



## Post-viral Fatigue: Implications for Long Covid

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### Author's contributions

The sole author designed, analysed, interpreted and prepared the manuscript.

### Article Information

DOI: 10.9734/AJRID/2021/v6i130182

#### Editor(s):

- (1) Dr. Hetal Pandya, SBKS Medical Institute & Research Center, India.
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- Complete Peer review History: <http://www.sdiarticle4.com/review-history/63884>

Review Article

Received 18 October 2020  
Accepted 23 December 2020  
Published 09 January 2021

### ABSTRACT

There has been extensive research on post-viral fatigue, and the present mini-review and commentary provides an overview of the effects associated with different infecting agents. Fatigue is not only a subjective state, rather it has an impact on our ability to carry out everyday functions, and its effect can be demonstrated using performance tasks. It is not surprising, therefore, that persistent effects of COVID-19 are observed, and the key features of Long Covid are reviewed here. Suggestions for further research which will provide a better understanding of Long Covid and provide a basis for prevention and management are also discussed.

*Keywords:* Common cold; influenza; epstein barr virus; chronic fatigue syndrome; Long Covid.

### 1. INTRODUCTION

#### 1.1 Post-viral Fatigue

The present mini-review and commentary article aims to provide a concise summary of post-viral

fatigue that can be understood by all readers. It has two main objectives. The first is to demonstrate that post-viral fatigue is frequent and common, and can be observed following infection with many different viruses. Generally, the magnitude of fatigue is related to the severity

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of the illness, and may in part reflect the recovery observed in any severe illness. The second aim is to describe the persistent effects seen after COVID-19 infection, and the condition now referred to as Long Covid. Following this, the questions that need to be addressed by future research are outlined.

This article has the following structure. First, post-viral effects of common upper respiratory tract infections (the common cold and influenza) are described. Following this, infections that lead to more persistent fatigue (e.g. Infectious mononucleosis) are discussed. This is followed by an account of the chronic fatigue following infection with herpes viruses and enteroviruses. Possible mechanisms underlying post-viral fatigue are then discussed. This is followed by a description of the chronic symptoms reported by some individuals following COVID-19 illnesses and now referred to as Long Covid. Long Covid is a new condition, and the research questions that need to be addressed are presented here.

### **1.2 After-effects of the Common Cold**

There has been extensive research on the effects of both experimentally-induced colds [1-6] and naturally-occurring colds [7-10] on performance. After-effects of experimentally-induced rhinovirus infections were examined in one study [11]. These results showed that the slower reaction times observed when the person was symptomatic were still present after the symptoms had gone. After-effects of naturally-occurring colds were observed in another study, but the tasks that were impaired differed from those that were sensitive during the symptomatic phase [12]. These results showed that the slower reaction times observed when the person was symptomatic were still present after the symptoms had gone. This could reflect the immunological changes that still occur after the symptoms have gone. Another possibility is that the volunteers had learnt the task when symptomatic, and this poor learning continued at the next test session when they were well. A study of the effects of naturally-occurring colds [13] supported the poor learning explanation.

### **1.3 After-effects of Influenza**

Post-viral fatigue following influenza can last for weeks rather than days. An early report [14] described anecdotal reports of accidents before and after influenza. Later research [15] suggested that the evidence for influenza

encephalopathy (drowsiness, confusion and epileptiform events) is well established. Post-influenza effects may occur, and these can influence the judgements of highly skilled staff as illustrated by the following case:

“The individual concerned was responsible for calibration of a spectrophotometer before commencing a day’s work ----- He had previously been off work for two days with influenza and returned alleging health ----- During the first part of the morning, he made eleven attempts to correctly prepare the instrument. On six occasions he stated his opinion that all the preparative procedures had been completed and that the instrument was ready for use. Each time, however, elementary faults were observed. Despite the incorrectness of the last calibration, the individual commenced work, compiling results which were finally discarded by himself three weeks later.”

Other research has examined the effects of post-viral fatigue following influenza on the performance of a battery of cognitive tasks [16]. The results showed impairments in reaction time, increased distraction, and poorer episodic and semantic memory.

