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The Putative Role of Viruses, Bacteria, and Chronic Fungal Biotoxin Exposure in the Genesis of Intractable Fatigue Accompanied by Cognitive and Physical Disability

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Abstract Patients who present with severe intractable apparently idiopathic fatigue accompanied by profound physical and or cognitive disability present a significant therapeutic challenge. The effect of psychological counseling is limited, with significant but very slight improvements in psychometric measures of fatigue and disability but no improvement on scientific measures of physical impairment compared to controls. Similarly, exercise regimes either produce significant, but practically unimportant, benefit or provoke symptom exacerbation. Many such patients are afforded the exclusionary, non-specific diagnosis of chronic fatigue syndrome if rudimentary testing fails to discover the cause of their symptoms. More sophisticated investigations often reveal the presence of a range of pathogens capable of establishing life-long infections with sophisticated immune evasion strategies, including Parvoviruses, HHV6, variants of Epstein-Barr, Cytomegalovirus, Mycoplasma, and *Borrelia burgdorferi*. Other patients have a history of chronic fungal or other biotoxin exposure. Herein, we explain the epigenetic factors that may render such individuals susceptible to the chronic pathology induced by such agents, how such agents induce pathology, and, indeed, how such pathology can persist and even amplify even when infections have cleared or when biotoxin exposure has ceased. The presence of active, reactivated, or even latent Herpes virus could be a potential source of intractable fatigue accompanied by profound physical and or cognitive disability in some patients, and the same may be true of persistent Parvovirus B12 and mycoplasma infection. A history of chronic mold exposure is a feasible explanation for such symptoms, as is the presence of *B. burgdorferi*. The complex tropism, life cycles, genetic variability, and low titer of many of these pathogens makes their detection in blood a challenge. Examination of lymphoid tissue or CSF in such circumstances may be warranted.

Keywords Immune · Inflammation · Oxidative stress · Toll-like receptor · Cognition · Depression · Chronic fatigue syndrome · Neurology · Psychiatry

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Abbreviations

CFS	Chronic fatigue syndrome
TNFα	Tumor necrosis factor
IL	Interleukin
NF-KB	Nuclear factor-KB
IFN	Interferons
TLR	Toll-like receptors
PAMPs	Pathogen-associated molecular patterns
DAMPs	Damage-associated molecular patterns
MAPK	Mitogen-activated protein kinase
ROS	Reactive oxygen species
RNS	Reactive nitrogen species
4-HNE	4-Hydroxynonenal
MDA	Malondialdehyde

EBV	Epstein-Barr virus
CAEBV	Chronic activated Epstein-Barr virus syndrome
ME	Myalgic encephalomyelitis
CEBVS	Chronic EBV syndrome
MS	Multiple sclerosis
MSRV	MS retrovirus
HHV	Human herpes virus
Th2	T helper 2
DCs	Dendritic cells
Bcl2	B cell lymphoma 2
BAX	Bcl-2-associated X protein
PCR	Polymerase chain reaction
NS1	Nonstructural protein
CNS	Central nervous system
CSF	Cerebrospinal fluid
TGF-β1	Transforming growth factor β1
MRI	Magnetic resonance imaging
HCMV	Human cytomegalovirus
Nrf2	Nuclear factor erythroid 2 [NF-E2]-related factor 2
mTOR	Mammalian target of rapamycin protein
Bf	Borrelia burgdorferi
PG	Prostaglandin
ERK	Extracellular signal-regulated kinase
COX-2	Cyclooxygenase 2
SC	Stachybotrys chartarum
NADH	Reduced nicotinamide adenine dinucleotide
JNK	c-Jun N-terminal kinase
FoxP3	Forkhead box P3
DON	Vomitoxin or deoxynivalenol
STAT3	Signal transducer and activator of transcription 3
iNOS	Inducible nitric oxide synthase

Introduction

Patients who present with severe, apparently idiopathic fatigue, together with profound levels of physical and or cognitive disability, present a considerable therapeutic challenge. The effects of psychological approaches are limited. In an open label study, counseling achieved a statistically significant but very slight reduction in self-perceived psychometric measures of fatigue and disability, compared with intermittent psychiatrist consultations, but produced no ameliorative effect on objective measures of disability [1]. The same pattern is observed in studies using differing exercise regimes. These approaches can once again produce significant, but very slight, improvements in self-perceived psychometric parameters, but either produce significant, but clinically unimportant improvements in scientific measures of disability [1] or even potential harm [2]. Many such patients are afforded the exclusionary, non-specific, diagnosis of chronic fatigue syndrome (CFS), according to a plethora of different selection criteria [3], if rudimentary testing does not reveal the cause of their symptoms.

