Review

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Review

Herpesvirus Infection as a Systemic Pathological Axis in Myalgic Encephalomyelitis/Chronic Fatigue Syndrome

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Abstract: Understanding the pathophysiology of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) is critical for advancing treatment options. This review explores the novel hypothesis that herpesviruses' infection of endothelial cells (ECs) may underlie ME/CFS symptomatology. We review evidence linking herpesviruses to persistent EC infection and the implications for endothelial dysfunction, encompassing blood flow regulation, coagulation, and cognitive impairment – symptoms consistent with ME/CFS and Long COVID. The paper provides a synthesis of current research on herpesvirus latency and reactivation, detailing the impact on ECs and subsequent systemic complications, including latent modulation and long-term maladaptation. We suggest that the chronicity of ME/CFS symptoms and the multisystemic nature of the disease may be partly attributable to herpesvirus-induced endothelial maladaptation. Our conclusions underscore the necessity for further investigation into the prevalence and load of herpesvirus infection within ECs of ME/CFS patients. This review offers a conceptual advance by proposing an endothelial infection model as a systemic mechanism contributing to ME/CFS, steering future research towards potentially unexplored avenues in understanding and treating this complex syndrome.

Keywords: Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS); endothelial cells; herpesvirus

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1. Introduction

Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) is a chronic condition characterized by unresolved fatigue, cognitive dysfunction, malaise, orthostatic issues, and post-exertional symptom exacerbation (PESE), among other symptoms [1]. The etiological cause is officially unknown, but viral infection is believed to be a precipitating factor and pathology is very much associated with viral activity [2-5]..

Herpesviruses are the most implicated in ME/CFS research [2, 4-10], and as such the relationship between herpesviruses and ME/CFS has been reviewed extensively [2, 4, 10-12]. Herpesviruses have the ability to infect a number of different cell types within the body, but exhibit preference for a particular population. For instance, the primary target cells of EBV are B-cells [13], whereas human cytomegalovirus (HCMV) attacks non-lymphoid cells, of which endothelial cells are a favoured cell-type for infection [14, 15]. That is not to say, however, that EBV, for example, is unable to infect cell types other than B-cells and cause significant pathological consequences.

Endothelial dysfunction is another prominent characteristic of ME/CFS pathology, and has been repeatedly demonstrated in older and more recent studies [16-24]. Blood flow, especially cerebral

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blood flow is perturbed and reduced in ME/CFS patients (van Campen et al., 2020b, van Campen et al., 2020a, van Campen et al., 2021b, Campen et al., 2022, Staud et al., 2018, Biswal et al., 2011, Boissoneault et al., 2019), as well as the perfusion of various brain regions (COSTA et al., 1995, Yoshiuchi et al., 2006, Shungu et al., 2012, Li et al., 2021). ME/CFS is not typically viewed as a vascular disease, but the aforementioned findings as well as evidence of endothelial and vascular dysfunction in Long COVID (Ambrosino et al., 2021, Haffke et al., 2022, Stahl et al., 2020, Turner et al., 2023), a disease that shares many symptoms with ME/CFS [25-28], begs the question as to whether or not endothelial and vascular pathology are important factors for ME/CFS pathology and symptom manifestation.

We have recently demonstrated hematological pathology in ME/CFS platelet-poor plasma (PPP) samples, specifically pertaining to platelet and clotting processes [29]. We found significant levels of amyloid fibrin(ogen)/microclots – the clotting material that is implicated in Long COVID [30-32] – in ME/CFS PPP samples. These microclots are therapeutically targeted with considerable success in Long COVID patients [33]. Other research groups have also demonstrated platelet abnormalities in ME/CFS cohorts [34-36], as well as abnormalities in clot formation and kinetics [37]. It is well-known that the integrity of endothelial cells and normal signalling thereof is paramount for the regulation of coagulation [38, 39], and this leads to the recognition that endothelial dysfunction might be, at least in part, responsible for the abnormalities in coagulation and platelet function observed in ME/CFS patients.

The ideas of impaired circulatory function, reduced tissue oxygen supply, and unmet metabolic demands revolving around endothelial dysfunction and its inability to correctly regulate vascular tone have been discussed in the context of ME/CFS pathology and symptom manifestation before, and have even been tied to symptoms including fatigue and cognitive dysfunction (Wirth and Scheibenbogen, 2020, Wirth et al., 2021, Wirth and Scheibenbogen, 2021)[40].

Circling back to viruses, very few or no studies have focussed on herpesvirus infection of the endothelium in ME/CFS and the consequences that this might have for pathology and symptom manifestation. It is acknowledged that herpesviruses can induce pathology independent of the endothelium, phenomena which certainly have relevance to ME/CFS and other diseases. However, here we aim to focus on herpesviruses and the endothelium or associated tissue. There are a number of different herpesviruses, but the focus here will be on the ones previously implicated in ME/CFS, such as HHV-4 (EBV), HHV-5 (HCMV), and HHV-6 [2-5, 41, 42]. For an overview of the idea presented in this paper, as well as a mind map for clarification, see Figure 1.

