

On the Pathogenic Hypothesis of Neurodegenerative Diseases

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ABSTRACT

Brain infections by pathogens (bacteria, viruses, fungi, and other microbes) can lead to transient or permanent neurologic or psychiatric dysfunctions. While the cause(s) of the major neurodegenerative disorders (Alzheimer, Parkinson, epilepsy, and others) remain(s) unknown, I have posited earlier that they are the consequence of a runaway brain autoimmune system that is unable to maintain homeostasis between opposing synaptoblastic and synaptoclastic pressures. I consider here the pathogenic hypothesis of these disorders with special attention given to viruses (measles, herpes, HIV, and others). After partially listing the pathogens found in the brain and briefly reviewing the brain infections they cause, I review in more detail the link between neurodegenerative disorders and viruses. It is clear that while viral (and other pathogenic) infections can damage the brain, there is currently no definitive study demonstrating that a virus (or other pathogen) can cause Parkinson or Alzheimer, or any number of other neurodegenerative disorders. A major issue remains the understanding of the long-deferred time interval (several decades) between a viral infection/inflammation and the manifestation of the disease. The pathogenic hypothesis remains a hypothesis whose rigorous testing is long overdue. Even if a definitive link were established, it may only be correlative, not causal. At this juncture, the runaway autoimmune disease explanation remains the only plausible one, everything else being the consequences of risks and correlations.

Key words: Alzheimer disease, brain infections, herpes, human immunodeficiency viruses, measles, multiple sclerosis, neurodegenerative diseases, Parkinson disease, pathogens

INTRODUCTION

Bacteria, viruses, fungi, and other microbes are part of a growing list of pathogens found in the brains of patients with neurodegenerative diseases (NDDs). Microbes in the brain may indicate meningitis or encephalitis, two diseases that are active infections with inflammation. For diseases such as Parkinson disease (PD), Alzheimer disease (AD), and other NDDs that were not thought to be infectious, finding pathogens in the brain is both surprising and concerning. Table 1 is a partial listing of some of the various pathogens found in the brain.^[1-3]

How do the organisms in Table 1, and others, get into the brain since it is protected by the blood-brain barrier (BBB)? They do so

when the barrier loses some of its impermeability. Other avenues for reaching directly the brain are: (a) Intra-nasal and sinus access, (b) the mouth (through the lingual nerve, which runs down the jawline and into the tongue), (c) the gut (through the vagus nerve, which travels through the neck and thorax to the stomach), and even (d) through the eye (through the olfactory bulbs), all of which connect to the brain by replicating and spreading.

THE MOUNTING EVIDENCE OF THE PATHOGEN-BRAIN CONNECTION

The pathogen-brain connection has been reported since before the mid-19th century and continues to this day. Thus in:

- 1835 – Doctors in Europe recorded connections between the influenza infection and psychosis.