Sophisticated tests, however, often reveal profound immunological abnormalities in such patients and evidence of active pathogen activity [4, 5]. A study of 375 patients with apparently idiopathic disabling fatigue revealed pathological stimulation of lymphocytes together with abnormally elevated and distributed pattern of $CD4^+$, $CD8^+$, and $CD19^+$ leucocytes in 53 % of patients and depleted levels of IgG_3 in 59 % of the study population. More than half had circulating immune complexes and many tested positive for anti-nuclear antibodies [6]. Moreover, greater than 70 % of patients also displayed objective signs of active pathogen invasion [6]. These results support earlier work by a team led by the same author, with patients once again suffering from apparently idiopathic fatigue of an infectious onset where 50 % of the patients displayed lymphadenopathy and 73 % had objective evidence of persistent Herpes virus activity [7]. These findings are by no means atypical, as we shall discuss; however, not everyone with apparently idiopathic fatigue has evidence of chronic pathogen activity, although many have a documented infectious history to their illness [8]. Moreover, many of the viruses and other pathogens shown to be active in many of these patients are normally latent and or asymptomatic in the general population.

How do we reconcile these observations and explain how some people display evidence of active pathogen activity, while others who are infected with the same pathogens do not, and why do some people develop a phenotype of severe intractable fatigue following an infection while, thankfully, the vast majority of the population do not? Variations in strain or tissue tropism are obvious potential causes, and this will be discussed later. However, the work of numerous researchers investigating the occurrence of polymorphisms in populations of people with apparently idiopathic fatigue may well shed some light on other potential variables. In a cohort of 80 people afforded a diagnosis of CFS, Carlo-Stella and fellow workers reported a pattern of cytokine polymorphisms, which would render the bearer highly susceptible to a prolonged or severe inflammatory response [9]. A similar pattern was seen in a recent study where the authors also noted that the pattern of cytokine polymorphisms in their "CFS" patients differed from those with a diagnosis of major depression [10]. The authors of another recent study examining the effect of cytokine polymorphisms on the severity of fatigue experienced by patients with HIV reported that the severity of fatigue was associated with polymorphisms in tumor necrosis factor (TNF)α, interleukin (IL)-1β, and nuclear factor (NF)-KB, providing further evidence of an association between inflammation and fatigue [11].

Quite subtle variation in the base sequences of genes governing the innate immune response can alter an individual's susceptibility to infection and the consequent

development of diseases in quite profound and specific ways [12, 13]. Functional polymorphisms in genes effecting or regulating the immune response are also a major factor in determining the trajectory and prognosis of infectious illnesses and are also predictive of enduring pathology [14]. Moreover, polymorphisms in TNF, IL-1β, interferons (IFNs), IL-6, and IL-10, acting individually or synergistically, can amplify the severity and duration of the immune response to acute pathogen invasion [14]. Helbig et al. reported that patients with polymorphisms in TNFα, IFNγ, and HLA-DRB alone, or in combination, developed long-term fatigue and disability following acute pathogen invasion, whereas patients free of such polymorphisms recovered normally [15, 16]. On a more generic level, the severity of acute illness and the level of pro-inflammatory cytokine production is deterministic of symptom severity and duration [17, 18]. Honsettre et al. [19] determined that patients who experienced abnormally elevated cytokine production during initial infection went on to develop chronic long-term pathology, while the patients with expected levels of cytokine production did not. It is also noteworthy that a prolonged and or severe infection can leave an individual with chronically activated microglia [20]. This effect can also be achieved via sequential lesser infections as the result of the development of microglial priming [21].

The question arises as to how this long-term pathology is achieved and maintained, and why severe or prolonged immune activity and inflammation can sometimes produce serious long-term sequelae, both in terms of immune dysregulation and incapacitating fatigue. Engagement of Toll-like receptors (TLRs) by pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs) leads to the initiation of the innate immune response [22]. Activation of the TLR2/4 complex induces the expression of intracellular signaling networks, such as NF-κB and mitogen-activated protein kinases (MAPK) with subsequent up-regulation of pro-inflammatory cytokines, reactive oxygen (ROS), and reactive nitrogen species (RNS) [22–24]. In genetically susceptible individuals, with the polymorphisms discussed above, an excessive or prolonged inflammatory response can lead to a massive cytokine surge, which in turn can lead to abnormally high production of reactive oxygen and nitrogen species including the very toxic peroxynitrie [20]. Elevated levels of ROS and RNS generated by TLR2/4 activation can attack an array of cellular molecules, including unsaturated membrane fatty acids, generating a range of damaged molecules, including protein carbonyls, 4-hydroxynonenal (4-HNE), malondialdehyde (MDA), and nitroso-protein adducts, and oxidized and degraded DNA. These can function as redox-derived damage-associated patterns or DAMPS [25, 26] exacerbating TLR2 and or TLR4 activity, thus provoking even greater synthesis of RNS, ROS, and pro-inflammatory cytokines in a self-sustaining, self-amplifying feed forward loop, called the "TLR-radical cycle" [22].

