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Letter to the Editor

Viruses in Cerebral Microbiome Cause Neuronal Diseases

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Foreword

Martin Korte at the Technische Universität Braunschweig in Germany and colleagues reported that the brains of the mice which were infected with the flu virus suffered memory deficits even after they'd seemingly recovered. It turned out that their brains were full of microglia even 30 to 60 days and more after infection first took hold. Researchers [ ] say such a "lag" is a reason why scientists have trouble in accepting the idea that viruses could cause neurodegenerative diseases [ ]. In science we often think of some cause and effect being often milliseconds, people say. Here, you're talking about decades. The virus goes in and then maybe decades later it can cause some potentially serious neurodegeneration [ ] such a long-term link is hard to demonstrate.

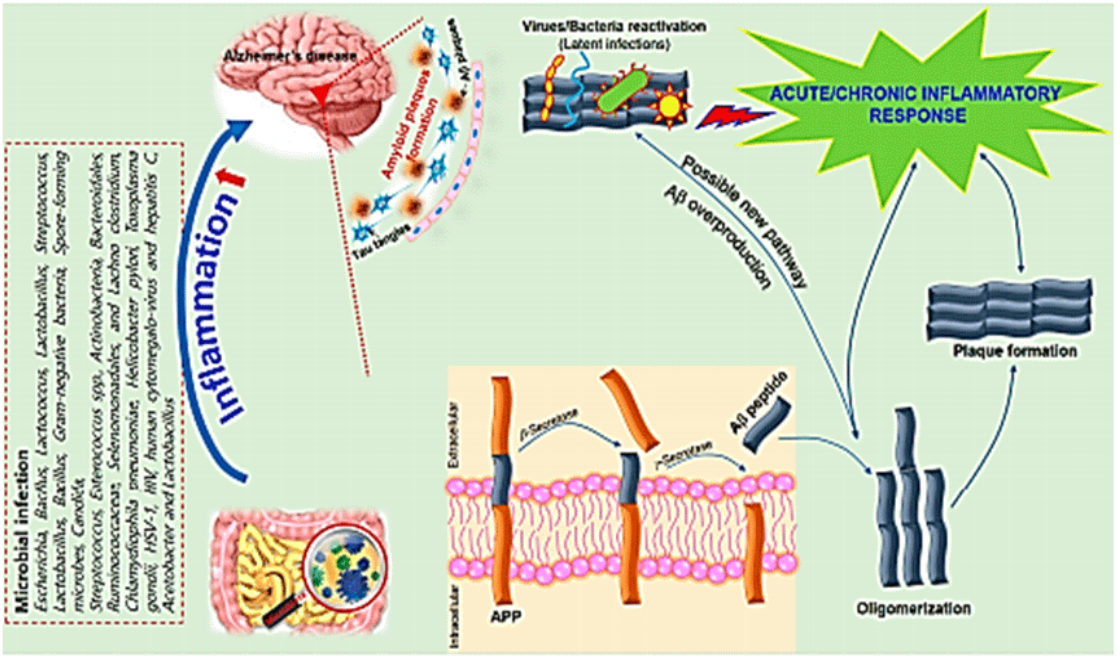

Figure 1

Figure: A schematic of the hypothetical chain of events via which brain infection may lead to pathological amyloid-β peptide (Aβ) plaque formation in the brain. The amyloid precursor protein (APP) is processed by secretases into different peptides, including Aβ. The gut microbiota plays a significant role in the development of Alzheimer's disease (AD) since Aβ functions as an antimicrobial peptide via oligomerization and plaque formation, trapping invading microorganisms, including bacteria, fungi, viruses, and protist. Aβ plaque formation in response to infection could result in a neuroinflammatory effect of microbiota on AD and neurodegeneration due to collateral damage in plaque-surrounding tissue. (Credit ref.

