Page 669 to 671

Volume 3 • Issue 2 • 2019

Editorial

Current Opinions in Neurological Science

ISSN: 2575-5447

The Pathogenic Brain

Alain L Fymat*

Professor, International Institute of Medicine & Science, California, U.S.A

***Corresponding Author:** Alain L Fymat, Professor, International Institute of Medicine & Science, California, U.S.A.

Received: April 13, 2019; **Published:** April 17, 2019

Volume 3 Issue 2 April 2019

The connection between influenza infection and psychosis has been reported in Europe as early as 1835. It became more apparent during the Spanish flu epidemic of 1918. As we recall, that epidemic, caused by the H1N1 virus (a subtype of the H1N5 virus), correlated with an epidemic of Parkinson disease a few decades later. In the U.S., between the 1940s and early 1950s, the diagnosis of Parkinson disease increased abruptly from 1-2% to 2.5-3% (that is, about 50% more people were diagnosed with the disease) before falling back to its previous rate of 1-2%. However, because of the unexplained geographically distant and delayed onset of Parkinson disease by several decades, that connection was cast aside. Bacteria, viruses, fungi, and other microbes are part of a growing list of pathogens found in the brains of patients with neurodegenerative diseases. Generally, brain infections by pathogens can lead to transient or permanent neurologic or psychiatric dysfunctions. Microbes in the brain may indicate meningitis or encephalitis, two diseases that are active infections with inflammation. For neurodegenerative diseases like Parkinson, Alzheimer and others that were not thought to be infectious, finding pathogens in the brain is both surprising and concerning.

Evidence has continued to accumulate linking the brain to various pathogens. But, how do these organisms get into the brain since it is protected by the blood brain barrier? They do so when the barrier looses some of its impermeability. Other avenues for reaching directly the brain are the intra-nasal and sinus access, the mouth through the lingual nerve, the gut through the vagus nerve, and even the eye through the olfactory bulbs, all of which connect to the brain by replicating and spreading. Thus, in 1974, Gamboa., *et al*. found viral antigens in the brains of deceased people affected by encephalitis lethargica. It was associated with (and some thought caused by) the 1918 Spanish flu epidemic and it was even speculated that the condition could be a precursor to Parkinson. Other scientists had also noted the connection between influenza and neural dysfunction. In 1997, Ogata., *et al*. reported that rats exposed to the Japanese encephalitis virus developed symptoms similar to human Parkinson.

At that time, this connection between viral infection and brain disease had been hotly contested because of other conflicitng experiments. In 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 found no sign of the virus. In 2003, Heiko Braak proposed the widely accepted hypothesis that Parkinson starts in the gut and moves into the brain, a process that may take place over 25-30 years over the life of the infected individual. However, in 2006, researchers at the U.S. Centers for Disease Control & Prevention, studying the effects of the influenza strain that caused the 1918 Spanish flu epidemic, did not see any signs of inflammation in the brains of infected mice. The above conflicting results suggested that more work was needed to link viral infection and neurodegenerative diseases.

Then, seminal experiments were conducted by Richard Smeyne. In 2008, observing ducks infected by the H5N1 virus, he 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). The virus was inducing inflammation and death into the parts of the brain that degenerate in Parkinson. He further remarked that in rodents, which have a much shorter lifetime than humans, the same travel from the gut to the brain as hypothesizd by Braak, may take only a few weeks as opposed to decades in humans. Even if they cannot reach the brain, the viruses can still play a role in neurodegeneration by triggering severe inflammation. In 2009, in other mice experiments, Smeyne also observed that H5N1 not only is not blocked by the blood brain barrier from entering the brain but it can easily infiltrate nerve cells in the brain and kill them, especially targeting the dopamine-producing neurons in the substantia nigra.