Degraded mitochondrial DNA is also known to act as a DAMP and activates TLR2 and TLR4 receptors [27, 28]. The TLR-radical cycle, once further activated by redox-derived DAMPs, may rapidly become self-sustaining and self-amplifying and may well underlie the excessive levels of nitro-oxidative stress and chronic immune activation seen in patients with neuroinflammatory, neurodegenerative, and autoimmune diseases [22]. It is also noteworthy that initial inhibition of mitochondrial function by ROS/RNS provokes the production of even higher levels of these entities creating a spiral of self-amplifying and self-sustaining mitochondrial dysfunction and bioenergetic failure [20, 29]. Microglia, once activated, provoke the activation of astrocytes, and this "dance" can also develop into self-sustaining and self-amplifying pathology [20]. The chronic dysregulation to the immune system, following an initial infection, could explain abnormal pathogen activity in certain individuals, and we now turn to a review of a number of pathogens seen active in people with apparently idiopathic fatigue, with an emphasis on the mechanisms by which they could produce chronic intractable fatigue accompanied by profound physical and cognitive disability. We shall comment on the role of polymorphisms in individual susceptibility to infection and disease trajectory in each case where data exists. We shall also comment on the capacity of each organism to affect the function of p53, given that interference with this transcription factor is a common replicative strategy, and that p53 plays a major role in the regulation of energy production at the basal level and in situations of increased energy demand [30]. The reader is referred to the work of Morris and Maes (2012) for a detailed explanation of the mechanisms underpinning the role of p53 in the generation and regulation of energy production [31].

Epstein-Barr Virus

Numerous research teams have described a chronic illness, normally preceded by severe symptoms of infectious mononucleosis. It is characterized by the presence of chronic or intermittent fever, lymph node tenderness or pain, unrelenting severe fatigue, sore throat, myalgia, headache and arthralgia without any sign of a clearly delineated underlying disease. This illness is called chronic activated Epstein-Barr virus syndrome (CAEBV) [32–35]. CAEBV is an illness where patients complain of severe fatigue. The symptoms of infectious mononucleosis including swollen lymph nodes, malaise and fever may persist for over 3 months. These symptoms persist due to an unusual pattern of latent Epstein-Barr virus (EBV) infection. EBV generally establishes a latent pattern of infection in B cells, which in many cases progresses asymptomatically, but is also capable of invoking numerous diseases

depending on the overall pattern involved in latency. In the case of CAEBV, however, EBV establishes a latent infection in NK cells and T cells, inducing the gene expression of active virus [36]. Interestingly, patients suffering from this illness commonly suffer a wide range of cardiovascular and neurological abnormalities, which is not typical of EBV infections as a whole [34, 35]. CAEBV is held to be a known cause of the symptom complex often described by a diagnosis of CFS. However, as a result of a "semantic strait-jacket" inserted into current CDC selection criteria, someone whose symptoms have a known cause cannot be classified as suffering from CFS [3, 37–39]. EBV was considered as one of the causes of an outbreak of an illness, historically described as myalgic encephalomyelitis (ME),which occurred in different geographical locations in the mid 1980s, when it was noted that some patients displayed high antibody titers to EBV [40]. A CDC committee later coined the term CFS to describe the core symptoms displayed by such patients and created the first entirely symptom-based case description [3]. At that point in time, however, patients with EBV infection, displaying similar symptoms to those displayed by patients in the outbreaks, were categorized under the diagnostic heading of CAEBV [41, 42]. However, when patients in later studies, who satisfied the requirements of that case description and thus were afforded a diagnosis of chronic fatigue syndrome, failed to display elevated tires to EBV, a consensus position developed that chronic EBV syndrome (CEBVS) and other EBV infectious diseases other than CAEBV were not related to the outbreaks or indeed causatively implicated in the production of the CFS symptom complex [43, 44].

The clinical characteristics of severe CAEBV infection are attributable to an immune-inflammatory response characterized by increased levels of pro-inflammatory cytokines, IL-10, and macrophage-colony-stimulating factor. Documented cases of CAEBV infection other than from Japan are rare, potentially suggesting that the illness remains underdiagnosed in other countries [45, 46]. Patients suffering from CAEBV commonly display antibodies directed at EBV early antigen, potentially indicating the presence of reactivated EBV [38]. CAEBV disease normally follows prolonged infectious mononucleosis in people with no apparent immunosuppression.

Several decision trees have been mooted for the diagnosis of the illness [35, 47]. The striking feature of disease involves infection of T and NK cells by EBV, but B cells which are the normal targets of EBV are invariably free of the virus in people with this illness. Many patients are serologically silent and thus high antibody titers are not a mandatory diagnostic feature [46]. Defects in EBV-specific cytotoxic T cell activity or natural killer activity aimed at cells infected with EBV have been reported by a number of research teams [48, 49]. The American experience of this illness in the work of Cohen et al. including patient responses to rituximab is well documented [50].

The diagnosis of the illness, once such a matter of controversy, has improved immeasurably with the advent of molecular diagnostic protocols involving new techniques [35, 37, 51]. Viral loads of some 10^2 five copies per microgram can be commonly detected in PMBCs [52, 53]. The pathophysiology appears linked to abnormalities in the lytic cycle, and abnormal proliferation of infected cells. Studies investigating variation in the genes governing the lytic cycle show the potential to expose the pathophysiology in more detail [54]. Variants with changes in EBV nuclear antigens (EBNA)-1 and EBNA-2 or lytic membrane protein have been detected in patients with CAEBV [35, 37, 51]. For a more detailed treatment of abnormalities in the replicative cycle and gene expression in CAEBV, the reader is referred to [35]. The continual production of pro-inflammatory cytokines in this syndrome is in direct contrast to the situation when EBV infects B cells, either acutely or following the establishment of a latent infection.

