

Post-Infectious Fatigue

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Abstract

Chronic fatigue syndrome (CFS) and Gulf War Syndrome are diseases of unknown etiology which are accompanied by severe fatigue as a main complaint. Yet there may be some kind of “post-infectious fatigue syndrome” following any infection by a virus.

Post-infectious fatigue, which is caused by many different viruses, includes chronic active Epstein-Barr virus (EBV) infection and it is thought that the onset of this disease is associated with latent EBV infection in a very unusual manner. As there may be an unusual latent infection with human herpesvirus 6 (HHV-6) which may be an etiology of CFS in the CFS patients, the study on latent infection is considered to be important for elucidating CFS and Gulf War Syndrome.

Key words Infection, Fatigue, Chronic fatigue syndrome, Gulf War Syndrome, Epstein-Barr virus, Human herpesvirus 6

Introduction

Fatigue is caused by many different factors, of which infection is one of the very important causes. Fatigue, which not only deteriorates work efficiency but also constitutes causes of various diseases and death from overwork, poses a serious health problem for people. In spite of such importance, however, the mechanisms of fatigue, by which fatigue is caused and felt, have been hardly known.

It is easy to identify the presence of fatigue which is caused by bacterial or viral infection, because the time and cause of fatigue are known clearly. Post-infectious fatigue, therefore, attracts attention as an important subject in the study of the mechanism of fatigue. Also, in view of the fact that many cases with chronic fatigue syndrome (CFS), in which severe fatigue of unknown etiology continues for long time, occur following infectious disease, the relationship between infection and CFS is considered to have an important meaning.

This paper examines knowledge currently available on the mechanism of fatigue and discusses the relationship of infection with severe post-infectious fatigue, particularly with the onset of CFS.

Mechanism of Fatigue

In general, “fatigue” is defined as decreased physical functions attributable to prolonged physical and/or mental stresses, while “tiredness” indicates the condition in which the brain recognizes decreased physical functions. Tiredness is an important biological signal, as are pain and drowsiness, to maintain biofunctions.

Becoming fatigued or feeling tiredness might require the presence of substances which increase or accumulate through fatigue and/or a fatigue transmitting substance which transmits fatigue to the brain. Lactic acid has been long considered as a major fatigue-causing substance. However it was reported recently that lactic acid is not a fatigue-causing but a fatigue-preventing substance.¹⁷ Presently, therefore, there is no proven

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Table 1 Pathogens reported as causing post-infectious fatigue

Organisms causing persistent or latent infection	Virus	Epstein-Barr virus, human herpesvirus 6, human herpesvirus 7, herpes simplex virus, human immunodeficiency virus, hepatitis C virus, parvovirus B19, Influenza virus
	Bacteria, etc.	Coxiella burnetii, Helicobacter pylori
Organisms causing no persistent or latent infection	Virus	polio virus, Coxsackie B virus, West Nile virus, smallpox vaccine, hemorrhagic fever with renal syndrome viruses
	Bacteria, etc.	Borrelia burgdorferi, Streptococcus pneumoniae, Trichinella spiralis, Trichinella pseudospiralis, Staphylococcus, Legionnaires

Organisms which have been reported as the causes of post-infectious fatigue are listed.

fatigue-causing substance or fatigue transmitting substance.

However, the most probable candidates for such fatigue-inducing or fatigue transmitting substances are cytokines, including interferon. This is strongly shown by the fact that the patients undergoing treatment of hepatitis virus using interferon or other cytokines feel severe tiredness.^{9,16,19} It is also reported that TGF- β is associated with the occurrence of fatigue.^{1,23} However, because the mutual interaction and association of multiple cytokines are involved in the production and activation of cytokines, it has not been identified which cytokine plays a central role in causing or transmitting fatigue.

Chronic Fatigue

Fatigue is usually cured with rest, whereas sometimes unrecoverable fatigue may be accumulated. The latter is defined as chronic fatigue and is divided roughly into two categories. One is the accumulation of physiological fatigue because of continuous labor without rest, and the other is the continuation of morbid fatigue accompanying disease. Accumulated physical fatigue may result in a tragic outcome known as “death from overwork” at worst, so it should not be neglected, although it is only the extension of the physical phenomena.