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- 1918 – The correlation (flu-brain) became much more apparent during the Spanish flu epidemic caused by the H1N1 virus, a subtype of H5N1, and epidemics of PD a few decades later. This, as yet not understood, delayed onset of PD is of particular importance.
- 1940s and early 1950s – In the U.S., the diagnosis of PD increased abruptly from 1–2% to 2.5–3% (that is, about 50% more people got PD) then fell back to its previous rate of 1–2%.
- 1974 – Gamboa *et al.* (Columbia University, New York City) found viral antigens in the brains of deceased people affected by encephalitis lethargica,^[4] which was associated with (and some thought caused by) the 1918 Spanish flu epidemic. It was speculated that the condition could be a precursor to PD. Since then, other scientists had also noted the connection between influenza and neural dysfunction.
- 1997 – Ogata *et al.* reported that rats exposed to the Japanese encephalitis virus developed symptoms similar to the human PD.^[5] At that time, this connection between viral infection and brain disease had been hotly contested.
- 2001 – Utilizing the technology known as polymerase chain reaction to look for the genome of the H1N1 virus in the preserved brain tissue of victims of encephalitis lethargica, researchers at the U.S. Armed Forces Institute of Pathology (Washington, D.C.) found no sign of the virus.^[6]
- 2003 – Heiko Braak proposed the widely accepted hypothesis that PD starts in the gut, manifesting as digestive tissues, and then moves into the brain, a process that may take place over 25–30 years over the life of the infected individual.
- 2006 – Researchers at the U.S. Centers for Disease Control and Prevention (Atlanta, Georgia), studied the effects of the influenza strain that caused the 1918 Spanish flu epidemic but did not see any signs of inflammation in the brains of infected mice.^[7] The above conflicting results suggest that more work is needed to link viral infection and NDDs.
- ~ 2008 – In ducks infected by the H5N1 virus, Richard Smeyne (St Jude Children’s Research Hospital, Memphis, Tennessee; later Thomas Jefferson University, Philadelphia) wondered whether a connection existed between the viral infection and the extensive neurodegeneration he observed (devastation of the substantia nigra, which is often damaged in Parkinson patients and obliteration of all the neurons). In people infected with H5N1, the symptoms are inflammation of the brain that leads to tremors and other motor malfunctions, that is Parkinsonism, involving only a subset of the disease’s symptoms. In sum, the virus was inducing inflammation and death into the parts of the brain that degenerate in PD. Rejoining the Braak hypothesis, Smeyne also suggested a possible pathway for the virus to spread from the body into the brain by infecting neurons first in the gut, then into the vagus nerve, and subsequently into the substantia nigra. Still, further, he remarked that in rodents, which have a much shorter lifetime than humans, the same travel from the gut to the brain may take only a few weeks as opposed to decades in humans. Even if they cannot reach the brain, the viruses nonetheless can still play a role in neurodegeneration by triggering severe inflammation.
- 2009 – In mice, Smeyne also observed that H5N1 not only is not blocked by the BBB from entering the brain but also it can easily infiltrate nerve cells in the brain and kill them, especially targeting the dopamine-producing neurons in the substantia nigra.^[8] Further, while H1N1 could not penetrate the BBB, it still caused central nervous system (CNS) immune cells (the microglia) to flow into the substantia nigra and the hippocampus, causing inflammation and cell death in the area.^[9] Interestingly, we have here two different flus, two different mechanisms, but the same effect! They induced inflammation and death in that part of the brain that degenerates in PD. It must be noted that Smeyne’s experiments are not the only ones to suggest that viral infections can contribute to NDDs, and the connection is not limited to influenza. As shown in Table 1, several different viruses, including measles and herpes, can give rise to symptoms of multiple sclerosis (MS) in rodents.^[10] In addition, levels of herpes virus are higher in the brains of people who died from AD than in those without the disease.^[10] Furthermore, some HIV patients develop dementia that appears to be associated with the infection.
- 2017 – After administering the toxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), a byproduct of a bad batch of synthetic heroin that led users to develop PD, Smeyne *et al.* observed that the treated mice developed signs of PD and lost 25% more neurons in the substantia nigra than uninfected mice treated with the toxin. He, then, concluded that whereas the H1N1 viral infection alone may not cause PD, it primed the nervous system to be sensitive to other things that would.

Notwithstanding, these several instances of the link between viruses and NDDs, they remain correlations or contributions but not causes of the diseases.

ON BRAIN INFECTIONS

As seen (at least in part from Table 1), brain infections can be caused by viruses, bacteria, fungi or, occasionally, protozoa, or parasites. (Another group of brain disorders, not discussed here, is the spongiform encephalopathies, which are caused by abnormal proteins called prions). Infections of the brain often also involve other parts of the CNS, including the spinal cord. They can cause inflammation of the brain