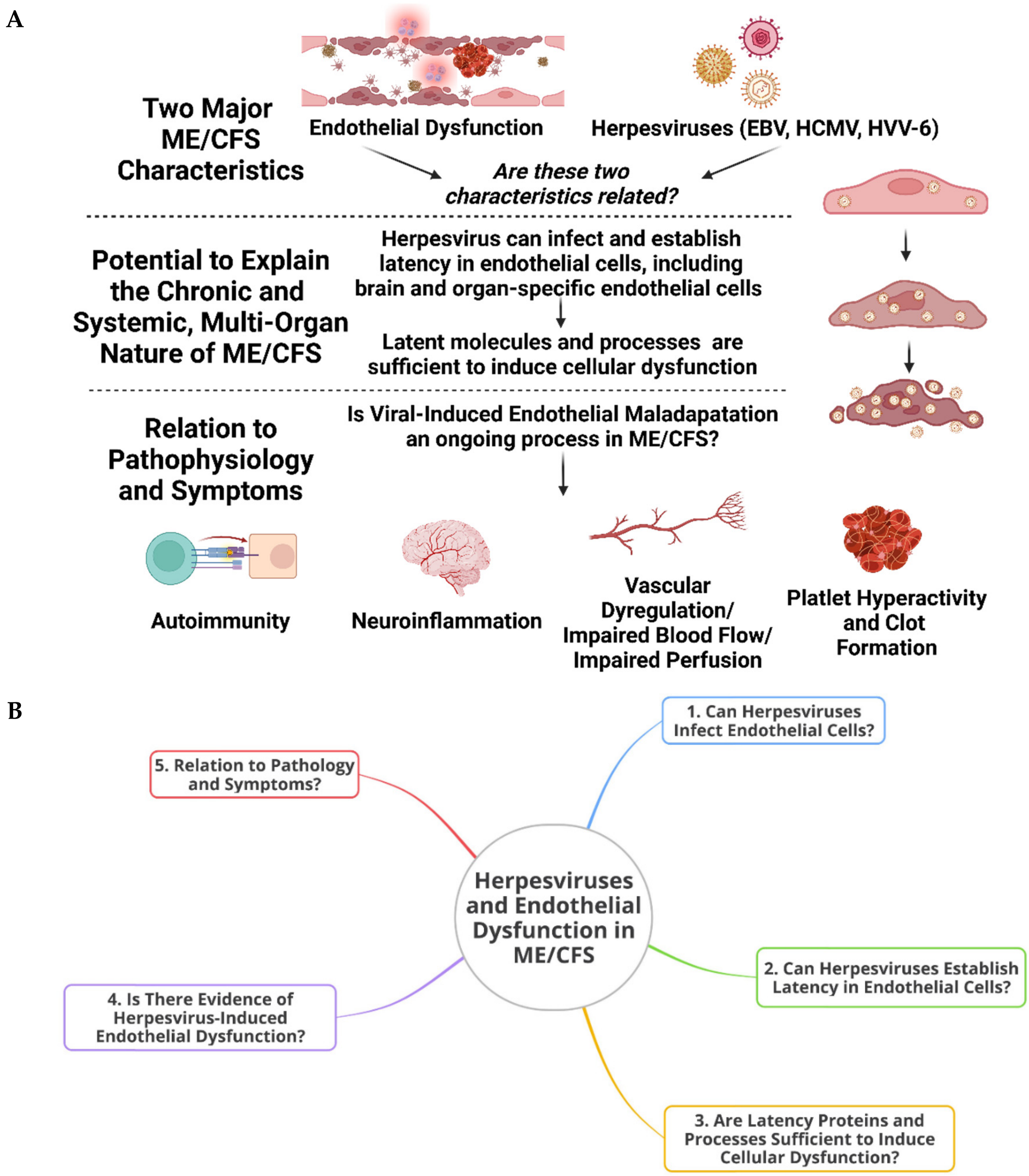

Figure 1. An overview of the present paper. A) A delineation of our thought-approach and B) a chronological mind map (created on https://app.ayoa.com/mindmaps).

2. Infection of Endothelial Cells By Herpesviruses, Latent Modulation, Systemic Complications, and the Potential for Long-Term Maladaptation

With relevance to the present idea, endothelial cells (ECs) are known to be able to succumb to infection by EBV [43-50], HCMV [14, 15, 51-56], and HHV-6 [57-62]. Other herpesviruses also infect ECs [63, 64]. Since herpesviruses are intimately associated with ME/CFS, this already provides reason to hypothesize that the endothelium in ME/CFS patients is, to some extent, infected by herpesviruses.

Next, it is important to state that herpesvirus latency, specifically, can occur in ECs. Herpesviruses establish lifelong infection/latency by either integrating their genome into the host genome or, more commonly, having the genetic material exist in the nucleus as an episome [65]. Both HHV-6 [59-61, 66, 67], and HCMV latently infects ECs (and smooth muscle cells) [14, 56, 68, 69], which are the HCMV's preferred cell type for infection. There are indications that EBV establishes latency in ECs [48, 49] and certainly evidence that EBV infects ECs (as will be discussed in the following sections); but the exact mechanisms around EBV latency in this cell type seems to be unestablished.

Active viral infection has been shown in ME/CFS [3, 41, 70, 71], but has not been specifically studied in an endothelial context. Active infection might not necessarily coincide with all symptoms as active infection is not necessarily a continuous process; hence active infection might fall short in providing a unitary explanation for daily symptoms. While active infection will certainly involve the endothelium, it may be true that latency is sufficient enough to induce endothelial dysfunction that brings about ME/CFS symptoms – that is, if herpesvirus latency occurs within ECs (it is possible that latency in non-ECs can indirectly cause endothelial dysfunction too, see later).

As with the development of bacterial dormancy [72, 73], herpesvirus latency is not a passive process [65, 74, 75], especially from the perspective of the host cell. For example, HHV-8 latency causes dysfunction of the endothelium, including increased permeability, disruption of endothelial cell junctions, activation of NF-κB, angiogenic disturbances, and increased protein phosphorylation [76-79]. There are viral proteins and nucleic material that regulate latency and reactivation, modulate host cell functions and proliferation, and ensure viral subversion of the immune system [65, 80]. The activity of herpesvirus latency and all the specific molecular processes that occur within the host nucleus (as well as those that occur in the cytosol and extracellularly) might bring about specific defects at the endothelial layer. The immune and neurological systems are certainly involved, but so might be the endothelium.

ME/CFS is a chronic condition, and the chronicity of symptoms bears an explanation. Herpesvirus infection of ECs might be able to explain the persisting nature of ME/CFS symptoms. Firstly, endothelium has a low turnover, with the entire population being replaced every 6 years in adults [81]. Other studies estimate anywhere from months to decades [82], but note that tissue-specific ECs vary in rates of turnover. Regardless, the idea is that the endothelium is a normally long-lasting tissue, and viral-induced dysfunction, especially caused by persisting viruses that can establish latency, may continue for the rest of an EC's life. Relevantly, EBV, HCMV, and HHV-8 inhibit apoptosis in ECs [83-85] and can increase the persistence of dysfunctional ECs. HHV-6 also inhibits apoptosis of host cells [86].

