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Historical Insight into Infections and Disorders Associated with Neurological and Psychiatric Sequelae Similar to Long COVID

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Long-term sequelae of coronavirus disease 2019 (COVID-19) due to infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) are now recognized. However, there is still a lack of consensus regarding the terminology for this emerging chronic clinical syndrome, which includes long COVID, chronic COVID syndrome, post-COVID-19 syndrome, post-acute COVID-19, and long-hauler COVID-19. In this review, I will use the term "long COVID". A review of the medical history and epidemiology of past pandemics and epidemics in modern literature review identifies common long-term post-infectious disorders, with the common finding of altered cognition. In the brain, the cerebral hypoxia induced by SARS-CoV-2 infection may be caused by mitochondrial dysfunction, resulting in "brain fog". Historically, the common symptom of altered cognition has been reported during earlier pandemics, which include the influenza pandemics of 1889 and 1892 (Russian flu), the Spanish flu pandemic (1918-1919), encephalitis lethargica, diphtheria, and myalgic encephalomyelitis (chronic fatigue syndrome or post-viral fatigue syndrome). There are similarities between chronic fatigue syndrome and the "brain fog" described in long COVID. During past viral epidemics and pandemics, a commonality of neural targets may have increased viral survival by conformational matching. The neurological and psychiatric sequelae of SARS-CoV-2 infection, or long COVID, may have emerged from neural effects that have emerged from an invertebrate and vertebrate virosphere. This review aims to present a historical overview of infections and disorders associated with neurological and psychiatric sequelae that have shown similarities with long COVID.

Keywords: COVID-19 • Diphtheria • Encephalomyelitis • Fatigue Syndrome, Chronic • Severe Acute Respiratory Syndrome Coronavirus 2

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Background

There is increasing awareness of the long-term symptoms and organ damage in patients with confirmed coronavirus disease 2019 (COVID-19) due to infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) that persist after the acute illness [1,2]. Although the term "long COVID" is now commonly used for these disorders, there is still no consensus on terminology, which includes chronic COVID syndrome, post-COVID-19 syndrome, post-acute COVID-19, and long-hauler COVID-19 [1,2]. In this review, I will use the term long COVID.

A recognized symptom of long COVID is "brain fog", which is characterized by fatigue and the lack of ability to concentrate and can severely affect memory and cognition [3,4]. The finding of altered cognition in long COVID has inspired this current re-examination of the pathological features of past pandemics and epidemics to determine whether this is a common finding in post-infectious disorders. A further reason for this review is to examine the recent hypothesis that hypoxia in the cerebral microenvironment following SARS-CoV-2 infection may result from virus-induced mitochondrial dysfunction [3,4]. This targeted effect on the brain following viral infection may have also occurred during earlier pandemics during the nineteenth and twentieth centuries. Historically, the common symptom of altered cognition has been reported during earlier pandemics. These include the influenza pandemics of 1889 and 1892 (Russian flu), Spanish flu pandemic (1918-1919), encephalitis lethargica, diphtheria, and myalgic encephalomyelitis (chronic fatigue syndrome or post-viral fatigue syndrome). There are similarities between the symptoms of chronic fatigue syndrome and the brain fog described in long COVID [4]. Viral infection, cerebral hypoxia, cognitive dysfunction, or brain fog may occur along a common pathway in the long-term pathogenesis of epidemic and pandemic infections, including COVID-19 [4]. This review aims to present a historical overview of infections and disorders associated with the neurological and psychiatric sequelae that have shown similarities with long COVID.

The Influenza Pandemics of 1889 and 1892 (Russian Flu)

The influenza pandemic of 1889 and 1892 was also known as the Russian flu. Recently, Honigsbaum and Krishnan highlighted the similarities between the post-infectious neurological conditions observed at the time of the Russian flu and those of COVID-19, or long COVID [5]. The authors reported that the terminology for the long-term effects of the Russian flu included neuralgia, neurasthenia, neuritis, nerve exhaustion, grippe catalepsy, psychosis, prostration, inertia, anxiety, and paranoia, which supported that there were long-term neurological effects from this infection [5].

