Neurodegenerative disease

https://doi.org/10.1038/s41582-023-00790-6

Viral pathogens increase risk of neurodegenerative disease

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A new study, drawing on data from national biobanks, adds to the growing evidence that exposure to common viral pathogens increases the risk of Alzheimer disease and other neurodegenerative diseases. These findings might provide insights into the initiating factors that lead to neurodegeneration.

REFERS TO Levine, K. S. et al. Virus exposure and neurodegenerative disease risk across national biobanks. *Neuron* https://doi.org/10.1016/j.neuron.2022.12.029 (2023).

Neurodegenerative diseases, which include conditions such as Alzheimer disease (AD) Parkinson disease (PD), amyotrophic lateral sclerosis (ALS), vascular dementia and multiple sclerosis (MS), are a class of progressive disorders defined by neuronal death. Each of these disorders is characterized by degeneration of distinct brain areas, and they present with overlapping but discrete symptoms that can include motor impairment, cognitive dysfunction, affective changes and/or dementia. With the exception of rare familial cases, the aetiopathogenic origins of these diseases are poorly understood; however, two common factors seem to be neuroinflammation and epidemiological links to viral infections[1].

Neuroinflammation was originally thought to be a consequence of neurodegeneration; however, subsequent research indicated that neuroinflammation can drive the onset and progression of neurodegenerative diseases. The idea of neuroinflammation as a driver of neurodegeneration was advanced by genome-wide association studies (GWAS) that identified immune-related genes, including *CD33* and *TREM2*, as risk factors for AD[2]. In addition, the ε4 allele of the apolipoprotein E gene (*APOE* ε4), which is the strongest known genetic risk factor for AD and accounts for approximately 10–20% of the risk of late-onset disease, has been hypothesized to exert its effects partially through neuroinflammatory processes[3]. These genetic factors increase the risk of developing neurodegenerative disease but are not sufficient to cause disease on their own. Instead, genetic risk factors are likely to work with environmental factors that underlie sporadic forms of neurodegenerative disease.

In a recent study, Kristin Levine and colleagues mined medical record data and found that viral infections were associated with an increased risk of several neurodegenerative diseases[4] (Table 1). This study is the most expansive of its nature, evaluating various viral agents and several neurodegenerative diseases from two different datasets: a nationwide Finnish biobank including over 300,000 individuals and a second biobank from the UK with data from nearly 500,000 individuals. Whereas previous studies generally focused on one disease and/or a single viral pathogen, Levine et al. probed medical records for associations between six neurodegenerative diseases — AD, ALS, generalized dementia, MS, PD and vascular dementia — and multiple viral pathogens. The strongest association found was between AD and viral encephalitis, although the exact virus was not identified. Influenza and pneumonia together showed significant associations with all the diseases examined except for MS. A previously reported association between Epstein–Barr virus (EBV) infection and MS[5] was replicated using the Finnish but not the UK dataset. This discrepancy might be attributable to differences between countries in how illnesses are reported in medical records[4].

> "The strongest association found was between AD and viral encephalitis"

The hypothesis that viral pathogens are an environmental risk factor for neurodegenerative diseases is not new, but it has gained support in recent years. Adding to the aforementioned GWAS data highlighting the role of immune genes in AD risk[2], a multiomic study identified increased levels of genomic DNA from human herpesvirus 6A and 7 in the brains of patients with AD compared with cognitively healthy controls, and viral abundance correlated with transcriptomic signatures linked to amyloid-β (Aβ) processing[6]. Another study published at the same time showed that, in a mouse model that developed Aβ pathology, infection with herpes simplex virus 1 (HSV1) directly incited and accelerated Aβ deposition[7]. Together, these data reinvigorated the microbial aetiology hypothesis of AD.

In 2021, we reviewed the evidence that microbial pathogens are a risk factor for neurodegenerative diseases[1], and several studies have since been published that support this hypothesis. Following on from the preclinical study highlighted above[7], HSV1 has been an important focus of clinical research into the link between viral infections and AD. A large population-based cohort study in northern Sweden[8], in which the patient population was selected on the basis of positive HSV1 carrier status and matched for sex and *APOE* ε4 status, found that treatment with an antiviral drug reduced the relative risk of developing AD by approximately 70%.

Another nested case–control study of several national registries in Sweden analysed the incidence of hospital-treated infections in individuals newly diagnosed with AD, PD or ALS[9]. To reduce the influence of surveillance bias, this study excluded infections experienced in the 5 years preceding diagnosis with a neurodegenerative disease. The results showed an increased risk of AD and PD, but not ALS, in individuals who experienced a hospital-treated infection 5 years or more earlier, and these associations persisted with infections treated 10 years or more before diagnosis. Multiple infections before the age of 40 years conveyed the greatest risk of AD and PD. This study found similar

Table 1 | Viral infections linked to neurodegenerative diseases

Disease	Infection
Alzheimer disease	Influenza and pneumonia
	Intestinal infections
	Meningitis
	Viral encephalitis
Amyotrophic lateral sclerosis	Influenza and pneumonia
Generalized dementia	Human papilloma virus
	Influenza and pneumonia
	Viral encephalitis
Multiple sclerosis	Epstein–Barr virus
	Herpes simplex virus
	Varicella zoster virus
Parkinson disease	Hepatitis C virus
	Influenza and pneumonia
Vascular dementia	Influenza and pneumonia
	Intestinal infections
	Varicella zoster virus

The table lists the viral infections that were found to be associated with an increased risk of neurodegenerative disease in the study by Levine et al.[4].

associations for bacterial, viral and other infections, but did not classify the data on the basis of specific infectious pathogens.

In a cohort study of more than 10 million US military personnel on active duty, infection with EBV, but not other viruses including cytomegalovirus, significantly increased the risk of MS[5]. Another study identified clonally expanded $CD8^+$ T cells specific for EBV antigens in the cerebrospinal fluid of patients with AD, although this study did not speculate on a causative link between EBV infection and AD incidence[10].

The brain is protected from most viral pathogens by the blood–brain barrier, but neurotropic viruses can subvert these protective measures to infect cells of the nervous system. Interestingly, the majority of associations identified in the study by Levine et al.[4] involved viruses that are considered to be neurotropic, including HSV, varicella zoster virus (VZV), some strains of influenza virus, and viruses that cause encephalitis or meningitis. The most common causes of viral encephalitis are HSV, VZV and West Nile virus, and although neurotropic viruses have long been recognized to cause post-infectious cognitive dysfunction, it is less clear whether these viruses cause classic neurodegenerative diseases.

"the majority of associations identified [...] involved viruses that are considered to be neurotropic"

Emerging infections should also be monitored for possible relationships with neurodegenerative disease. For example, SARS-CoV-2, the viral cause of COVID-19, primarily manifests as a respiratory infection but is also linked to cognitive dysfunction. Whether this dysfunction is attributable to viral entry into the brain or to widespread inflammation that affects brain function is not fully understood. Considering the strong association between influenza and pneumonia and several neurodegenerative diseases, future studies should examine the potential links between SARS-CoV-2 and these diseases and explore the molecular and cellular mechanisms that underlie these associations.

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Published online: 2 March 2023

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Competing interests

The authors declare no competing interests.