Major morbid fatigue includes post-infectious fatigue and chronic fatigue syndrome (CFS). Although the etiology of CFS is unknown, the involvement of infection with some pathogenic organism is suspected. Post-infectious fatigue and CFS, therefore, are not irrelevant.

Diagnostic criteria to define CFS can be sim-

plified as follows: (1) A condition with serious tiredness which forces the absence from school or work for several days per month and continues for over 6 months or recurs many times; (2) No other disease is identified.

The patients with 8 or more of the following symptoms, which are often observed in CFS, are definitively diagnosed as CFS: 1) slight fever or chill, 2) throat pain, 3) swollen lymph nodes, 4) feeling of exhaustion of unknown etiology, 5) muscle pain, 6) general weariness, 7) headache, 8) joint pain, 9) psychoneurotic symptoms (memory impairment, confusion, impaired concentration, depression), 10) sleep disorders (insomnia, hypersomnia) and 11) sudden onset of symptoms (within several hours to several days).

Of these symptoms, 1), 2), 3), 5), 8) and 11) are often observed in virus infections, such as the common cold. The reasons why such symptoms are included in the diagnostic criteria are that the patients suspected of having CFS very frequently display symptoms similar to those of infectious diseases, and that CFS is considered to be caused by continuous fatigue following infection with some infecting factor. As a result, the study of post-infectious fatigue is important also for identifying the unestablished etiology of CFS.

Examples of Post-Infectious Fatigue

Many cases have been reported as post-infectious fatigue cases and, as shown in Table 1, the pathogenic organisms or infecting factors associated with the fatigue are wide ranging. This paper explains some cases which have important meaning for the subsequent studies and the understanding of post-infectious fatigue.

Table 2 Various latent infection forms of Epstein-Barr virus (EBV)

Type of latent infected cell	Form of latent infection	Manifested latent infected gene	Associated morbidity
B cell	latency 0	EBER 1, EBER 2, BARTs	Latent infection in healthy people
	latency I	EBER 1, EBER 2, BARTs, EBNA 1	Burkitt's lymphoma, etc.
	latency II	EBER 1, EBER 2, BARTs, EBNA 1, LMP-1, LMP-2A, LMP-2B	Nasopharyngeal carcinoma, etc.
	latency III	EBER 1, EBER 2, BARTs, EBNA 1, EBNA 2, EBNA 3A, EBNA 3B, EBNA 3C, EBNA-LP, LMP-1, LMP-2A, LMP-2B	In vitro immortalization or reactivation (?)
NK cell/T cell	latency II	EBER 1, LMP-1, LMP-2A	CAEBV

There are many different patterns of latent EBV infection, and the type of latency-associated gene, which appears, and the associated disease differ in each form. Latent infection with EBV infection usually occurs in B cells, while in chronic active EBV infection latent infection is established in NK cells and T cells.

Acquired immunodeficiency syndrome (AIDS)

Post-infectious fatigue is caused by various pathogenic organisms, and mass outbreak of post-infectious fatigue suggests an epidemic of some pathogenic infection. This is often an epidemic of a known pathogenic organism, such as influenza, but an unknown or unreported pathogen in the area can be discovered and identified sometimes as a cause of post-infectious fatigue. For example, until human immunodeficiency virus (HIV) was established as a cause, acquired immunodeficiency syndrome (AIDS) had attracted attention as a disease accompanied by fatigue of unknown etiology.¹⁵

Post-Rickettsia infectious fatigue

Coxiella burnetii, is an organism which causes Q-fever, belongs to the family Rickettsiaceae, and infects humans via cattle and pet animals. Many patients with Q-fever complain of symptoms such as fever, headache, muscle pain, respiratory symptom and strong systemic weariness. Infection with *Coxiella burnetii* often ends as acute infectious disease, whilst in about 5% of the patients, *Coxiella burnetii* remains in the body long after acute infection, and progresses to chronic Q fever.