The Spanish Flu Pandemic (1918-1919) and Encephalitis Lethargica

The long-term neurological effects of the Spanish flu pandemic of 1918 and 1919 included Parkinsonism, catatonia, and "encephalitis lethargica" [5,6]. The term encephalitis lethargica was first used by the Austrian neurologist Constantin von Economo in 1917 after he identified an increased number of patients in Vienna with meningitis and delirium during the winters of 1916 and 1917 [7]. In 1918, disorders that were similar to encephalitis lethargica were reported elsewhere in Europe and the United States, with a peak in cases in 1923 and a decline over the course of the decade [7]. Ravenholt and Foege showed that in Seattle, Washington, clusters of deaths from encephalitis lethargica significantly increased a year after the winters of 1918 to 1922 [8]. Importantly, they also showed that in American Samoa, which largely escaped the 1918 and 1919 influenza pandemic, there were very few cases of encephalitis lethargica [8]. In comparison, in Samoa (formerly known as Western Samoa), where 8000 influenza deaths occurred, there were 79 deaths due to encephalitis lethargica between 1919 and 1922 [8].

Diphtheria

In 1935, an outbreak of "atypical poliomyelitis" was identified in doctors and nurses at the Los Angeles County Hospital during a citywide poliovirus epidemic [9]. However, the affected hospital staff were adults with symptoms that included severe headache, painful oculomotion, and gastrointestinal symptoms, and some patients presented with "mental dullness" and a lack of ability to concentrate, which indicated cerebral involvement [9]. Also, the results of the examination of the cerebrospinal fluid in 53 of 59 cases studied were normal, which was a key difference from typical poliomyelitis [9]. The authors also noted a high seasonal incidence of diphtheria at the time of the poliovirus outbreak, and 24% of patients had positive diphtheria throat cultures and a sore throat [9].

Myalgic Encephalomyelitis (Chronic Fatigue Syndrome or Post-Viral Fatigue Syndrome)

In the latter half of the twentieth century, there were several epidemics of benign myalgic encephalomyelitis in London, Iceland, Australia, and Florida [10]. In 1956, benign myalgic encephalomyelitis was first described, and in 1959, Acheson described outbreaks of paralytic illness that were at first thought to be poliomyelitis but differed clinically and epidemiologically and supported the term benign myalgic encephalomyelitis [10]. Acheson reported that women were more affected with myalgic encephalomyelitis than were men. Common symptoms included

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headache, myalgia, paresis, and mental symptoms, but there was an absence of fever and no patient mortality [10]. An outbreak at London's Royal Free Hospital in 1955 identified malaise as the third most common symptom, after headache and sore throat, with some symptoms that persisted for months or years in a few cases [10]. Acheson concluded that in cases of myalgic encephalomyelitis, convalescence was prolonged by fatigue and recurring myalgia [10]. However, although recovery was usually complete within 3 months, in a proportion of cases, there was fluctuating myalgia and paresis, partial remissions and exacerbations, and depression, emotional lability, and a lack of concentration [10]. Acheson concluded that benign myalgic encephalomyelitis was probably due to infection by an unknown agent or a group of related agents [10].

Chronic Fatigue Syndrome and Brain Fog in Long COVID

A recently described symptom of long COVID is the condition of brain fog, or the reduced ability to concentrate, which is similar to chronic fatigue syndrome, which was first described in the late 1980s [11]. In the early 1990s, several publications reported that patients were presenting with debilitating fatigue and cognitive dysfunction, often following the onset of an infection [12]. The initial reports on what came to be known as chronic fatigue syndrome lacked consensus on the terminology, definition, and criteria for diagnosis, which was also similar to the initial reports on benign myalgic encephalomyelitis [12], and is also similar to the current status of long COVID [1,2]. In 1990, British scientists at Oxford University proposed a definition and set of criteria for the diagnosis of chronic fatigue syndrome, which focused on fatigue as the main symptom, which was described as severe enough to disable both physical and mental function, and which lasted for at least 6 months [12]. Also, a subtype of chronic fatigue syndrome was identified, which was named "post-infectious fatigue syndrome" [12]. The diagnostic criteria for post-infectious fatigue syndrome were the same as for chronic fatigue syndrome, but the symptoms were identified clinically to have begun after the onset of infection [12]. In support of the neurological-related hypotheses proposed in previous centuries, research on chronic fatigue syndrome has increasingly shown the involvement of the central nervous system, autonomic nervous system, and the immune system [13-15].

Conformational Matching and the Virosphere

A recurrent component of the disorders described in viral infections affects cognition, which may indicate similarities in underlying physiological processes, including the brain fog that is associated with long COVID [3,4]. There may also be a commonality of neural targets that might increase viral survival and, therefore, may assist the development of novel therapeutic strategies to restore normal neural function [16]. The evolutionary conservation of critical stereo-selective molecules and those that emerged randomly, for example, virus components, may be used as specific future therapeutic targets to prevent viral replication and spread [16]. The neurological and psychiatric sequelae of SARS-CoV-2 infection, including brain fog and confused mental states, may assist viral replication, infectivity, and viral persistence [16].