Table 1: Pathogens in the brain

Pathogen	Origin/cause	Effects
<i>Porphyromonas gingivalis</i> (<i>P. Gingivalis</i>) bacterium	Mouth	Some of the proteins made by this microbe have been found in brains
<i>Fusobacterium nucleatum</i> bacterium		
<i>Prevotella intermedia</i> bacterium		
Herpes simplex virus		Lives for years in nerve cells that supply the face and lips. Can migrate back up the same route into the brain producing a mild inflammatory response Shows higher levels in Alzheimer patients Can lead to MS
Measles virus		Can cause MS and subacute sclerosing panencephalitis
Herpes Simplex Virus (HSV 1, 2)		Can cause encephalitis, meningitis, and disseminated infection in immunocompromised patients Possible link to NDD (Parkinson, Alzheimer, etc.)
HIV (1, 2)		Can cause dementia, Parkinson-like, and Alzheimer-like disease
H1N1 virus (HSV1, 2)		Delayed PD Encephalitis lethargica (a possible precursor of AD) May not cause PD, but may prime the CNS and, with the addition of toxin (s), lead to PD
H5N1 virus (a subset of H1N1)		Parkinsonism (symptoms: Brain inflammation, tremors, other motor malfunctions) May degenerate into PD
Fungi <i>aspergillus</i>		Brain infection as cysts
Protozoa <i>Toxoplasma gondii</i>		
Parasites <i>Taenia solium</i> , pork tapeworm		
Syphilis	<i>Treponema pallidum</i> (a spirochete type of bacterium)	Can live in the body for decades, eventually infecting the brain and causing dementia
Lyme disease	<i>Borrelia burgdorferi</i> carried by the deer tick <i>Ixodes</i>	
<i>Ehrlichia</i>		Infects white blood cells
<i>Babesia</i> (relative of the malaria parasite)		Infects red blood cells
<i>Bartonella</i>		Infects blood vessels
AD	Many different organisms. Furthermore, by sterile inflammation not from invading pathogens	Also harbors fungi

Augmented from Reference^[1]

(encephalitis), and the layers of tissue (meninges) that cover the brain and the spinal cord (meningitis). Often, bacterial meningitis spreads to the brain itself, causing encephalitis. Similarly, viral infections that cause encephalitis often also

cause meningitis. Usually, in encephalitis and meningitis, infection is not confined to one area but may occur throughout the brain, within the meninges, along the entire length of the spinal cord and over the entire brain. Infection may also be

confined to one area (empyema in an existing space in the body; abscess).

Sometimes a brain infection, a vaccine, cancer, or another disorder may trigger a misguided immune reaction, causing the immune system to attack normal cells in the brain (an autoimmune reaction) as a result of which the brain becomes inflamed (so-called post-infectious encephalitis). In summary, brain infections may manifest as follows: Diffuse infection resulting in encephalitis, sometimes affecting specific areas on the brain; inflammation of the brain secondary to meningeal or parameningeal infections or focal infection (e.g., due to a brain abscess or to fungal or parasitic brain infections). Encephalitis is most commonly due to viruses (herpes simplex, herpes zoster, cytomegalovirus, West Nile virus, HIV, and prion disease).

Bacteria and other infectious organisms can reach the brain and meninges in several ways by being carried by the blood, entering the brain directly from the outside (for example, through a skull fracture or during surgery on the brain), or spreading from nearby infected structures (for example, sinuses or middle ear).

LINK BETWEEN VIRUSES AND NDDS

Some viruses can enter the body through the nose and mouth and move to the brain by replicating and spreading through the olfactory bulbs, the lingual nerve which runs down the jawline and into the tongue, or the vagus nerve which travels through the neck and thorax to the stomach. Viral infections may cause brain damage, but we are uncertain whether the injuries play a role in NDDs although some studies do suggest a connection.

When interacting with the nervous system, viral particles can cross the BBB in a number of ways:

- Direct crossing: Through infection of endothelial cells;
- Trojan horse approach: By infecting monocytes that cross the BBB before replicating and bursting out of the white blood cells once inside the brain;
- Invoking an immune response: Not crossing the BBB directly but invoking an immune response that may spur cytokines or chemokines to breach the BBB.