While H1N1 could not penetrate the barrier, it still caused central nervous system immune cells (the microglia) to flow into the substantia nigra and the hippocampus, causing inflammation and cell death in the area. Interestingly, we have here two different flus, two different mechanisms, but the same effect - inflammation and death in that part of the brain that degenerates in Parkinson. Other experiments than Smeyne's suggested that viral infections can contribute to neurodegenerative diseases. The connection is not limited to influenza but extended to several different viruses, including measles and herpes that can give rise to symptoms of multiple sclerosis in rodents. In addition, levels of herpes virus were found to be higher in the brains of people who died from Alzheimer than in those without the disease. Also, some HIV patients developed dementia that appears to be associated with the infection. Lately, in 2017, after administering the toxin MPTP (a byproduct of a bad batch of synthetic heroin that led users to develop Parkinson), Smeyne., et al. Additionally observed that the treated mice developed signs of Parkinson, losing 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 Parkinson, it primed the nervous system to be sensitive to other things that would. All of the above experiments are prompting a reconsideration of the pathogen connection to the brain.

Now, infections of the brain often also involve other parts of the central nervous system including the spinal cord. They can cause inflammation of the brain (encephalitis) and of 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). 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). Sometimes a brain infection, a vaccine, cancer, or another disorder may trigger an autoimmune reaction as a result of which the brain becomes inflamed. Encephalitis is most commonly due to viruses (herpes simplex, herpes zoster, cytomegalovirus, West Nile virus, HIV and prion disease).

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. Mice infected with viruses such as measles and herpes suffered the same kind of damage to their oligodendrocytes as patients with multiple sclerosis do. It is unclear whether the viruses invaded the oligodendrocytes directly or simply provoked the mice's immune systems to attack the cells (an autoimmune reaction), but the end result was demyelination of neurons. One of the viruses that induced multiple sclerosis symptoms in mice was herpes virus 6 which has also been tentatively associated with the onset and development of Alzheimer. Indeed, over the past few decades, tentative links have been documented between viral infections and Alzheimer. From a review of data from brain banks and published studies, Joel Dudley., et al. found that Alzheimer patients had elevated levels of viruses such as human herpes viruses 6 and 7 in four key brain regions. Based on genetic and proteomic data, they also found that human herpes virus 6 may induce gene expression that spurs the development of the protein amyloid β which forms plaques – one of the hallmarks of Alzheimer.

While viruses may not cause the disease, their presence suggests that pathogens may play a part in neurodegenerative diseases 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. Further, in the case of HIV, beginning in the 1990s, it was shown that it could traverse the blood brain barrier, infiltrate the brain, and spur neuronal death and a loss of synaptic connections. In late 2010, it was further shown that patients with HIV developed dementia and loss of brain matter that mirrors what is seen in Alzheimer. More recently, other studies showed that HIV patients develop plaques of amyloid β (like in Alzheimer) and can also develop slowness in movement and tremors (like in Parkinson). Lastly, in 2019, Korte., et al. 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 and can remain high for up to 120 days (equivalent to more than 10 years in human time).

More recently, 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 were treated with Tamiflu for the week after they were infected. Both groups were allowed to recover before being given a low dose of a toxic material (MPTP), and (c) a control group received neither the vaccine nor the flu treatment. They determined that while (c) developed Parkinson-like symptoms, (a) and (b) developed no neurodegenerative effects. In other words, mice were protected against Parkinson-like symptoms by either prophylactic treatment (with a vaccine) or by early treatment (with Tamiflu). Extrapolating these results from mice to humans, if valid, the logical conclusion would be that if a person gets a pathogen infection, vaccination or at least treatment with Tamiflu may treat the influenza but also help prevent the complications of influenza infection.

In summary, the long time lag between viral infection and the development of neurodegenerative diseases is exactly the reason why scientists have had (and continue to have) trouble accepting that viruses could cause the diseases. The 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 hope of preventing long-term damage.

The pathogenic hypothesis remains a hypothesis whose rigorous testing is long overdue. Not with standing the several instances of the link between viruses and neurodegenerative diseases, even if a definitive link were established, it may only be correlative not causal. While the cause(s) of the major neurodegenerative disorders (Alzheimer, Parkinson, epilepsy, and others) remain 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. At this juncture, this runaway autoimmune disease explanation remains the only plausible one and the root cause of neurodegenerative diseases, everything else amounting to consequences of risks and correlations.