EBV nuclear antigen 1 induces production of ROS, thereby contributing to the development of oxidative stress [55, 56]. The production of the BZLF-1 (Zta, ZEBRA) immediate and early proteins upon entry of EBV into the lytic cycle leads to the depletion of mitochondrial membrane potential, dramatic changes in mitochondrial morphology, and inhibits mitochondrial replication [57, 58]. A range of EBV proteins, e.g., BZLF-1, inhibit the transcriptional activity of p53 via a number of different mechanisms, including the accelerated degradation of the phosphorylated transcription factor, and the induction of a range of detrimental post-translational modifications [59–61]. EBV may infect the brain, and EBV-related infections of the central nervous system (CNS) can be initiated by active or reactivated virus or by chronic viral infection [62, 63].

EBV is the virus most commonly implicated in the development of multiple sclerosis (MS), and it was recently established that latent EBV can induce a range of innate immune responses, e.g., IFNγ production, and drive neuroinflammation in active MS [64]. This neuroinflammation and pattern of immune activation may be exacerbated by the reactivation of the MS Retrovirus (MSRV), whose envelope protein can engage with TLR4 receptors on immune cells in the brain [65]. Activation of TLR4 by MSRV envelope leads to the production of pro-inflammatory cytokines and the induction of nitrosative stress, which results, among other things, in a significant reduction in the capacity of oligodendrocytes to differentiate, impeding their ability to facilitate re-myelination [66]. The ability of EBV to reactivate MSRV is regarded by many as one of the major reasons why the association between the presence of EBV and the development of MS is so strong [67]. Functional polymorphisms in the gene complex responsible for the production of IL-1∃ and IL-12 regulate both individual susceptibility to EBV infection and illness trajectory [68, 69]. It is also worthy of note that reactivation of EBV, even if present at a very low titer, leads to the excessive production of inflammatory cytokines and resultant widespread

inflammation provoked by the presence of dUTPase, one of the early proteins produced by the replicating virus [70].

Human Herpes Virus

HHV6A and HHV6B are indirectly or directly associated with neurological diseases either via de novo infection in otherwise healthy children, or as a result of reactivation in immunocompetent adults [71, 72]. The weight of evidence indicates that HHV6 is a causative agent in immune-competent adults, as IgM to the virus is often found in such circumstances [73, 74]. Both strains of HHV6 are also strongly implicated in the pathogenesis of idiopathic encephalitis [72, 75]. HHV6A and B and have been proposed as putative causal or con-causal agents in numerous inflammatory diseases commonly associated with pathological levels of fatigue, such as Sjögren's syndrome [76, 77], systemic lupus erythematosus (SLE) [78, 79], and rheumatoid arthritis [78, 79]. There is also a body of research indicating that HHV6 plays a role in the pathogenesis of multiple sclerosis. The possibility that viral activity is caused by immunomodulatory medication is remote in light of evidence that HHV6 is detected in the activated astrocytes and microglia of acutely diagnosed treatment-naive patients [80]. HHV6 titers are significantly higher in patients suffering acute flare up of disease and, intriguingly, only HHV6A detected in such circumstances, but both serotypes are detected in patients in remission. In contrast, studies report that only HHV6B is present in healthy controls [81]. It is also worthy of note that HHV6 reactivation, as measured by the number of gadolinium-enhancing lesions, correlates significantly and positively with longitudinal changes in disease activity [82]. Finally, there is also accumulating evidence that HHV6A and/or HHV6 infection plays a major role in the pathology endured by many people with apparently idiopathic fatigue, accompanied by profound multidimensional pathology afforded the non- specific diagnosis of CFS. In numerous studies, the virus has been detected in patients so diagnosed at significantly higher levels than healthy controls [83–85]. Ablashi and fellow workers reported elevated IgM levels in CFS patients as compared to controls and elevated levels of antibody to HHV6 early antigen in 54 % of patients compared to 8 % of healthy controls [86]. This echoes findings reported by another research group [87].

Some studies have suggested that both viruses can induce a T helper (Th)2 profile in T cells through the inhibition of IL-12 secretion by dendritic cells (DCs), and macrophages and through the induction of IL-10 production [88]. In contradiction, other reports have shown that HHV6 infection upregulates the levels of pro-inflammatory cytokines, such as IL-1β, TNFα, and IFNγ in peripheral blood mononuclear cells [89, 90]. The latter effects may well explain why HHV6 infections are associated with dramatically elevated cellular levels of oxidative stress [91]. A combination of elevated inflammatory cytokines and oxidative stress induces mitochondrial dysfunction [29]. HHV6 is also capable of inducing mitochondrial dysfunction and impaired energy metabolism in other ways. For example, HHV6 early proteins interact with other proteins, leading to a reduction in mitochondrial membrane potential [92]. HHV6 can also inhibit mitochondrial function via increased levels of B cell lymphoma 2 (Bcl-2)-associated X protein (BAX) and decreased levels of Bcl-2 [93].