This ability of herpesviruses to establish latency in (endothelial) host cells, along with the long life span of ECs, means that herpesvirus-infected endothelium and the resulting complications may persist for months to years. This is a timeline which is in accord with the chronicity of ME/CFS symptoms. Hence, it is plausible that ME/CFS ECs undergo chronic maladaptation as a result of (latent) herpesvirus infection, which might be important for the maintenance of pathology and symptom manifestation. Furthermore, this may be an ongoing phenomenon in other diseases too.

A particular significance of this reasoning is its focus on the cell type that we are postulating to be involved and infected. ECs are the interface between blood and tissue. They enable gas exchange, nourishment, and waste clearance, regulate inflammatory processes, secrete bioactive amines that contribute to hematological and vascular homeostasis, and perform many other essential physiological functions. Any dysfunction in these cells and their functional processes are likely to contribute to or induce pathology. Furthermore, the vasculature extends into every organ system, and hence such endothelial dysfunction might account for the multi-organ and systemic nature of ME/CFS pathology.

3. Latent Infection by Herpesviruses is Sufficient to Bring About Cellular Dysfunction, and Might Hold Relevance to Endothelial Dysfunction and Symptom Manifestation in ME/CFS

Herpesviruses are persistent viruses that affect host cells for a lifetime, supporting the notion that latency might be able to cause chronic pathologies like ME/CFS, in susceptible individuals. It is emphasized that persistent, latent infection is not a passive process and in fact exerts pathological effects on the host [74, 75, 87, 88]. Hence, herpesvirus reactivation and active infection may not be a necessity for the manifestation of ME/CFS symptoms, although it is expected to exacerbate any issues. Here, we aim to show that latent proteins from herpesviruses are sufficient to induce cellular dysfunction, and hint at the idea that they and latency-related processes contribute to the endothelial and vascular dysfunction – as well as other pathophysiological characteristics – observed in ME/CFS.

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Herpesviruses use a number of proteins and microRNAs to drive latency, evade immune surveillance, regulate host processes, and coordinate the transition to active infection [65, 89]. Studies of HHV-8 and ECs have shown significant dysfunction as a result of infection, where multiple cell signalling pathways are disturbed by viral activity [90]. Most notably, Liu et al (2010) demonstrated that latent proteins cause the activation of a Notch ligands and receptors, and induce the expression of endothelial precursor markers prompting a state of differentiation. It has also been shown that HHV-8 latency causes increased permeability, disruption of endothelial junctions, activation of NF-κB, and angiogenic disturbances (Guilluy et al., 2011, DiMaio et al., 2011, Grossmann et al., 2006)[76, 77, 79]. These studies, although conducted on HHV-8, provide mechanistic evidence for the present idea of herpesvirus-induced endothelial dysfunction, and are represented in Figure 2.

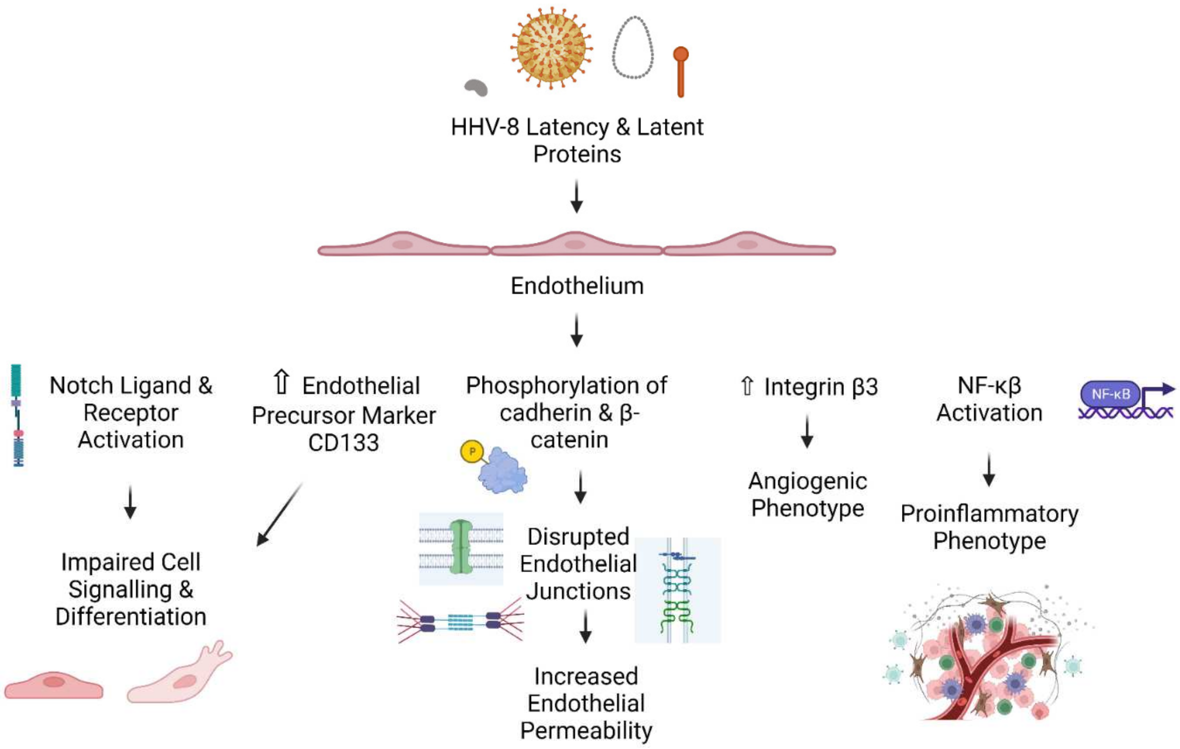

Figure 2. Mechanisms by which HVV-8 latency and associated proteins cause endothelial dysfunction.