Once inside the brain, viruses can infect cells or their myelin sheath and kill them. They do not necessarily have to enter the brain to cause damage, though. They can also spark an immune response that activates microglia, which then consume otherwise healthy neurons.

However, the flu-Parkinson connection is not the only link between viruses and neurological problems.

The broader link between viruses and neurodegeneration can be seen from the following developments that took place in the late 1980s–early 1990s.

Measles and herpes viruses connection with MS

Mice infected with viruses such as measles and herpes suffered the same kind of damage to their oligodendrocytes (cells in the CNS that produce the myelin, the insulating fatty sheath wrapped around the axons of neurons) as patients with MS do. It is unclear whether the viruses invaded the oligodendrocytes directly or simply provoked the mice immune systems to attack the cells (an autoimmune reaction), but the end result was demyelination of neurons.

Measles, herpes, and HIV viruses connection with Alzheimer-like and Parkinson-like disease

- Measles and Herpes Viruses: One of the viruses that induced MS symptoms in mice were herpesvirus six which has also been associated with the onset and development of AD. Indeed, over the past few decades, tentative links have been documented between viral infections and AD. For example, reviewing data from brain banks and published studies, Dudley *et al.* (Icahn School of Medicine and Mount Sinai, New York City) found that AD patients had elevated levels of viruses such as human herpesviruses 6 and 7 in four key brain regions. Based on genetic and proteomic data, they also found that human herpesvirus six may induce gene expression that spurs the development of the protein amyloid β , which forms plaques – one of the hallmarks of AD.^[11] However, in the same way, that “*risk is not causation, and risk management is not cure but palliation,*” we can further state that “*correlation is not causation.*” While viruses may not cause the disease, their presence suggests that pathogens may play a part in NDDs after all. Compared to previous musings on the pathogen hypothesis, we now have more powerful genetic and other sequencing methods that can take a more unbiased look at the microbial DNA/RNA landscape of brain tissue.^[12]
- HIV Virus: The following sequence of events shows that it could cause AD-like or PD-like brain damage. Thus, in the:
 - 1990s – Scientists showed that HIV could traverse the BBB, infiltrate the brain, and spur neuronal death and a loss of synaptic connections.
 - Late 2010s – Patients with HIV developed dementia and loss of brain matter that mirrors what is seen in AD.^[13]
 - More recently, other studies showed that HIV patients develop plaques of amyloid β (like in AD) and can also develop slowness in movement and tremors (like in PD).
 - 2019 – Korte *et al.* (Technische Universität Braunschweig, Germany) reported that the brains of mice infected with certain strains of the flu virus suffered memory deficits even after they

seemingly recovered. It turned out their brains were full of microglia even 30–60 days after the infection first took hold.^[14] Normal levels of microglia can return to normal range ~ 60 days post infection with neurons in young mice recovering completely along with the animal's performance. Still, microglia levels can remain high for up to 120 days (equivalent to >10 years in human time).

The long time lags between viral infection and the development of NDDs are exactly the reason why scientists have had (and continue to have) trouble accepting that viruses could cause NDDs. The long-term link is difficult to demonstrate except perhaps in rodent studies. We need to better understand how the brain responds to viral infection long after our immune system has cleared the infection from our bodies. This will help us develop ways to mitigate the neurological effects. Further, understanding how infections trigger the immune system could lead to ways to down-regulate glia-driven inflammation in the hope of preventing long-term damage.^[15] For instance, this author has posited that AD and perhaps other NDDs as well maybe but a manifestation of a runaway autoimmune disease.^[16-23]

More closely to us, Smeyne *et al.* conducted another experiment on mice in which (a) one group of mice received an H1N1 vaccine 30 days before infecting the animal with the virus and (b) another group of mice was treated with Tamiflu for the week after they were infected. Both groups were allowed to recover before being given a low dose of toxic material (MPTP), and (c) a control group received neither the vaccine nor the flu treatment. They determined that while (c) developed PD-like symptoms, (a) and (b) developed no neurodegenerative effects. In other words, mice were protected against PD-like symptoms by either prophylactic treatment (with a vaccine) or by early treatment (with Tamiflu). Extrapolating these results from mice to humans, the logical conclusion would be that if a person gets a pathogen infection, vaccination or at least treatment with Tamiflu may treat influenza but also help prevent the complications of influenza infection.