HHV6 also interferes with the p53 network. In particular, a HHV6 protein produced during infection leads to the accumulation of p53 in the cytoplasm, inhibiting its transcriptional activity and hence any positive modulation of cellular energy production [94, 95]. While the ability to infect and alter the proliferation and cytokine secretion pattern of T lymphocytes is well documented, it must be emphasized that both HHV6 strains can also establish active or latent infections in the brain [96]. HHV6A in particular can establish active infections in astrocytes and oligodendrocytes [97, 98], and is far more efficient in doing so than HHV6B [96]. HHV6A can induce or increase cytokine production in astrocytes via binding to the cytosolic TLR9 receptor [99] and very likely the membrane receptors TLR2 and TLR4 [96]. There is no direct evidence that HHV6 infection can lead to increased intestinal barrier permeability, but intriguingly, its presence has been detected in gut biopsies taken from patients with a CFS diagnosis at levels far higher than those present in healthy controls [100].

Functional polymorphisms in TLR9 receptors, which are activated following Herpes virus infections, lead to a significantly higher expression in the receptors in female MS patients compared to those who were polymorphism free [101]. Reactivation of HHV6, even in immunocompetent individuals, leads to dysregulation within signaling pathways governing the innate immune response, and increased levels of neuropathology [96]. The specificity and sensitivity of recent serology assays for the presence of IgG and IgM antibodies to HHV6 in the blood compartment are high [102], and the presence of HHV6 can readily be detected by nested polymerase chain reaction (PCR) following culture of peripheral mononuclear blood cells extracted from an infected patient. The most recent assays can discriminate between DNA from actively replicating HHV6A and that from chromosomally integrated virus [103]. However, due to the neurotropism of the virus, a negative result for either serology or PCR carried out in any blood compartment cannot rule out the presence of HHV6A or HHV6B in the brain [96].

Parvoviridae

Parvovirus infections in general, and Parvo B19 infections in particular, are not merely acute and self-limiting as once

thought, but almost invariably lead to long-term, and probably lifelong, viral persistence in the bone marrow, lymphoid tissue, and the brain, even in the absence of overt viraemia [104–106]. Parvoviridae also display an almost bewildering level of genetic diversity with a base rate substitution rate, per site per year, rivaling that of HIV and other RNA viruses [107, 108]. The genetic variability displayed by Parvo B19 has prompted the taxonomic division into four genotypes. Curiously, while all four genotypes are routinely found in tissues, the same is not true of circulating virus, which displays far less genetic diversity. The presence of all four genotypes in tissues and the extensive genetic diversity displayed by each genotype, means that the long-term persistence of Parvo B19 in various cellular types, is characterized by the presence of genetically labile quasispecies [104, 105, 109, 110]. Pathological levels of fatigue are experienced by people who display evidence of acute or chronic Parvovirus B12 infection [111–113]. The presence of elevated levels of pro-inflammatory cytokines in the blood of many chronically infected people [113, 114] is indicative of a state of chronic inflammation.

The presence of nonstructural protein (NS)1 and B19 proteins lead to the up-regulation of nuclear factor-6B (NF-6B) reactive oxygen species and inflammatory cytokines by activating a range of TLRs including TLR9, TLR7, and TLR4 [115, 116]. It is probable that TLR9 is responsible for detecting B19 proteins during initial infection [117]. Nonstructural protein (NS1) also increases the transcription of the TNFα and IL-6 genes directly, up-regulates the production of STAT-3, and down-regulates the expression of several genes involved in the immune response [118]. Elevated levels of STAT-3 lead to the down-regulation of p53 [31] and hence, this may be a mechanism, by which B19 compromises the regulation of energy production within infected cells. The presence of NS1 leads to mitochondrial depolarization and elevated ROS production, which persists throughout the period of infection [119, 120]. There is also evidence of decreased mitochondrial numbers in infected cells [121], which may reflect the fact that the survival of B19-infected cells is enabled by increased mitochondrial autophagy [122].

There is an accumulating body of evidence demonstrating an association between Parvovirus B19 infections with the development of a wide variety of neurologic manifestation, including Guillain-Barre syndrome [123]. It is not clear whether the interaction of the Parvovirus with the central nervous system (CNS) is due to direct infection or as a result of autoimmune processes [124]. Douvoyiannis and colleagues reported on the presence of Parvovirus B19 in a cohort of patients with a range of neurological conditions, which likely stemmed from infection by this virus. Parvovirus B19 DNA was detected in the cerebrospinal fluid (CSF) in 81 % of patients, and the serum in 85 % of patients. Specific antibodies, however, were only detected in 33 % of CSF samples. Interestingly, there were no differences in the prevalence (25 %) of neurological sequelae between immunocompetent patients, and those with altered immunity [125]. There is also evidence that functional polymorphisms in the genes coding for IFNγ and transforming growth factor β1 (TGF-β1) are associated with a greater likelihood of developing symptoms following Parvovirus B19 infection [113]. Current serology assays have a high sensitivity and specificity to the presence of the VP2 structural protein of parvovirus in blood compartments [102]. In similar vein, B19 DNA can readily be detected by PCR following culture of PMBCs extracted from infected people [103]. However, there is a caveat, as B19 DNA can be detected in tissue by PCR, when examination of any blood compartment is negative [102].