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[1]) Our brain system, the spinal cord, and its surrounding structures may become infected by a large variety of germs. Bacteria and viruses [ ] are the most commonones. Parasites, fungi, viruses and other microbes can infect the central nervous system (CNS), although more rarely viruses have the power to induce alterations and degenerations of neurons by different direct and indirect mechanisms. Virus infections of the brain are rare in the immune normally reacting host. But neurotropic viruses have developed mechanisms to exploit weaknesses in immunological defense mechanisms that eventually allow them to reach and infect CNS neurons. Once in the CNS, these viruses can induce significant neuronal dysfunction and degeneration of specific neuronal populations, sometimes leading to devastating, life-threatening consequences for the host. Here, we examine viruses with the ability to infect neurons and their resulting pathologies, their modes of entry to the CNS, and the cellular and molecular alterations that these viruses induce in neuronal cells. Both inside and out, our bodies harbor an array of microbes [ ]. While a diverse collection of bacteria are the major players, we also host single-celled organisms, as well as viruses and other microbes (fungi for example) – including viruses that attack bacteria. These are dubbed the human microbiota. Your body's microbiome is all the genes our microbiota contains, however colloquially the two terms are often used interchangeably. Many other significant roles of our microbes include influencing the immune system, providing nutrients for our cells and preventing colonization by harmful bacteria and viruses. The figure that has been used out since is that microbes outnumber our own cells by about 10 to one. But a study from recent years suggests that microbial cells and human cells coexist in somewhere around a 1.3 to one ratio – suggesting they only slightly outnumber our own cells, although that doesn't count viruses and viral particles. The role of the microbiota in infections and neurodegeneration remains predominantly unknown. In this view, we may consider an intriguing hypothesis: viral infections and inflammation precede neurons and immune cells in the brain, causing neuronal populations vulnerable to degeneration in the face of subsequent insults. These activated inflammatory pathways may represent opportunities for therapeutic intervention before the onset of neurodegenerative disease [ ].Viruses are defined as neurotropic preferentially infect neurons and can cause severe, and sometimes fatal, brain inflammation (encephalitis). More commonly, viruses enter the central nervous system (CNS; the brain and spinal cord) asymptomatically during systemic infections either by crossing the blood-brain barrier (BBB) or via the peripheral nervous system (PNS; nerve tissue outside of the CNS) [ ].

Is There A Chance For The Remedy For Cerebral Viral Infections?

Infecting germ causes inflammation. Depending on the area of the infection, different names are given to the diseases: Meningitis, Encephalitis Myelitis,(Myelitis is a rare clinical syndrome in which an immune-mediated reaction causes neural injury to the spinal cord.) and Abscess.