### **1.4 Tularemia (Rabbit Fever)**

One of the earliest studies of experimentally-induced infection [17, 18] induced a febrile disease characterised by headache, nausea, myalgia and depression. The results showed that those who became ill had an average drop in performance of over 25%, and after recovery, they were still 15% below the healthy control group.

### **1.5 Infectious Mononucleosis (IM)**

While IM is usually a self-limiting disease, it is now recognised that in a minority of previously normal patients, symptoms and signs may persist for months or years after the initial diagnosis [19-25]. Research [26] has shown that the post-viral effects of IM include impairments of episodic and working memory which are similar to effects observed in chronic fatigue syndrome [27, 28]. Indeed, Epstein Barr viruses have been implicated as the possible causal mechanism of chronic fatigue syndrome [29].

### **1.6 Others Viruses that Lead to Post-Viral Fatigue**

A recent review [30] has examined chronic viral infections in chronic fatigue syndrome.

### 1.6.1 Human Herpesviruses

There are nine human herpesviruses and members of the *Herpesviridae* family, *Beta-herpesvirinae* subfamily, and *Roseolovirus* genus are the most widely studied pathogens in chronic fatigue syndrome. Rasa et al. [30] reviewed twenty-nine studies investigating associations between human herpesvirus 6 and/or 7 and chronic fatigue syndrome. Eleven of these studies revealed a correlation between these viruses and chronic fatigue syndrome. Some of this research should be treated with caution due to small sample sizes. There is also the possibility that these infections can contribute to a sub-group of patients rather than the whole sample. The viruses could also trigger other responses, such as autoimmune, metabolic and psychological disturbances, which could be responsible for chronic fatigue.

### 1.6.2 Enteroviruses

There are more than 70 different enteroviruses that can infect humans. The role of enteroviruses in chronic fatigue syndrome has been suspected for over three decades, but the data from the literature have been controversial. Rasa et al. [30] reviewed sixteen studies investigating enteroviruses in chronic fatigue syndrome. Eleven of these studies showed an association between enteroviruses and chronic fatigue syndrome.

### 1.6.3 Human parvovirus

B19V is an immunomodulating single-strand DNA virus belonging to the *Parvoviridae* family (*Parvovirinae* subfamily, *Erythrovirus* genus). Studies of this virus and chronic fatigue syndrome have yielded conflicting results.

### 1.6.4 Retroviruses

XMRV belongs to the *Retroviridae* family (*Orthoretrovirinae* subfamily, *Gammaretrovirus* genus). Despite early suggestions that this was present in those with chronic fatigue syndrome, later research in many countries failed to replicate these findings. Other retroviruses (HTLV-I and II, HIV-1/2 and spuma viruses) have also been studied. However, a retroviral aetiology in chronic fatigue syndrome has not been supported.

### 1.6.5 Ross river virus

Another virus that causes post-viral fatigue is a single-stranded positive-sense RNA virus – Ross

River virus (RRV). Early research [31] showed that post-viral fatigue was present up to thirty months after the initial infection with RRV. Such disorders were correlated with elevated levels of pro-inflammatory cytokines [32] which may influence the CNS.

## 1.7 Mechanisms Linking Viral Infections to Chronic Fatigue

One commonality between viruses linked to chronic fatigue syndrome is that they establish persistent infections. In order to do this, the viruses must evade immune cells and alter immune cell function [see 30 for a review]. Persistent infection is related to immunosuppression and activated immune complexes, which may result in chronic inflammation. This may lead to alterations in the regulation of cytokine production. An increase of inflammatory mediators might explain the symptoms of chronic fatigue syndrome. Viral infection may also influence cellular immunity, which then leads to viral re-activation.

Chronic fatigue has also been considered to be a mitochondrial disease [33]. Many of the viruses mentioned above can modify host mitochondria in a variety of ways which can provide plausible explanations for their involvement in chronic fatigue syndrome. The viruses implicated in chronic fatigue syndrome influence mitochondrial metabolism and bioenergetics in a variety of ways. The end points of this are enhanced viral replication and defence against anti-viral mechanisms.