Mycoplasma

Many people infected with a range of mycoplasma species experience severe levels of fatigue [126, 127]. Mycoplasma species induce an immune response via a number of different mechanisms. The first involves engagement with the TLRs, notably TLR2 [128–130], leading to the up-regulation of IL-12, IFNγ and other pro-inflammatory cytokines [131, 132]. Interestingly, Mycoplasma species infection leads to the generation of a wide range of DAMPs including those normally released following cellular necrosis [133]. Mycoplasma antigens are also capable of activating the inflammasome [134, 135], with subsequent elevation of IL-1α, IL-18, and ROS levels and a concomitant decline in the mitochondrial membrane potential [136–138]. Elevated levels of ROS and oxidative stress are an almost invariant finding in people infected by Mycoplasma species [139]. Despite invoking such a powerful immune response, and being such simple organisms, Mycoplasma species can readily establish chronic infections in infected hosts using a range of highly sophisticated immune evasion strategies [140]. Broadly, these strategies are enabled by an excessive rate of spontaneous mutations in the genes for the production of a plethora of surface antigens and direct invasion of peripheral mononuclear blood cells and erythrocytes. This is an extremely complex topic and the reader is referred to the work of [140, 141] for details.

However, it is worth noting that a recent study bears graphic testimony to the sophistication of the immune evasion employed by this simple organism with the discovery of protein M [142]. This protein, produced by replicating Mycoplasma species, binds indiscriminately to all antibodies and blocks the union of antigen and antibody, which has been described as the ultimate decoy system largely negating the specific activity of the humoral response to Mycoplasma species [142]. While host cell responses vary with stage of infection [143], these evasion strategies enables Mycoplasma species to establish persistent infections in non-phagocytic lysosomes via endocytotic uptake [144]. The bacteria can also establish

persistent infection in endothelial cells provoking the production of pro-inflammatory cytokines, which are a source of inflammation likely contributing, in part, to the development of chronic oxidative stress [145]. The presence of DNA in PMBCs in patients without any evidence of historical infection indicates widespread tissue dissemination following initial infection [146]. While mitochondrial depolarization and elevated oxidative stress are established causes of incapacitating fatigue, Mycoplasma species also suppress the production and activity of p53 as part of the replicative strategy [147, 148].

The brain is the second most common site of *Mycoplasma pneumoniae* infection after the lungs [149] and evidence of infection is readily detected by T2-weighted magnetic resonance imaging (MRI) [150]. The organism is a known cause of Guillain-Barre syndrome and encephalitis in adults and children, likely via the secretion of a neurotoxin [149, 151]. A number of authors have also suggested a causative role in some patients with Mycoplasma species especially in females [152]. Finally, Nijs et al. reported that 68 % of patients afforded a diagnosis of CFS were chronically infected with at least one Mycoplasma species compared to 56 % of controls [127]. This finding was supported in a review of studies where the author concluded that overall the data revealed that 50 % of patients appear to be infected compared to 10 % of controls [126]. Interestingly, a functional polymorphism in a gene coding for a vital component of the NALP-3 inflammasome confers an increased risk of developing serious chronic pathology following a Mycoplasma infection [153]. The detection of Mycoplasma in PMBCs by PCR appears to be relatively straightforward for Mycoplasma species infecting leucocytes [146].

Cytomegalovirus

Human cytomegalovirus (HCMV) infection can cause severe life-threatening pathology in immuno-compromised individuals [154, 155]. However, HCMV invasion can also produce debilitating symptoms, and sometimes progressive pathology in immune-competent people [156, 157]. Such an infection often gives rise to a relapsing mononucleosis type syndrome characterized by severe fatigue, malaise, and myalgia [158, 159]. The presence of HCMV can provoke the transcription of NF-KB and the subsequent production of pro-inflammatory cytokines and IFNs, via the engagement of TLR2/4 and CD19 receptors [160, 161]. Polymorphisms in TLR2 appear to enhance an individual's susceptibility to lytic infection and the development of subsequent pathology [162]. Other authors have reported that TLR polymorphisms or epigenetic changes in the methylation state of their gene promoter regions influence the duration and magnitude of the immune response to HCMV infection [163]. On the other hand, heterozygosity in TLR2 and TLR4 receptors diminishes the risk of infection by this virus in adults [164].

HCMV, like other Herpes viruses, has the capacity to establish persistent life-long infections [165]. Viral inhibition of apoptosis appears to be the prime mechanism enabling this persistence [166, 167]. This suppression of programmed death pathways is probably mediated by the transcription of HCMV encoded immediate early genes targeting the extrinsic pathway [168] and the viral mitochondria localized inhibitor of apoptosis protein targeting the intrinsic pathway [169]. However, viral-induced programmed cell death is a prerequisite for the transmission of progeny virus and is also the prime cause of HCMV-induced pathology [170, 171]. There is evidence that the protein US28 facilitates this pro-apoptotic property of HCMV [172]. Patients infected with HCMV display a reduced T cell response to mitogens and a number of antigens and reduced natural killer activity [173, 174]. HCMV expresses several homologues for a number of chemokines and IL-10 as part of an evolutionary conserved strategy for interfering with and avoiding the hosts' immune system [175, 176].

This immune evasion strategy is further evidenced by the virus's ability to suppress the maturation and differentiation of DCs and inhibit their capability to stimulate the proliferative and cytotoxic properties of T lymphocytes and their migration in response to geographically elevated levels of chemokines [177–179]. HCMV infection results in a number of effects on host mitochondria including increased mitochondrial biogenesis and an increase in mitochondrial activity [180]. Cellular invasion by the virus leads to significant changes to the proteins mediating contact between the endoplasmic reticulum and mitochondria, coupled with increased calcium signaling to the organelle with the aim of up-regulating bioenergetics performance to maximize the production of progeny [181]. However, HCMV invasion induces mitochondrial fragmentation in non-permissive cells [182].