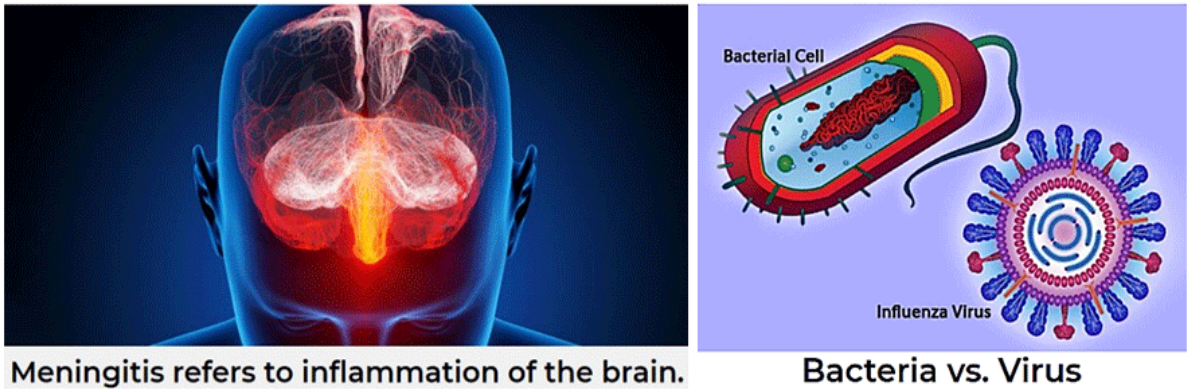

Figure 2

Viral meningitis is characterized by milder symptoms, it requires no specific treatment, and cures completely. Viral infections are two to three times more common than bacterial infections. In contrast, Bacterial meningitis is a very troublesome disease. It may result in a learning disability, speech defects, hearing loss, seizures, loss of extremity function, Research based on using a mouse model of West Nile virus, the scientists demonstrated that oral antibiotics not only alter the bacterial abundance and community structure in the gut, they also impair the development of optimal antiviral T-cell responses. Detailed results appeared in Cell Reports, in an article entitled, "Oral Antibiotic Treatment of Mice Exacerbates the Disease Severity of Multiple Flavivirus Infections" [ ]. The article suggests that antibiotic use can account, at least in part, for the great differences in disease severity that are observed when people are infected by viruses. There are sorts of meningitis that are unpredictable, and cannot be prevented. There are effective vaccines, however, against certain types of bacteria.

The *Haemophilus influenzae* type B vaccine is often called the Hib vaccine. Hib vaccines are safe. These are standard immunization for children.A vaccine against bacterial meningitis can also prevent other forms of infection A vaccine against bacterial meningitis is available in the U.S. It is applied for young people and for people at high risk for disease (like people with defects in the immune system).

Viruses and Neurodegeneration [9]

Viruses cause changes and deteriorations of neuronal tissues. They are ableto interfere with the host immune system, regions of nervous tissue imply that they can react with the same pathways involved in Neurodegenerative diseases (NDs) in humans. Supporting this, many similarities between classical NDs and virus-mediated neurodegeneration (non-classical) have been shown at the anatomic, sub-cellular, genomic and proteomic levels suggesting that viruses can explain neurodegenerative disorders mechanistically.