Chronic Q fever accompanied by *Coxiella burnetii* infection for over 6 months is often more severe than acute Q fever. Chronic Q fever occurs in acute Q fever patients from one year to 20 years after the first infection and is often

accompanied by infectious endocarditis.^{2,6} Chronic Q fever patients complain of symptoms such as weariness, insomnia and joint pain. As these symptoms can continue for several to over ten years, they may be diagnosed as chronic fatigue syndrome (CFS).

Chronic active EBV infection

When it was found that some patients with severe persistent fatigue had high antibody titers to Epstein-Barr virus (EBV), EBV was considered as one of the causes of CFS. However, since EBV infection showing CFS-like symptoms was then recognized as chronic active EBV infection (CAEBV),^{4,7} other EBV infectious diseases than CAEBV are considered as unrelated to CFS.^{21,22} CAEBV is a disease in which the symptoms of infectious mononucleosis (IM) appearing at the first EBV infection, such as fever, pharyngitis, swollen lymph nodes and hepatosplenomegaly continue for over 3 months, and CAEBV patients complain severe fatigue. IM is a disease often observed in acute EBV infection and subsides with disappearance of symptoms in 1–3 months. One of the reasons why IM-like symptoms continue for a long time in CAEBV is the different pattern of EBV latent infection. EBV latently infects B cells in general and this latent infection progresses asymptotically in many cases, but it may cause various diseases depending on the pattern of latent infection (Table 2). In case of CAEBV, EBV latently infects NK cells and T cells, and induces active virus gene expression.¹⁰ It is considered that this produces abnormal

immunoreactions and causes fever and intense weariness.

Of the three cases mentioned above, chronic Q fever and CAEBV particularly show CFS-like symptoms, and can be said to be the cause of CFS. However, according to the present diagnostic criteria, diseases of known etiology are not CFS so they are not categorized as such. This means that the identification of pathogenic organism like chronic Q fever and chronic active EBV infection is most important for identifying the etiology of the CFS that occurs following infection. Also, the example of CAEBV suggests that the infection with the same EBV may present completely different symptoms, depending on the pattern of EBV presence, particularly the pattern of latent EBV infection, and lead to persistent fatigue.

Chronic Fatigue Syndrome

As previously mentioned, the fact that infection with various organisms causes post-infectious fatigue has been known for decades. However, it appears that the morbidities such as “post-infectious fatigue” and “post-viral infectious fatigue” came to the attention of the public following an outbreak known as the “Lake Tahoe mystery”, in which CFS-like symptoms affected a large number of people in the geographical area around Lake Tahoe in Nevada, USA. At this time, the concept of a “fatigue epidemic” was proposed.³ This condition posed a serious social problem, and many infection specialists launched investigation of its etiology. The concept of chronic fatigue syndrome (CFS) was proposed also for this Lake Tahoe incidence.

The morbidity named “Gulf War Syndrome” made public know the importance of post-infectious fatigue. Gulf War Syndrome is a disorder observed in many veterans discharged from military service in the Gulf war which started in 1991. Their main symptoms are muscle pain, night sweats, skin rashes, headache and diarrhea, and central nervous symptoms such as impairment in memory or concentration.^{5,8} Many researchers consider that Gulf War Syndrome is caused by infection through some factors including biological weapon.¹⁸ Gulf War Syndrome is considered as a kind of CFS which supports the argument that the identification of the infectious factor is most important in examining the etiology of CFS.

In fact, the observation of abnormal production of 2-5A synthetase and RNase L, indicators of interferon production in CFS patients, suggests that tiredness, a symptom seen in CFS is associated with the abnormal interferon production.²⁰ This is one of the reasons why CFS is considered as a kind of post-infectious fatigue.

The diagnostic criteria for defining CFS include those which are known as the symptoms of infectious disease such as slight fever or chill, sore throat, swollen lymph nodes and sudden onset of disease. In other words, it cannot be denied that these criteria were established on the assumption that the most probable cause of CFS was post-infectious fatigue.