CONCLUSION

Viral (and other pathogens) infections can damage the brain, but there is currently no definitive study demonstrating that a virus (or other pathogens) can cause PD or AD or any number of other NDDs. Viruses and other pathogens can cause a lot of different brain diseases, but this remains only a hypothesis whose rigorous testing is long overdue. A major roadblock in definitively establishing the link between pathogens and NDDs remains our lack of understanding of the long-delayed onset of the disease after the infection/inflammation. Further, even if a definitive link were established, it may only be correlative, not causal. At this juncture, this author's assertion that the root cause of AD (and other NDDs) may be a runaway

autoimmune disease that is unable to maintain homeostasis between opposing synaptoblastic and synaptoclastic pressures, everything else being the consequences of risks, correlations, remains the only plausible explanation.

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APPENDIX 1

Overview of Herpes Viruses that Infect Humans

Table 2 lists the eight types of herpes viruses that infect humans (HHSV 1-8). Of these, types 1, 2, 4, and 6 might play a role in NDDs. After initial infection, they all remain latent but may subsequently reactivate and transmit to other people. Because they do not survive long outside a host, their transmission usually requires intimate contact with a person shedding the virus. Viral shedding occurs from lesions but can occur even when lesions are not apparent. This very contagious viral infection is spread by direct contact with sores or sometimes contact with an affected area when no sores are present. After the initial infection, HSV remains dormant in nerve ganglia, from which it can periodically emerge, causing symptoms.

Epstein-Barr virus HHV 4 and HHV 8 (also known as Kaposi sarcoma-associated herpesvirus (KSHV), can cause certain cancers, a topic not considered here.

APPENDIX 2

Familial and Autoimmune Encephalitis

Encephalitis is inflammation of the brain that occurs when a virus, vaccine, or something else triggers inflammation. The spinal cord may also be involved, resulting in a disorder called encephalomyelitis.

Because inflammation plays a role in the development of NDDs, the consideration of encephalitis is opportune. It is most commonly due to viruses, such as HSV 1, 2, varicella zoster, cytomegalovirus, or West Nile virus. It can occur in the following ways: (a) A virus directly infects the brain; (b) a virus that caused an infection in the past becomes reactivated and directly damages the brain; and (c) a virus or vaccine triggers a reaction that makes the immune system attack brain tissue (an autoimmune reaction).

Sometimes, bacteria cause encephalitis, usually as part of bacterial meningitis (called meningoenophalitis). Brain infections due to an autoimmune reaction sometimes develop in people who have cancer. Protozoa – such as amebas, the protozoa that cause toxoplasmosis (in people who have AIDS), and those that cause malaria can also infect the brain and cause encephalitis.

Interestingly, infections that can directly lead to encephalitis can occur in epidemics as, for example, the 1918 Spanish H1N1 flu epidemic noted above.

TYPES OF ENCEPHALITIS

Encephalitis Spread By Viruses

There are several types of vira encephalitis, including:

- La Crosse encephalitis: It is caused by the La Crosse virus (also called California virus). It accounts for most cases in children. Many cases are mild and undiagnosed. Fewer than 1% of infected people die from it.
- Eastern equine encephalitis: It affects mainly young children and people older than 55. In children younger than 1 year, it can cause severe symptoms and permanent nerve or brain damage. Over half of infected people die.
- West Nile encephalitis: This virus also causes a milder infection called West Nile fever, which is much more common. West Nile encephalitis develops in fewer than 1% of people who develop West Nile fever. About 9% of people with West Nile encephalitis die. However, those who have only West Nile fever usually recover fully.
- St. Louis encephalitis: Infection is more likely to affect the brain in older people. Epidemics once occurred about every 10 years but are now rare.
- Western equine encephalitis: For unknown reasons have largely disappeared since 1988. It can affect all age groups but is more severe and more likely to affect the brain in children younger than 1 year.