EBV is a heavily studied herpesvirus, most notably due to its ability to transform lymphocytes and epithelial cells into malignant phenotypes [91, 92], and for its role in causing infectious mononucleosis. In fact, it is well known that EBV latent genes and their products specifically interrupt cell cycles and promote oncogenesis [89], and both latent and lytic gene products illicit notable immune responses [93]. Epstein-Barr Nuclear Antigens (EBNAs) are a group of proteins encoded by EBV which are essential for viral genome replication and transcription, the establishment and regulation of latency (even though some function for lytic processes), and immune evasion [94-96]. Other latency-associated molecules encoded by EBV include latent membrane proteins (LMPs) and EBV-encoded small RNAs (EBERs) [97, 98].

EBNA-1 significantly increases ROS production in the host cells that they infect, and, via this mechanism, contributes to DNA damage and the inhibition of the repair thereof [99-101]. It inhibits apoptosis and enhances cell survival, contributing to its recognition as an oncoprotein [102]. Expression of this latent protein in ECs is associated with higher IL-6 production [48], and hints at the potential of an EBV-infected endothelium to adopt a proinflammatory phenotype with a range of downstream consequences, including immune activation, increased clotting propensity, and vascular dysregulation. Immune responses against EBNA-1 also lead to the production of autoantibodies [103, 104], which might have relevance to autoimmunity in ME/CFS [105-107]. EBNA-1 is also associated with an upregulation of IL-8, hypoxia-inducible factor-1 alpha, and vascular endothelial growth

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factor (VEGF) [108], of which the latter two promote angiogenesis and influence vascular integrity and dynamics.

EBV's LMP-1, via NF-κB, increases the expression of cyclooxygenase (COX) 2, prostaglandin E_2, and VEGF [109]. In fact, LMP-1 is capable of activating several forms of NF-κB involving a number of different signalling mechanisms [110], and also activates JAK3, p38, mitogen-activated protein kinases, and several STAT-related proteins [111, 112]. Importantly, in ECs LMP-1 leads to NF-κB activation and increased expression of IL-1β, IL-6, IL-8, monocyte chemotactic protein-1, RANTES, ICAM-1, VCAM-1, and E-selectin; and the inhibition of caspase-3 and hence the reduction of apoptotic tendencies [113]. This study emphasizes the potential cellular dysregulation that occurs in ECs as a result of herpesvirus latency, as well as localized and potentially systemic physiological disturbances, including the activation and binding of immune cells and platelets to the endothelium.

Endocan is upregulated by LMP-1, again via NF-κB, and levels of endocan and LMP-1 are positively correlated in patient tissue samples [114]. Endocan can promote endothelial dysfunction and cardiovascular disease by increasing inflammation, oxidative stress, and the expression of adhesion molecules [115]. LMP-1 increases the sumoylation of proteins related to cellular migration and transcriptional activity [116] and also increases glycolytic processes and interferes with host metabolism [117-119]. LMP-1 also modulates host epigenetic processes [120-122] and hinders DNA repair mechanisms [123].

Host protein synthesis is inhibited and autophagy and the regulation thereof is interrupted by LMP-1 [124], and this latency protein also activates the unfolded protein response [125]. Lastly, LMP-1 also interferes with mitochondrial regulation and cell metabolism by altering the phosphorylation of the mitochondrial dynamin-related protein 1 [126]. LMP-2A exerts potent anti-apoptotic effects and aids in immune evasion by reducing the reactivity of CD8+ T cells to cells infected by EBV [127, 128]. RNAs from EBV, EBERs, are also associated with cellular dysfunction and proinflammatory processes [129], and represent other mechanisms by which EBV latency can bring about cellular dysfunction. Figure 3 represents the mechanisms discussed by which EBV latency proteins EBNA-1 and LMP-1 can induce cellular dysfunction in endothelial cells.

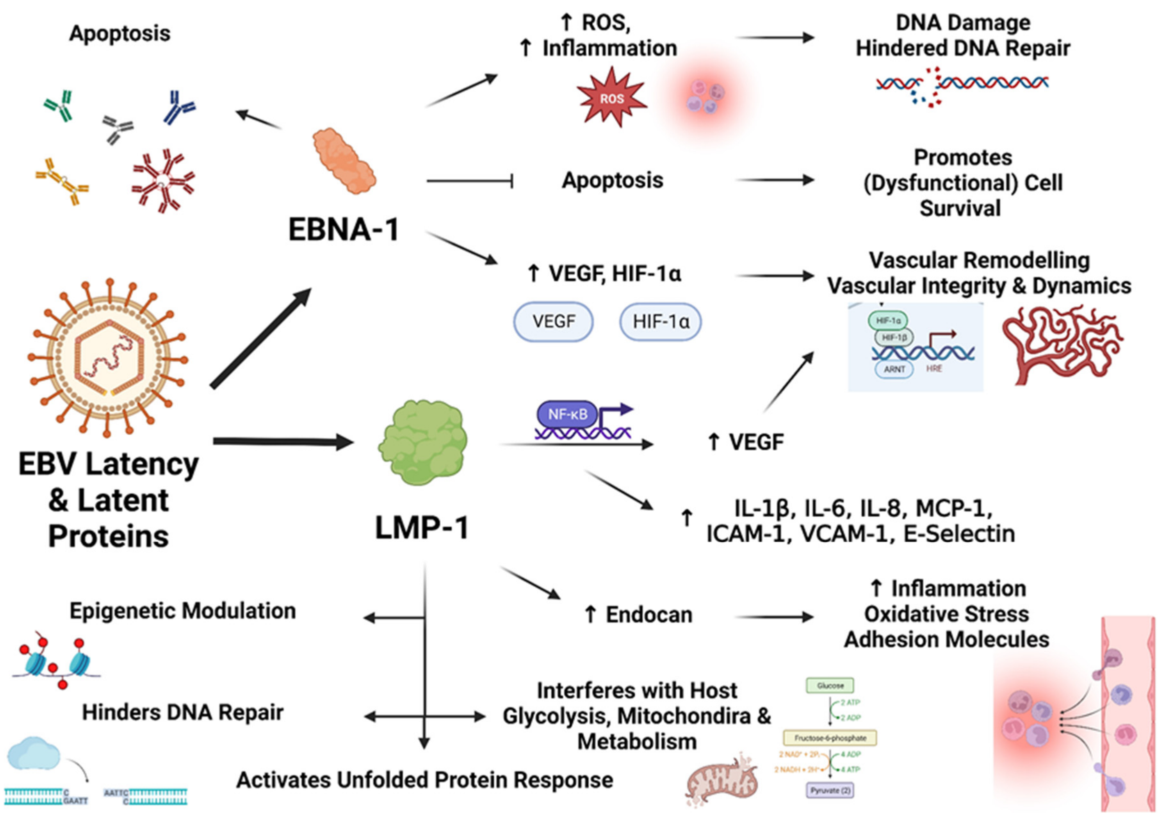

Figure 3. Some mechanisms by which EBV latent proteins EBNA-1 and LMP-1 can induce cellular dysfunction in endothelial cells.