Viruses contribute to autoimmune diseases in a variety of ways and autoimmune signature in chronic fatigue syndrome has become a topic of recent interest [34]. At least in a subset of patients, elements of autoimmunity and mitochondrial dysfunction observed in chronic fatigue may have a viral pathogenesis. It may be that an underlying immune dysfunction acts as a predisposing factor to either an exceptionally strong acute infection, an inability to clear the virus or both. Lack of analysis of molecular mechanisms linking viral pathogens to chronic fatigue syndrome has restricted our understanding of the condition.

## 2. LONG COVID

Most people infected with SARS-2-CoV-2 either remain asymptomatic or recover quickly. However, a subgroup develop severe persistent

symptoms [35-37], and this has been referred to as *Long Covid* [38]. As the emergence of Long Covid is very recent, it is not too surprising that we know relatively little about it. Factors which predispose people to Long Covid are poorly understood, and the incidence of it is unknown. Little is known about the pathogenesis or duration of Long Covid. There is a lack of awareness of the syndrome, no known treatment, but a realisation that it may become a significant world health issue.

### 2.1 Symptoms Reported by Those with Long Covid

The symptoms reported by those with Long Covid are many and varied. Table 1 shows examples of the symptoms.

The above symptoms vary between individuals and may also show changes from day to day in a given individual. Long Covid shows a strong resemblance to chronic fatigue syndrome, and patients have had their symptoms ascribed to mental health problems. Research on

Long Covid started with anecdotal reports and more detailed case histories [39]. This was followed by retrospective studies from a number of countries. These examined the percentage of patients with Long Covid lasting thirty days or more. All studies reported that over fifty per cent of their samples reported fatigue, and this was true from thirty to seventy-five days after the onset of the symptoms. One prospective study [40] found that in a cohort of Long Covid patients studied four months after onset, impairment was observed in one or more organ systems. However, these result contrast with those from Wuhan, China, where eighty-six per cent of patients were asymptomatic three or four weeks after discharge from the hospital.

### 2.2 Future Research on Long Covid

Many of the questions that need to be addressed about Long Covid are those which researchers have covered in past research on post-viral and chronic fatigue syndrome. These issues are summarised in Table 2.

**Table 1. Symptoms of Long Covid**

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Severe Fatigue
Reduced physical capacity
Respiratory problems
Fever
Headache
Joint pain
Vertigo or tinnitus
Palpitations
Anosmia or ageusia
Cognitive problems – “brain fog”
Peripheral neuropathy
Skin rash
Anxiety and depression

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**Table 2. Long Covid: Future research issues**

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1. A case definition is needed.
2. Is Long Covid a single syndrome or are there a number of distinct syndromes?
3. Are there distinct groups of symptoms? e.g. respiratory v systemic symptoms
4. Is the length of symptoms the best method of classifying sub-groups?
5. What physiological systems are affected in Long Covid (cardiovascular; pulmonary; CNS; renal function; muscles)?
6. What percentage of infected people develop Long Covid (what is the incidence of Long Covid)?
7. What are the risk factors for developing Long Covid?
8. What mechanisms underlie the persistence of Long Covid? (genetics; viral persistence; immunological changes; inflammation; biochemistry and haematology)?
9. What are the best methods of preventing and managing Long Covid?
10. There is a need to raise awareness of Long Covid and to engage all stakeholders in the development of healthcare strategies.

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### 3. CONCLUSIONS

Post-viral fatigue has been recognised and studied for a long time. The present article summarises previous research on post-viral fatigue. Upper respiratory tract infections often lead to short-lived fatigue, and this demonstrates the importance of considering time periods when the person no longer has the acute symptoms. More severe infections can lead to long-lasting fatigue, and there is good evidence that human herpesviruses and enteroviruses can lead to chronic fatigue syndrome. It is not surprising, therefore, that a severe disease such as COVID-19 can lead to persistent syndromes. Long Covid has recently been recognised, and the features of the condition are described here. At the moment, we are at the stage of having identified the condition. Further urgent research is now required to get a better understanding of underlying risk factors and mechanisms, and to develop appropriate prevention and management strategies.

### CONSENT

It is not applicable.

### ETHICAL APPROVAL

It is not applicable.

### COMPETING INTERESTS

Author has declared that no competing interests exist.

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*Peer-review history:*  
*The peer review history for this paper can be accessed here:*  
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