Moreover, infection of leucocytes by the virus results in oxidative damage to mitochondrial DNA and the development of systemic oxidative stress [183]. The development of oxidative stress and chronic inflammation following HCMV infection is an important mechanism driving the development of pathology [184]. In line with that view, there is strong evidence that the products of lipid peroxidation up-regulate the promoter region of the virus [185]. HCMV has a number of positive effects on cellular antioxidant defense systems, presumably evolved to maintain host cell viability. One such effect is the up-regulation of nuclear factor erythroid 2 [NF-E2]-related factor 2 (Nrf-2) and Haem oxygenase, which in turn can activate the glutathione and thioredoxin systems [186]. Viral invasion leads to a virtually immediate up-regulation of cellular ROS and hydrogen peroxide production, which prevents the inhibition of the mechanistic mammalian target of

rapamycin protein (mTOR) and provokes the up-regulation of reduced glutathione [187].

p53 promotes the efficient transcription of HCMV genes, but this is at the cost of a loss of ability to initiate or regulate the activity of host genes likely via its sequestration in the cytoplasm [188]. This sequestration is effected via the binding of HCMV early proteins pUL29 and UL28, which adversely affects the ubiquitin status of the transcription factor [189]. The infection of primary brain pericytes results in the accelerated production of viral progeny and is a major contributor to the development of neuroinflammation and potentially frank encephalitis [190]. Another likely contribution to the development of neuropathology stems from the virus's ability to establish a productive infection in astrocytes and provoke defensive actions from microglia [191, 192]. The pattern of chemokine and cytokine production by astrocytes and microglia differs following infection, with astrocytes secreting many chemokines and microglia mainly secreting pro-inflammatory cytokines [192]. One such chemokine secreted by infected astrocytes is TGF-β1, which acts to stimulate the replication of HCMV [191]. Replication of the virus is indirectly involved in the pathogenesis of Guillain-Barre syndrome, which uncommonly results from primary HCMV infection or endogenous reactivation in immune-competent middle-aged or older adults [193, 194]. HCMV reactivation in patients with intact T cell function but abnormalities in innate immune activity provokes an exaggerated and persistent immune and inflammatory response associated with the development or exacerbation of disease [195]. The detection of replicating virus, following culture of host PMBCs, is readily achieved by PCR, with primers targeting the detection of early replicating proteins [196].

Borrelia burgdorferi

Severe intractable fatigue accompanied by profound physical and or cognitive impairment is a common presentation in patients with a laboratory confirmed infection of *B. burgdorferi* (Bf) even many years after apparently successful antibiotic treatment [197–199]. Other symptoms include a recurrent flu-like malaise, low-grade fever, and myalgia [200]. The spirochete employs a number of immune evasion strategies, which aid the establishment of a persistent infection, including antigenic variation, the production of complement inhibiting, or complement resistant proteins and the secretion of a protease, enabling its localization in "sanctuary sites" in the extracellular matrix [201, 202]. It is not surprising therefore that Bf infection stimulates the production of a range of chemokines and cytokines by macrophages including IL-8, IL-10, TNFα, IL-6, and IL-1β, leading to the generation of systemic inflammation, largely independent of the activation of the complement system [203, 204]. Bf-mediated immune activation and inflammation is effected by spirochete LPS engagement with TLR2 and TLR4 [205]. The type of receptor engaged appears to vary somewhat with immune cell type as the production of cytokines and chemokines by surface engagement of LPS with human monocytes is affected solely via the TLR-2 MYD88 pathway [206]. Moreover, the range of inflammatory mediators produced via phagocytic internalization of Bf by monocytes is affected via the activation of the cytosolic TLR8 receptor [207]. It is also worthy of note that Bf RNA is also antigenic and provokes the production of types I, II, and III IFNs as well as the synthesis of NF-κB dependent pro-inflammatory cytokines via the activation of the TLR7 receptor [208].

It is of interest that the degree of innate immune stimulation following monocyte ingestion is much greater for live Bf than heat-killed isolates. Additionally, in vivo infection depletes monocyte number via apoptosis in a titre-dependent fashion [209]. The internalization and subsequent degradation within the phagosomal compartments of macrophages, monocytes, and dendritic cells of Bf enables the release of spirochete nucleic acid and a range of other microbial products such as LPS, which can provoke a widespread and powerful inflammatory response [210]. Testimony to the presence of a chronic inflammatory environment is borne by the presence of MDA, 4-HNE, and isoprostane in the CSF, urine, and encephalic fluid [211]. High serum levels of nitric oxide and nitrotyrosine indicate excessive levels of protein nitration and lipid peroxidation in patients with neuroborreliasis, which act to amplify the underlying inflammatory processes in patients suffering from this illness [212, 213]. It is also worth noting that a range of prostaglandin metabolites including 8-iso prostaglandin (PG)F2 display an eightfold increase in the urine of infected people compared to healthy controls. Curiously, we have been unable to locate any research specifically investigating the effects of Bf infection on mitochondrial dysfunction and we are not aware that any such research has ever been conducted. However, given the magnitude of chronic inflammation induced by the presence of this spirochete mitochondrial dysfunction secondary to the presence of such an environment is very likely to occur [20].