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UL138 is a latency-associated protein produced by HCMV [130, 131] and is expressed in infected ECs [132]. UL138 upregulates host EGFR/PI3K/AKT signalling to maintain latency and in turn increases its own expression via EGR-1 [132], and interferes with the function and expression of transport proteins, such as the multidrug resistance-associated protein-1 [133]. It increases levels of TNF-α bound to cell membranes and leads to tumour necrosis factor receptor 1 hyperresponsiveness [134], which prompts immune activation and proinflammatory processes.

US28 from HCMV, while not considered a latency-associated protein, is expressed during both latent and lytic infection and is a potential target for therapy in vascular disease as it increases inflammation and modulates the activity and migration of smooth muscle cells [135, 136]. US28 interferes with a variety of cell signalling pathways in ECs including STAT, phospholipase C, GPCR, and NO pathways, and can increase cellular NO expression [137, 138]. It binds chemokines including monocyte chemotactic protein 1 and RANTES [139]. US28 increases leukocyte adhesion to the endothelium and aids viral dissemination [140]. Furthermore, antibodies directed against US28 bind to ECs and induce endothelial damage and apoptosis [141]. ECs exposed to these antibodies increase expression and release of HSP60 which can go on to stimulate TLR4 and lead to proinflammatory sequelae in circulation and in the vasculature [142]. It must be noted that US28 itself, not the antibodies directed against it, acts in an anti-apoptotic manner [143]. Importantly, HMCV-infected ECs express US28 on their cell membranes [143].

In ECs, U94, a latency-associated protein from HHV-6 [144], reduces cell migration and angiogenic potential (by desensitizing the response to VEGF), and thus leads to prolonged wound healing [66, 145]. U94 increases the expression of human leukocyte antigen G, which is believed to underlie its effects on angiogenesis [58]. This latent protein from HHV-6 also shows anticancer potential as it inhibits DNA repair genes and aspects of the cell cycle, and leads to apoptosis via the intrinsic pathway [146]. While U94 shows potential in cancer therapy, its effects on DNA repair and cell function might not be so favourable in non-malignant, healthy cells.

Ultimately, latency-related molecules and processes are sufficient to induce (endothelial) cellular dysfunction. Latency of herpesviruses, especially when carried out in a particular cell type (such as ECs), might have consequences for systemic physiology. The extent to which this is an ongoing process in ME/CFS warrants further investigation.

4. Evidence for Herpesvirus-Induced Endothelial Dysfunction

We next present the links between herpesvirus infection and endothelial pathology, specifically (Table 1). This will focus on direct and indirect mechanisms, but will not be exclusive to latency-related molecules and processes.

Table 1. Links between herpesvirus infection and cellular dysfunction in ECs.

Links Between Herpesvirus Infection and Endothelial Dysfunction	References
EBV	
ECs infected with EBV exhibit a proinflammatory phenotype, along with NF-κB and TLR9 activation, increased interferon, cytokine, and adhesion molecule expression, and increased clotting propensity	[50, 113, 147]
ECs increase expression of markers associated with vascular injury, such as endothelin-1, thrombospondin 1, and heparan sulfate proteoglycan 2	[50]
Monocytes have the ability to transfer EBV infection to ECs	Monocytes have the ability to transfer EBV infection to ECs
Microvascular brain ECs infected by EBV exhibit a proinflammatory phenotype and lead to leukocyte recruitment	[49, 148]
Upregulation of endothelial adhesion marker VCAM-1 upon infection	[149]
EBV-infected macrophages induce proinflammatory sequelae in ECs, and increase adhesion molecule expression	[150]
EBV dUTPase compromises blood-brain barrier integrity	[9]
EBV alters cholesterol, polysaccharide, nucleotides, nucleic acid and proline moieties in infected brain microvascular ECs	[147]

EBV-infected ECs of genital origin express LMP-1 on their membranes	[151]
Endothelial microenvironment is influenced by EBV infection	[152]
Extracellular vesicles from EBV-infected cells damage endothelial gap junctions, and prompt endothelial-to-mesenchymal transitions	[153]
Modulation of host autophagy in endothelial cells	[154]
Exosomes containing EBV-proteins can cross brain ECs and enter the central nervous system	[155]
EBV protein-containing exosomes can lead to long-term endothelial dysfunction	[156]
HCMV	
HCMV establishes latent infection in ECs	[68, 69, 157-159]
ECs of the microvasculature in the brain, lungs, heart, and gastrointestinal tract are target infection sites, but so are large vessel ECs	[14, 160, 161]
Reactivation causes endothelial dysfunction	[162]
HCMV can cause significant infection even when multiplicity of infection is low	[163]
MicroRNA (UL112) interferes with cell signalling pathways	[164]
HCMV infection is associated with endothelial inflammation and vascular disease, and the virus is localized in atherosclerotic plaques and non-plaque tissue surrounding lesions	[161, 165-168]
HCMV increases atherosclerotic development in mice models with apolipoprotein E deficiency	[169]
HCMV induces the expression of leukocyte adhesion molecules on ECs and subsequent leukocyte activation and recruitment	[140, 170-174]
Leukocytes undergoing transendothelial migration can be infected by infected ECs	[174]
In a patient with HCMV infection, ECs were found to be abnormal and containing viral inclusion bodies	[175]
The secretome of HCMV-infected fibroblasts contains over 1000 different proteins, most notably a profile that induces angiogenesis and wound healing in ECs	[176]
HCMV interferes with DNA protection mechanisms in ECs, specifically by interfering with the ataxia telangiectasia mutant pathway	[162]
EC autophagy is upregulated by HCMV	[173]
HCMV disrupts the mitochondrial transmembrane potential of endothelial mitochondria and leads to the release of cytochrome c and subsequent apoptosis	[177, 178]
HHV-6	
HHV-6 infection is associated with endothelial dysfunction and a greater extent of endothelial damage than HCMV	[66, 179, 180]
HHV-6 infects ECs but does not induce cytolytic effects, which led to the conclusion that ECs act as a reservoir for HHV-6 in vivo	[57]
HVV-6 is able to maintain a low-level of replication within ECs	[60, 67]
An association between HHV-6 and endothelial dysfunction coupled to microcirculatory defects has been demonstrated	[181]
The induction of endothelial dysfunction by HHV-6 and subsequent influence on perfusion have been alluded to	[182]
HHV-6 antigens, DNA, and virus particles are found in ECs and associated vascular tissue from patients suffering from various cardiovascular diseases	[62, 183-187]
Cardiac dysfunction, specifically reduced LVEF is associated with HHV-6 DNA persistence in endomyocardial biopsies, and is ameliorated when HHV-6 latency is resolved	[188]
Considered to be a major cause of viral myocarditis	[189]
HHV-6 also infects the CNS and ECs lining its vasculature	[190-192]
HVV-6 is implicated in neurological disease	[193-198]
Much like EBV, HHV-6 uses TLR9 to upregulate inflammation and promote lymphocyte filtration, as was revealed from a study where mice infected with	[199]