Table 2: Eight types of herpes virus infect humans

Common Name	Other Name	Typical Manifestations
Herpes simplex virus-mimicking Type 1	Human herpes virus 1	Gingivostomatitis, keratoconjunctivitis, cutaneous herpes, genital herpes, encephalitis, herpes labialis, viral meningitis, esophagitis, pneumonia, disseminated infection, hepatitis
Herpes simplex virus-mimicking Type 2	Human herpesvirus 2	Genital herpes, cutaneous herpes, gingivostomatitis, neonatal herpes, viral meningitis, disseminated infection, hepatitis
Varicella-zoster virus	Human herpes virus 3	Chickenpox, herpes zoster, disseminated herpes zoster
Epstein-Barr Virus	Human herpesvirus 4	Infectious mononucleosis, hepatitis, encephalitis, nasopharyngeal carcinoma, Hodgkin lymphoma, Burkitt lymphoma, lymphoproliferative syndromes, oral hairy leukoplakia
Cytomegalovirus	Human herpesvirus 5	CMV mononucleosis, hepatitis, congenital cytomegalic inclusion disease, retinitis, pneumonia, colitis
Human herpesvirus 6	Human herpesvirus 6	Roseola infantum, otitis media with fever, encephalitis
Human herpesvirus 7	Human herpesvirus 7	Roseola infantum
Kaposi sarcoma-associated herpes virus	Human herpesvirus 8	Not a known cause of acute illness but has a causative role in Kaposi sarcoma and AIDs-related non-Hodgkin lymphoma that grow primarily in the pleural, pericardial, or abdominal cavities as lymphomatous effusions. Also linked with multicentric Castleman disease

Source: Kenneth M. Kaye, Merck Manual

- Powassan virus infection: It usually causes mild or no symptoms and has been associated with cases of encephalitis. The virus is similar to the one that causes tick-borne encephalitis. However, the infection can also cause severe encephalitis with headache, vomiting, seizures, loss of coordination, speech problems, or coma. Up to 15% of people with severe encephalitis die. The vaccine that is effective against tick-borne encephalitis is not effective against the Powassan virus.
- Japanese encephalitis virus: A common cause in Asia and the Western Pacific
- Venezuelan equine encephalitis: It occurs mainly in travelers returning from areas where the virus is common.
- Zika virus: It may cause fever, joint and muscle aches, headache, and a red, bumpy rash. Having Zika virus infection during pregnancy can cause microcephaly and severe brain damage in the baby.^[22]

Encephalitis Spread by Ticks

They include:

- Tick-borne encephalitis: It usually causes a mild flu-like illness that clears up within a few days. A vaccine is available.
- Colorado tick fever: It is a flu-like illness. Occasionally, it causes meningitis or encephalitis.

Encephalitis Spread by Mosquitoes

Several viruses that cause encephalitis were once present in only a few parts of the world but now are spreading, probably because travel has increased. These viruses include the:

- Chikungunya virus: It can lead to severe encephalitis and even death, especially in infants and people over age 65.

AUTOIMMUNE ENCEPHALITIS

Encephalitis can result from reactivation of a virus, including:

- HSV 1.
- HHV 3.
- JC virus: It causes a usually fatal disorder called progressive multifocal leukoencephalopathy that is common among people who have AIDS or other conditions that impair the immune system;
- Measles virus: If reactivated, it leads to a usually fatal disorder called subacute sclerosing panencephalitis years after measles occurs.
- A reactivated infection, which can occur long after people have the infection, can severely damage the brain.