The origins of the SARS-CoV-2 virus are currently under investigation. However, the SARS-CoV-2 RNA virus is believed to be zoonotic with an origin in bats and a vertebrate intermediary host that resulted in transmission to humans. This RNA virus may continue to pass between humans and vertebrates. Before the current COVID-19 pandemic, previous studies on RNA viruses from invertebrate species showed their divergence to form new families [17]. Understanding RNA virus biodiversity has revealed the evolutionary history of the viruses, characterized by host switching and co-divergence [17]. The increased understanding of the invertebrate virome has revealed genomic flexibility with frequent recombination and complex genomic rearrangement [17]. Therefore, our historical understanding of the long-term clinical sequelae of RNA viruses, such as SARS-CoV-2, will benefit from an evolutionary understanding of the vertebrate virome. The neurological and psychiatric sequelae of SARS-CoV-2 infection, or long COVID, may have emerged from neural effects that have emerged from an invertebrate and vertebrate virosphere [17].

Conclusions

This review of infections and disorders associated with the neurological and psychiatric sequelae of SARS-CoV-2 infection provides a historical context for long COVID. The comparisons made in this review are assisted by the availability of medical archives and literature, advances in diagnosis and epidemiological research, and the ability to rapidly access medical information resources. Data from past epidemics and pandemics may be used to identify common acute and chronic syndromes, including neurological and psychiatric sequelae with similarities to the conditions currently described in patients with long COVID.

Conflict of interest

None.

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References:

1. Del Rio C, Collins LF, Malani P. Long-term health consequences of COVID-19. JAMA. 2020;324(17):1723-24
2. The Lancet. Facing up to long COVID. Lancet. 2020;396(10266):1861
3. Wang F, Kream RM, Stefano GB. Long-term respiratory and neurological sequelae of COVID-19. Med Sci Monit. 2020;26:e928996
4. Stefano GB, Ptacek R, Ptackova H, et al. selective neuronal mitochondrial targeting in SARS-CoV-2 infection affects cognitive processes to induce "brain fog" and results in behavioral changes that favor viral survival. Med Sci Monit. 2021;27:e930886
5. Honigsbaum M, Krishnan L. Taking pandemic sequelae seriously: From the Russian influenza to COVID-19 long-haulers. Lancet. 2020;396(10260):1389-91
6. McCall S, Vilensky JA, Gilman S, Taubenberger JK. The relationship between encephalitis lethargica and influenza: A critical analysis. J Neurovirol. 2008;14(3):177-85
7. Reid AH, McCall S, Henry JM, Taubenberger JK. Experimenting on the past: The enigma of von Economo's encephalitis lethargica. J Neuropathol Exp Neurol. 2001;60(7):663-70
8. Ravenholt RT, Foege WH. 1918 influenza, encephalitis, parkinsonism. Lancet. 1982;2:860-64
9. Meals RW, Hauser VF, Bower AG. Poliomyelitis – the Los Angeles epidemic of 1934: Part I. Cal West Med. 1935;43(2):123-25
10. Acheson ED. The clinical syndrome variously called benign myalgic encephalomyelitis, Iceland disease and epidemic neuromyasthenia. Am J Med. 1959;26(4):569-95
11. Valasquez-Manoff M. Feature. What if you never get better from COVID-19? New York Times. Jan 26 2021. *https://www.nytimes.com/2021/01/21/magazine/covid-aftereffects.html*
12. Sharpe MC, Archard LC, Banatvala JE, et al. A report – chronic fatigue syndrome: guidelines for research. J R Soc Med. 1991;84(2):118-21
13. Komaroff AL. Inflammation correlates with symptoms in chronic fatigue syndrome. Proc Natl Acad Sci USA. 2017;114(34):8914-916
14. Montoya JG, Holmes TH, Anderson JN, et al. Cytokine signature associated with disease severity in chronic fatigue syndrome patients. Proc Natl Acad Sci USA. 2017;114(34):E7150-58
15. Hornig M, Montoya JG, Klimas NG, et al. Distinct plasma immune signatures in ME/CFS are present early in the course of illness. Sci Adv. 2015;1(1):e1400121
16. Stefano GB. Conformational matching: A possible evolutionary force in the evolvement of signal systems. In: Stefano GB (ed.), CRC Handbook of comparative opioid and related neuropeptides mechanisms. Boca Raton: CRC Press Inc.; 1986; 271-77
17. Shi M, Lin XD, Tian JH, et al. Redefining the invertebrate RNA virosphere. Nature. 2016;540(7634):539-43

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