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HHV-6 subtypes resulted in CNS infection and viral persistence in brain tissue for up to 9 months	
HHV-6 induces cellular inflammation and upregulates the expression of IL-8, RANTES, and monocyte chemoattractant protein-1 in ECs, even in a latent state, without viral DNA replication	[57, 59, 200]
It can also promote the reactivation of EBV	[201]
Lymphatic ECs also succumb to latent infection by HHV-6, where EC angiogenic and migratory properties are modulated	[66]

5. Herpesvirus-Induced Endothelial Dysfunction and Its Relevance To ME/CFS

We have discussed the potential of herpesviruses to infect and establish latency in ECs, how their latent proteins and processes are sufficient to induce (endothelial) cell dysfunction, and some of the evidence of herpesvirus-induced endothelial dysfunction. Now, we want to touch on some of the pathophysiological characteristics of ME/CFS and how they might relate to the present discussion thus far.

6. Endothelial Cells, Smooth Muscle Cells, Substance Exchange, Vascular Dysregulation, and Perfusion: What Role Might Herpesviruses Have to Play in the Dysregulation of Blood Flow Observed in ME/CFS?

One of the most important findings in ME/CFS research is that of reduced cerebral blood flow in patients, even in those without tachycardia and hypotension [202-205]. The orthostatic symptoms associated with ME/CFS are not due to deconditioning [206, 207], suggesting an underlying defect in blood flow regulation, perhaps related to autonomic dysfunction [208]. Viral infection of vascular cells, such as ECs and smooth muscle cells, and neurons might contribute to these blood flow and perfusion abnormalities of ME/CFS.

As we have seen, herpesviruses can significantly affect ECs and result in structural and functional changes, which have consequences for the physiological roles of ECs. Endothelial dysfunction is associated with and contributes to impaired tissue perfusion [209-213], and there is even evidence demonstrating an association between herpesviruses and impaired perfusion of tissues [50, 174, 214].

EBV and HHV-6 are associated with reduced cerebral blood flow and perfusion of particular regions [214-216]. Furthermore, Farina et al (2021) demonstrated that skin perfusion is significantly reduced in patients with higher EBV loads in the blood compared to patients with low or undetectable viral loads (hence, EBV load is inversely associated with blood perfusion; refer to the adopted Figure 4). Bentz et al (2006) also demonstrated that HCMV disrupted junction proteins of ECs and increased the permeability of an in vitro endothelial layer [174].

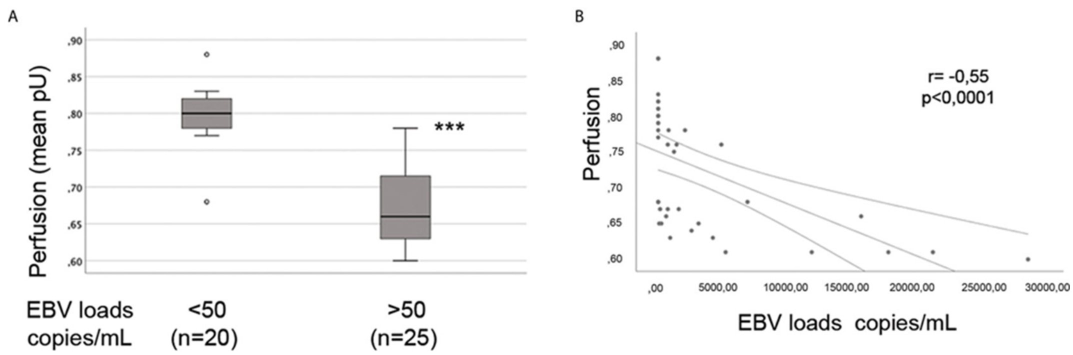

Figure 4. Adopted figure from [50] showing that EBV load is inversely associated with hand skin perfusion (Open Access).

HHV-6 encephalopathy is associated with reductions in cerebral blood flow and perfusion of the frontal lobe [215], as well as perturbations in coronary microcirculation [181]. Similarly, EBV encephalitis is also associated with reduced cerebral blood flow [214]. Caruso et al (2002) showed that large vessel ECs, specifically aortic ECs are more susceptible to infection by HHV-6 than are ECs of the microvasculature [57], and might have relevance to reduced cerebral blood flow in ME/CFS. Latent HCMV infection has been documented in smooth muscle cells from patients suffering from atherosclerosis [217] and abdominal aortic aneurysm with resulting functional changes including enhanced cell proliferation [218]. Patients with a history of HCMV infection display signs of endothelial dysfunction and blood flow dysregulation [219].