Herpesvirus and Chronic Fatigue Syndrome

CFS is a disease which lasts far longer than post-infectious fatigue. It is considered, accordingly, that the infection causing CFS is a persistent or latent infection with some virus. It is known that once infecting herpesvirus establishes latent infection and then produces some symptoms by frequent reactivation. Since these properties of herpesvirus can explain why the symptoms of CFS patients repeat remission and exacerbation, the theory that herpesvirus is a cause of CFS is supported by many people. Among various herpesviruses, particularly HHV-6 and EBV, are often indicated to be associated with CFS. HHV-6 was isolated in 1986 from patients with acquired immunodeficiency syndrome (AIDS) and malignant lymphoma. This was at the time when many patients who were presenting CFS-like symptoms were found in the area near Lake Tahoe (USA), (op. cit), leading to the recognition of CFS as a disease. Since this new-discovered virus was detected in the patients with “fatigue epidemic”, HHV-6 was considered as the most probable candidate for the causative virus for CFS.³ As EBV was detected frequently in the patients presenting CFS symptoms, the association of EBV with CFS was also strongly suspected. However, CFS-like diseases associated with EBV were categorized, (op. cit), as “chronic active EBV infection”, and was defined as a different disease from CFS of unknown etiology.

Initial infection with HHV-6 in the early childhood, causing exanthem subitum, is followed by life-long latent infection in peripheral blood. As

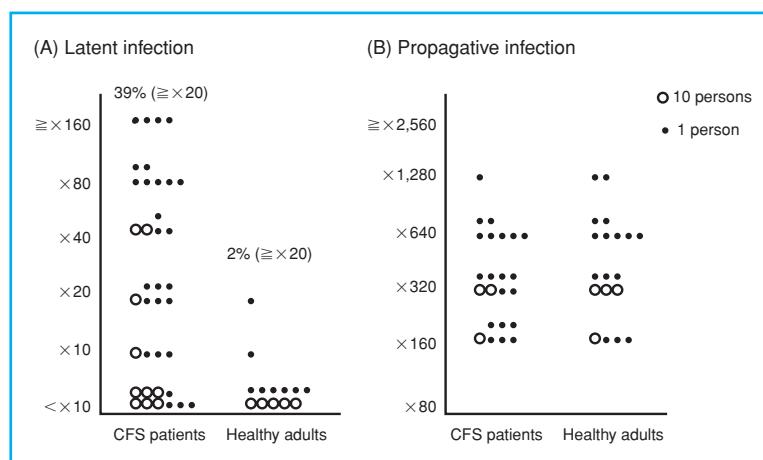


Fig. 1 Antibody titers to HHV-6 latent infection protein and structural protein

Antibody (A) to gene protein, which specifically appears in the latent HHV-6 infection, and the antibody titers (B) to virus structural protein, which mainly appears in the propagative infection, were examined in CFS patients and healthy adults. The antibody to structural protein often used in regular examination shows no significant difference between CFS patients and healthy adults, but that to latent infection protein shows substantial difference.