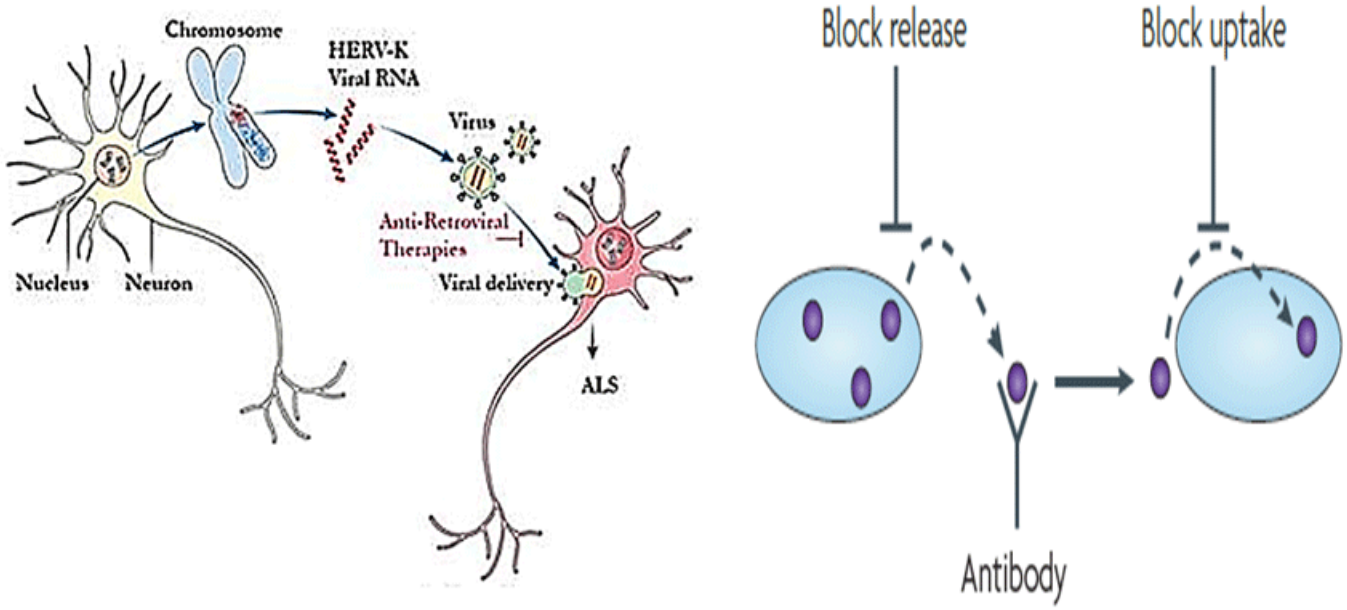

Figure 3

Insidious Infection

Once re-activated in one neuron, HERV-K particles might induce neurodegeneration in its neighbors. If so, anti-retroviral therapy might help. [Courtesy of Avindra Nath.credit ref [,]. For example, a hibernating retrovirus, prodded from slumber, can provoke neurodegeneration. Human endogenous retrovirus-K pumps out viral RNA and proteins in a subset of amyotrophic lateral sclerosis cases. Moreover, rousing HERV-K in cultured cells killed neurons, and doing the same in mice sickened them in an ALS-like manner. In addition, there is no evidence that HERV-K could be transmitted from person to person like an infectious virus. Some wonder if any HERV-K retroviral DNA hiding in the human genome can produce a competent, infectious virus. If so, it might transmit Amylotropic Lateral Sclerosis (ALS) from cell to cell (see image above). Some believe the viral infectious spread (prion-like) [6] would likely incorporate glia somehow, as well as neurons. Scientists have called HERV-Ka "dead virus", which is able to express toxic gene products but not to assemble a complete infectious particle. Might some researchers have a functional HERV-K genome, waiting to be revived? One of the most vicious neurodegenerative diseases, is the Creutzfeldt–Jakob disease (CJD).Dr. Laura Manuelidis Reports and stresses that the results of the transmission [ ] experiments with human emphasize the centrality of an exogenous infectious pathogen that can exist in symbiosis with its host for extended periods. Many latent or persistent viruses can cause neurodegenerative disease and may have a role in late-onset dementias. There is evidence to believe that CJD infections may share properties with some of the latent viruses in causing dementia, and several retroviral mechanisms may be operative in CJD. In order to clarify viral-like attributes of the CJD agent we have closely followed infectivity and find the following: 1) the CJD agent has a virus-like size and density, and is biochemically separable from most host-encoded prion protein (PrP); 2) Endogenous retroviral IAP RNA sequences of 5,000 bases, as well as several gag-like nucleic acid binding proteins, co-purify with infectivity in preparations treated with high concentrations of anionic detergents and exhaustive nuclease digestion. They signify

the purification of true viral cores rather than aggregation artifacts, and diminish claims that there are no protected nucleic acids of > 50 bases in highly purified infectious preparations; 3) In established hamster CJD, temporal studies show the agent has an effective doubling time of approximately 7.5 days in the brain, consistent with complex host-viral interactions common to slow viral infections; 4) PrP-res does not correspond to titered levels of infectivity either in a biochemical or an in vivo setting but may function as a viral receptor that can modulate disease expression. Interestingly, functional changes in glial cells occur earlier than PrP-res changes, and indicate an important role for glial cells in evolving infections; 5) Human-rodent transmission studies suggest that CJD, or a CJD-like variant can be a common but latent infection of humans, with a relatively infrequent expression of neurological disease. Susceptibility to disease can rest on host attributes and possibly age-related co-factors. Nonetheless, fundamental viral principles are also operative. Agent strain variants, viral burden, and the routes of infection are critical parameters for latency and disease expression. The properties described above have led me to return to the inclusion of CJD (and scrapie) in the panorama of conventional slow viral infections of the brain, as initially proposed by Sigurdsson. Identification of virus-specific molecules is essential for elucidating the role of these agents in the spectrum of human dementias. Already in 1992, Krister Kristensson [ ] published on the possibility of viral infections as causes for neurodegenerative disorders."Viruses have the capacity to induce alterations and degenerations of neurons by different direct and indirect mechanisms". (credit ref. [8]).

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