Nitric oxide signalling, which is essential for blood flow regulation, is hindered by HCMV, as it upregulates the P38-MAPK pathway which in turn inhibits endothelial nitric oxide synthase (eNOS) [220]. Also necessary for vascular control, specifically vasoconstriction, are endothelins, of which HCMV decreases endothelin-1 in ECs and smooth muscle cells [221], but increases the receptor for endothelin-1 in ECs [222]. HCMV modulates smooth muscle cell migration, proliferation, and expression of platelet derived growth factor receptor beta [223]. Apoptosis of smooth muscles cells are inhibited via a p53-related mechanism by immediate-early proteins produced by HCMV and is proposed to contribute to the accumulation of cells in atherogenic lesions [224]. Furthermore, smooth muscle cells grown from such lesions express HCMV immediate-early proteins [225]. Consequently, HCMV features can occupy a central role in aetiology of dysregulated blood flow and pressure due to its infection of and effect on ECs and vascular smooth muscle cells – namely, its ability to interfere with NO and endothelin signalling, induce proinflammatory sequelae, and activate the renin-angiotensin system [220, 221, 226].

In a histopathological examination of penile tissue from two males with and two males without a history of COVID-19 infection, viral RNA was detected and virus particles were found in the proximity of ECs in the COVID-positive patients [227]. Furthermore, eNOS expression was also decreased in the COVID-positive samples. The researchers inferred that systemic (and of course localized) COVID-19-induced endothelial dysfunction can result in erectile dysfunction. If this is the case, then it emphasizes the extent to which virus-infected/affected ECs can impair tissue perfusion.

Viruses (and bacterial LPS) can damage the glycocalyx of the endothelial layer [228-232]. A damaged glycocalyx impairs perfusion and also increases risk of mortality in hospitalised patients [213, 233-237]. As mentioned earlier, these herpesviruses can also damage endothelial cellular junctions and hence endothelial barriers [153]. HHV-6 can cause fibrosis in ECs [238], and may have implications for perfusion and the ability to exchange substances across vessel walls. These are possible mechanisms by which herpesviruses might bring about impairments in vessel regulation, blood flow, and perfusion.

Hence, infection of ECs and smooth muscle cells by herpesviruses might play a contributory role to the blood flow deficits and vascular dysregulation observed in ME/CFS [202-205, 239]. Investigation of vascular tissue from patients can further inform our understanding of vascular dysfunction and impaired tissue perfusion in ME/CFS. Furthermore, herpesviruses might also contribute to this issue by infecting neurons and causing dysregulation of autonomic control [107, 208, 240].

7. Herpesviruses, Endothelial Cells, Platelets & Coagulation

Related to the platelet-related abnormalities of a procoagulant phenotype found in ME/CFS patients [29, 34-37], there have been cases where EBV infection caused/was associated with severe cardiac and vascular issues, including myocarditis, vasculitis, disseminated intravascular coagulation, venous thromboembolism, thrombotic thrombocytopenic purpura, deep vein thrombosis, and stroke [241-249], emphasizing EBV's role in hematological and vascular pathology. EBV infection of ECs causes a significant increase in von-Willebrand factor (VWF), VEGF, and platelet endothelial cell adhesion molecule-1 (PECAM) levels [152], which contribute to procoagulant processes. ECs participate in coagulation processes and the regulation thereof, and hence minor cellular disturbances such as an increase in endothelial vWF expression caused by EBV [152] will have significant effects on clotting processes.

Thrombotic processes and events are associated with HCMV infection [175, 250-261]. It has been proposed that HCMV brings about thrombotic complications due to its modulation of the endothelium and dysfunction thereof [54, 262]. HCMV can greatly influence the phenotype of ECs and bring about procoagulant effects [263]. ECs infected with HCMV increase surface expression of adhesion molecules, with some related to coagulation [170]. In a patient suffering from thrombosis without predisposing risk factors, HCMV infection was present and ECs from the patient were found to be abnormal and containing viral inclusion bodies [175]. These endothelial viral inclusion bodies contain virions and HCMV-specific proteins, along with the lysosomal marker LAMP-1 [159]. They are believed to aid in viral maturation in ECs, and lead to the release of virus particle/protein-containing exosomes in fibroblasts. Another such case with simultaneous HCMV infection, along with the presence of antiphospholipid syndrome, was treated successfully with anticoagulants [255]. Antiphospholipid syndrome may result due to antigen similarities between viral and human phospholipids [256, 264]. Acute CMV infection has also been documented alongside venous and pulmonary embolisms [259, 265], and thromboembolic processes in patients with AIDS [266].

HMCV directly binds to platelets via toll-like receptor 2 (TLR2) and induces platelet activation, leukocyte adhesion and recruitment, VEGF expression, and proinflammatory sequelae [267]. HMCV can induce platelet adhesion and aggregation within infected ECs too [54]. A mechanism by which HMCV-infected ECs induce platelet activation and aggregation occurs involves vWF, as HCMV-infected cells increase intracellular and extracellular expression of this molecule [54]. Platelet aggregation was inhibited when vWF or the platelet receptor for vWF was blocked, but not when the GPIIIb/IIa receptor (which binds fibrinogen) was blocked. Blocking of ICAM-1 also decreased the extent of platelet aggregation, highlighting its role in thrombogenic processes. Rahbar et al (2005) also noticed an increase in P-selectin on non-infected cells treated with the extracellular fluid of HCMV-infected ECs, which is in accord with our findings of increased P-selectin expression on platelets in an ME/CFS cohort [29]. Treatment with ganciclovir inhibited this procoagulant effect of HCMV-infected ECs [54]. Ultimately, Rahbar et al (2005) concluded: 'Hence, HCMV may promote thrombosis and disseminated intravascular coagulation as a result of endothelial injury—or, as we have found, possibly by increasing the surface expression of vWF, perhaps by causing the translocation of already formed vWF present in Weibel-Palade bodies to the cell surface'. This is in accord with the current hypothesis of virus-induced endothelial maladaptation, and also provides reason for the coagulation and platelet abnormalities observed in ME/CFS.