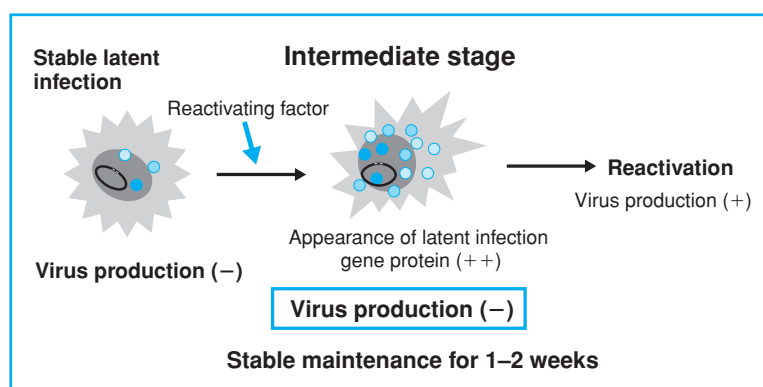


Fig. 2 Intermediate stage of HHV-6

HHV-6 shows the expression of mRNA from the gene (latent infection gene) which appears specifically in a stable latent infection stage. However, the mRNA does not produce protein, because its translation to protein is inhibited. However, the enhancement of transcription of latent infection genes and the removal of inhibition of the translation in the intermediate stage leads to active manifestation of the latency-associated virus protein, but no virus production (reactivation). It is thought that this stage lasts for several days to several weeks, followed by virus production in those progressing to reactivation. It is estimated that the intermediate state is important for the virus to prepare efficient reactivation and to the reproduction and maintenance of virus genes.

In view of the fact that CFS patients show abnormal immunoreaction to the latent infection protein which appears in this stage, it is considered that the presence of a large number of cells in this intermediate stage for a long period of time is associated with the onset of CFS.

the rate of infection of this virus is almost 100% in almost all countries, the antibody positive rate in adults is almost 100%. Whether or not a virus is associated with a particular disease is examined generally by identifying whether a patient has been infected with the virus, based on the presence of serum antibody, and whether the

patient's past history is correlated with the occurrence of the disease. However, this examination cannot be applied to HHV-6, as HHV-6 incidence rate is 100% (Fig. 1B).

However, if HHV-6 infection follows a special pattern similar to CAEBV infection, it may possibly present CFS-like symptoms. To examine

such a special-pattern latent infection it seems important to identify an HHV-6 gene specific to the latent EBV infection and its encoded protein, which appears specifically in the latent EBV infection and plays an important role in the diagnosis and research of latent infection, such as a gene corresponding to Epstein-Barr Nuclear Antigen (EBNA).

Latent HHV-6 Infection and Chronic Fatigue Syndrome

HHV-6 establishes latent infection in macrophage and in the brain, and manifests latency-associated gene, mRNA specific to latent infection.¹¹⁻¹⁴

In order to know the mechanism by which CFS is contracted, we researched to identify a special latent HHV-6 infection state, and latent HHV-6 infection protein corresponding to EBNA. The study revealed that HHV-6 had a third stage between latency and reactivation, in which the manifestation of the latent infectious gene is promoted (Fig. 2). This intermediate stage is observed in the first phase where HHV-6 commences reactivation, but is completely different from the reactivation in the respect that no virus is produced.

In order to examine the relationship between latent infection protein, whose manifestation is promoted in the intermediate stage, and disease, CFS patients' serum antibody titers to the cells in which latent infection protein is well manifested were examined. This examination revealed that about 40% of the CFS patients showed antibody reaction to latent HHV-6 infection, whereas healthy subjects showed virtually no reaction (Fig. 1A). It is possible that what is reacting with the infection is a virus protein which appears specifically in the latent HHV-6 infection, and

has EBNA-like functions and diagnostic significance that is important in the diagnosis of latent infection and reactivation of EBV. We considered that such immunoreaction, which is clearly different between CFS patients and healthy subjects, is undoubtedly associated with CFS morbidities. On the other hand, what is examined usually by using serum antibody titers against HHV-6 is the antibody that appears when HHV-6 proliferates, particularly the antibody to structural protein required in virus formation. As shown in Figure 1B, the antibody titers to the protein involved in the HHV-6 productive infection show no significant difference between CFS patients and healthy subjects. This explains why no difference in HHV-6 infection between CFS patients and healthy subjects is observed in the regular examination.

It is considered that the higher antibody titers to the protein that appears and increases in the intermediary stage in latent HHV-6 infection in CFS patients suggest the presence of cells in this intermediate stage in the body of CFS patients. The cells constituting latent HHV-6 infection and the intermediate stage are macrophage and glia cells. This is consistent with the fact that CFS presents immunological and psychiatric symptoms.

Conclusions

It is considered that the issue of post-infectious fatigue is critical for investigating the etiology of CFS and Gulf War Syndrome, both of which present severe fatigue. However, knowledge about persistent and latent infection with pathogenic organism is indispensable for the investigation, and further progress of the investigation is required.

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