reports have demonstrated encephalopathy, optic neuritis, transverse myelitis and seizures following *M. pneumoniae* infection (Candler and Dale, 2004). Harjacek *et al.* (2006) reported eight cases of reactive arthritis following *M. pneumoniae* infection, one of which was diagnosed as juvenile ankylosing spondylitis. A prospective case-control study of patients with Guillain-Barré syndrome (GBS) found that 15% of GBS patients had a preceding *M. pneumoniae* infection and that this infection seemed to be associated with the syndrome (Sinha *et al.*, 2007). Bilateral Bell's palsy and aguesia have also been linked to *M. pneumoniae* infection (Trad *et al.*, 2005).

Recently, *M. pneumoniae* was associated with a case of Kluver-Bucy syndrome, a rare neurobehavioral syndrome that involves visual agnosia, excessive oral tendencies, hypermetamorphosis, loss of normal fear and anger responses, and altered sexual behavior (Auvichayapat *et al.*, 2006). The researchers found that the patient's *M. pneumoniae* titers were elevated and an MRI revealed left temporal horn dilation and asymmetry of the temporal lobes. After antibiotic treatment, the titers were reduced to normal and none of the symptoms recurred. Another interesting case of an adolescent with acute *M. pneumoniae* infection revealed severe obsessive-compulsive disorder,

cognitive decline and deficient executive functioning continuing four years after onset of the illness (Termine *et al.*, 2005). MRI studies of this patient revealed bilateral striatal necrosis with compensatory enlargement of the lateral ventricles. In a rare case of co-infection with both *Mycoplasma pneumoniae* and *Steptococcus pneumoniae,* an 11-year-old girl experienced sudden onset of tetraplegia, abnormally brisk deep tendon reflexes, mild cerebellar dysfunction and fifth cranial nerve palsy (Manteau *et al*., 2005). After treatment with erythromycin and dexamethasone, the patient regained normal neurologic functioning.

Because *M. pneumoniae* is a fairly common and widespread organism, this is an interesting new area of research into the infectious causes of neuropsychiatric disorders and chronic illness.

Human Parvovirus B19

Human parvovirus B19 is the cause of the common childhood illness, erythema infectiosum or "fifth disease". Infection with parvovirus B19 is common and typically asymptomatic. However, it has been associated with neuropathies, meningoencephalitis, rheumatic disease, vasculitis and chronic fatigue syndrome (Kerr, 2005). Although parvoviruses have long been known to cause brain pathology in animals, there is little evidence for invasion of the nervous system by this virus in humans. However, a recent study was done to analyze the dorsolateral prefrontal cortices of a large number of brain samples from healthy controls and subjects with schizophrenia and bipolar disorder (Hobbs, 2006). Nested polymerase chain reaction and DNA sequencing analysis demonstrated parvovirus B19 sequences in 14.4% to 42.3% of the specimens, although

there was no difference among the different groups. This is some of the first evidence for neuroinvasion of the human brain by parvovirus B19, so a great deal more studies will be necessary in this area before any true neuropsychiatric effects of this virus can be recognized.

Borna Disease Virus

While the infection of humans with the Borna disease virus (BDV) is still a controversial topic, a few recent studies have found evidence of BDV-related RNA in patients, and have suggested a role for this in mood and other psychiatric disorders. Miranda *et al*. (2006) found BDV RNA in the peripheral blood cells of 33.33% of psychiatric disorder patients as compared to 13.33% of healthy controls. After cloning all of their positive PCR samples, they found that the sequences were more than 98% homologous with GenBank Borna disease virus. Another group (Güngör *et al*., 2005) found equal concentrations of anti-BDV antibodies in the serum of patients with subacute sclerosing panencephalitis (SSPE) and in normal patients, but found that very high levels of anti-BDV antibodies in SSPE patients correlated with earlier onset and greater severity of illness. They hypothesized that BDV may not destroy neurons, but rather cause changes in neurotransmitters, cytokines and chemokines, thus hastening the course and severity of SSPE. While little is known still about the role of this virus in human disease, it may prove to be an important topic of research for the future.

Chronic Fatigue Syndrome

Chronic fatigue syndrome (CFS), also known as myalgic encephalomyelitis, is a highly controversial, poorly understood and severely debilitating disorder that has been associated with a number of infectious agents. These include enteroviruses, Epstein-Barr virus, cytomegalovirus, human herpes virus-6 (HHV-6), parvovirus B19, hepatitis C, *Chlamydia pneumoniae*, and *Coxiella burnetii* (Devanur and Kerr, 2006). In general, a diagnosis of chronic fatigue syndrome is based on the clinical picture, but recent research has shown strong evidence for post-infectious causes and for the role of some serological and immunological markers.

A recent prospective cohort study by Hickie *et al.* (2006) followed 253 patients with acute infections of Epstein-Barr virus, *Coxiella burnetii* (Q fever) or Ross River virus (epidemic polyarthritis). After 12 months, they found that twelve percent of participants had a prolonged illness characterized by neurocognitive problems, mood changes, musculoskeletal pain and a disabling fatigue. Eleven percent of participants also met the diagnostic criteria for chronic fatigue syndrome, and this syndrome was predicted by the severity of the acute illness. The researchers did not find that demographics or psychological or microbiological factors predicted participants' outcome. Interestingly, a study by Vernon *et al.* (2006) found abnormal expression of several different genes in patients with post-infective fatigue syndrome following acute Epstein-Barr virus infection. Many of these genes play a role in mitochondrial functions, including the cell cycle and fatty acid metabolism, and this could be a factor in the severe fatigue symptoms that patients experience.

Chapenko *et al*. (2006) studied the possibility that infection with human herpesvirus-6 (HHV-6) or human herpesvirus-7 (HHV-7) could be a potential trigger for development of chronic fatigue syndrome. Their research demonstrated that patients with chronic fatigue syndrome had a significantly higher rate of dual, but not single-virus, infection with HHV-6 and HHV-7 in their peripheral blood leukocytes when compared to patients with unexplained chronic fatigue and normal blood donors. They also found significantly decreased numbers of CD3+ and CD4+ cells and significantly increased numbers of CD95+ cells in patients in which both viruses were simultaneously activated. They concluded that these viruses may be involved in the pathogenesis of chronic fatigue syndrome and that their reactivation may provoke changes in lymphocytes.

Chronic fatigue syndrome is a good example of a neuropsychiatric disorder for which an infectious agent is a likely cause, but a clear culprit and mechanism are yet unknown. It is possible that CFS is a single disease that can be caused by any number of different microbes or viruses, but it is also possible that many different organisms are capable of producing a clinical picture similar to CFS. Not only is CFS a complicated illness, it is also a highly controversial one that provokes arguments over its causes, treatments, and even its legitimacy as a true illness. This makes it very difficult for CFS patients to get diagnosed, and even if they are diagnosed, to get treated. In that respect, it epitomizes many of the challenges faced by doctors who research and treat neuropsychiatric disorders with infectious or unknown causes.

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