The HCMV membrane contains phospholipids that enable the assembly of prothrombinase [268], a procoagulant protein that leads to thrombin generation. HCMV infection is also associated with a decrease in protein S and subsequent thrombosis [257]. We have recently discovered reduced protein S levels in an ME/CFS cohort via DIA LC-MS/MS techniques. Whether this finding is related to HCMV infection in the ME/CFS population is undetermined, but seems plausible as ECs – which succumb to HCMV infection – are responsible for regulating protein S expression.

HHV-6 infection is associated with prothrombotic states [70, 180]. Specifically, it is associated with thrombotic microangiopathy – whether this is related to fibrinaloid microclots which are found in both Long COVID and ME/CFS cohorts requires further investigation [29, 31].

Hence, there is reason to suspect that the clotting and platelet abnormalities noted in ME/CFS arise from the consequences of herpesvirus-infected ECs, as well as other procoagulant effects of herpesviruses independent of endothelial cells. ECs are extremely important for the homeostasis of the coagulation system. Virus-induced endothelial maladaptation may underlie findings of abnormal coagulation, platelet hyperactivity and platelet aggregation in ME/CFS cohorts [29, 34, 35].

8. Herpesviruses and Neurological Issues in ME/CFS: Implications at the Cerebro-Endothelium?

Endothelial dysfunction has been associated with cognitive dysfunction in vascular dementia [269] coronary artery disease [270], obesity [271], postoperative cognitive dysfunction [272], type II diabetes [273], sleep apnoea [274], and the elderly [275]. Endothelial markers, such as endothelial lipase, positively correlates with cognitive impairment [276]. A systematic review inferred an 'intrinsic' relationship between endothelial dysfunction and vascular cognitive impairments [277]. These studies, along with those demonstrating endothelial dysfunction in study cohorts, suggest that endothelial dysfunction might have a significant role to play in the neurological issues suffered by ME/CFS patients.

As we've discussed in this paper, many of the herpesviruses are capable of infecting brain microvascular ECs, which act as viral reservoirs from which CNS infection can ensue. Furthermore, a compromised BBB is an expected consequence. Importantly, EBV and HHV-6 have been detected in CNS tissue from deceased ME/CFS patients [5] – cerebrovascular ECs might be the reservoir/latent site for these viruses in patients. EBV infection is associated with cognitive impairments [278, 279], and EBV proteins, including EBV dUTPase, are posited to contribute neuroinflammation and subsequent neurological issues in ME/CFS [9]. HMCV is associated with impairments in cognition, with possible mechanisms involving the virus' immediate-early 2 protein [280, 281]. HHV-6 is also associated with cognitive impairments [282-285]. HHV-6 antigens have been found within ECs from the frontal lobe of a fatal case of herpesvirus infection [191], and in a mice study, HHV-6 infection of the CNS persisted and induced proinflammatory cytokine production via TLR-9 [199].

Infection of brain ECs and other vascular cells (as well as neurons and glial cells) by herpesviruses and subsequent vasculitis in brain blood vessels might lead to inflammation, CNS infection, oxidative and NS damage, and symptom expression including cognitive dysfunction and even fatigue and PESE. Neurological pathology might also ensue as a result of autoimmune processes in the central nervous system, whereby molecular mimicry involving EBV and other herpesviruses antigens result in autoantibodies directed against brain antigens, for example, glial cell adhesion molecule [104]. This may have relevance to ME/CFS, and tie together working hypotheses on endothelial dysfunction and neurological symptoms in ME/CFS [286] with herpesvirus activity.

9. Ways Forward

It is of interest to determine whether ECs from patients suffering from ME/CFS (and controls) are infected with herpesviruses. This would be the first step in confirming this idea as presented in this paper. ECs, and brain microvascular ECs specifically, can be extracted and isolated via a number of techniques [287-290]. Other vascular tissue cells, such as smooth muscle cells, should also be isolated and tested for herpesvirus infection. Whilst there have been studies that have demonstrated reduced permeability of endothelial linings as a result of herpesvirus infection, and studies associating herpesvirus infection with perfusion deficits, further experiments focussing on these phenomena and the molecular processes involved, from a post-viral perspective, are necessary.

10. Conclusion

We have presented the idea that herpesvirus infection of ECs might be an important, overlooked phenomenon that can, in part, account for the pathophysiology and symptoms of ME/CFS and, potentially, Long COVID. This idea is somewhat novel, but is not unprecedented [71, 79, 90, 162, 262]. Endothelial dysfunction and herpesvirus activity are two characteristics of ME/CFS pathology that have yet to be officially linked. Perhaps latent infection of ECs alone (that is, without active infection) is sufficient to bring about pathology and subsequent symptoms, and may provide a explanation for daily symptoms, the chronicity of symptoms, and the multi-organ, systemic nature of ME/CFS.

Importantly, the load of EC infection, i.e., how widespread in the systemic vasculature herpesvirus infection is, and perhaps the tissue- and organ-specific site of infection are likely vital factors that determine the manifestation of symptoms as a result of this hypothesized pathophysiological process. It is acknowledged that herpesviruses infect many cell types, so the infection of ECs by herpesviruses is likely not responsible for all ME/CFS pathology and symptoms. For example, infection of immune cells and manipulation of immune processes by herpesviruses contribute to ME/CFS pathology, and likely account for much of the immune disturbances seen in this population; similarly, infection of cells of the nervous system might account neurological deficits, and even vascular dysregulation. However, we want to bring attention to the possibility of endothelial infection, as this is somewhat of an understudied topic, especially in the context of ME/CFS.

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Further studies are required to determine the extent of herpesvirus infection of the endothelium in ME/CFS patients, and also need to take into account the possibility of tissue- or organ-specific sites of infection. This is a difficult phenomenon to prove, especially when considering the ability of herpesviruses to cause pathology in certain individuals and in certain physiological states, and hence requires diligent and elaborative study and experimentation. It is possible that this idea of herpesvirus latency-induced endothelial maladaptation might turn out to be irrelevant, but herpesvirus-induced endothelial dysfunction, with and without direct infection of ECs, will still be relevant for ME/CFS pathology and symptom manifestation. Hence, a more refined focus on herpesviruses and endothelial function and health in ME/CFS (and Long COVID) is warranted.

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