The provocation of an inflammatory response is also the mechanism by which Bf induces severe neuropathology in some 20 % of chronically infected people. Entry into the CSF following the establishment of a chronic infection is likely established via routes that do not involve the blood. Once present, the spirochete provokes a powerful inflammatory response [201, 214]. This response involves the secretion of nitric oxide together with pro-inflammatory cytokines and chemokines from macrophages, monocytes, and DCs, with the secreted chemokines acting to summon the invasion of B lymphocytes and activated $CD8^+$ T cells [201]. Whether the spirochete transverses the blood–brain barrier and enters the brain by a transcellular route or via endothelial cell junctions is

still a matter of debate, but once present, inflammation and apoptosis of oligodendrocytes is effected by direct activation of MAPK kinases, notably extracellular signal-regulated kinase (ERK), with the concomitant up-regulation of p53-governed pathways [215]. The interaction of primary brain parenchymal cells with the spirochete provokes the release of IL-6, IL-8, TNFα, and cyclooxygenase 2 (COX-2) from glial cells, as well as inducing glial and neuronal apoptosis [216]. It is also noteworthy that Bf infection induces cellular apoptosis in the dorsal root ganglion [217]. Activation of microglia by engagement of TLR1, TLR2, and CD19 on the surface of these glial cells is another major source of neuroinflammatory mediators such as NF-κB, PGE2, pro-inflammatory cytokines, and IL-6, whose chronic presence leads to neuronal apoptosis and the elevation of p53 [218, 219].

Finally, there is now considerable evidence of the presence of persistent, cystic, or atypical granular or rolled Bf, which acts as a highly localized source of extracellular or intracellular neuroinflammation [220]. Evidence that polymorphisms in immune genes could protect the bearer from the development of long-term pathology following Bf infection was provided in a study by Schroder et al. who reported that a polymorphism in the TLR2 receptor gene impaired immune activation by the spirochete and reduced the risk of developing chronic neuroborreliosis [200].

The most recent third-generation serology assays appear to have a greater sensitivity for the detection of Bf in the CSF than earlier methodology [221]. However, the tendency to test such assays in patients with Lyme disease without the confirmed presence of Bf or a sole focus on antigens, only produced by an actively replicating spirochete, makes the reliability of such assays very difficult to assess [221]. The low levels of circulating spirochete in the blood make its detection in this compartment by PCR a challenge [222]. However, the use of DNA amplification strategies and a multi-locus PCR approach combined with mass spectroscopy appears to have the sensitivity needed to reliably detect the presence of Bf in that compartment if present [222]. However, at present, there is no validated PCR method for the detection of Bf putatively present in the blood or CSF in patients with any recall of a historical tick bite but displaying clinical symptoms of neuroborreliosis. The absence of any PCR or serological assay with the capacity to detect the presence of Bf in patients displaying the clinical symptoms of neuroborreliosis is highly problematic as there is now overwhelming evidence demonstrating that Bf establishes a persistent infection in the brain (reviewed in [223]). PCR assays on frontal lobe tissue are capable of revealing the presence of Bf DNA but are invasive procedures [223]. Other options for detection involve culture, electron microscopy, and direct microscopy of tissue biopsies but these are of little clinical utility [200]. Oligoclonal bands in the CSF of infected people on MRI examination, which can confuse a diagnosis of MS, would suggest the use of this mode of examination as an invaluable diagnostic aid [200].

Chronic Mold and Mycotoxin Exposure

People with a documented history of chronic mold exposure can display a wider range of symptoms, which include severe fatigue, malaise, and severe neurocognitive impairment, which appear to be related to the length of exposure [224–226]. The origin of the symptoms has been a matter of some controversy. It was initially held that such signs and symptoms could not be due to inhalation of fungal spores. These matters are reviewed in the work of Hope [227]. However, the focus of research appears to have changed from the potential toxicity caused by the inhalation of viable fungal spores, to a study of the pathogenic potential of nanoparticulate fragments of hyphae and conidia coated with mycotoxins such as the trichothecenes family [228–231]. There is now robust evidence demonstrating that these particles can be released at some 300 times the concentration of spores and that the viable spore count is in no way predictive of their levels [232]. There is also evidence demonstrating that nanoparticulate *Stachybotrys chartarum* (SC) fragments can be aerosolized at approximately 500 times greater levels than spores. T2 mycotoxins inhalation is more toxic than systemic or dermal administrations [233]. Several studies illustrate the aerosolized mycotoxins. For example, subjects chronically exposed to SC in an indoor environment have significant more trichothecenes in the sera than controls [234]. Trichothecene mycotoxins are routinely detected in the air of buildings contaminated by SC [229].

A number of fungi produce trichothecenes mycotoxins including *Stachybotrys* and *Fusarium* [235]. Trichothecene mycotoxins cause multisystemic effects including nervous disorders, cardiovascular alterations, and immunosuppression [236]. A study investigating Satratoxin A exposure demonstrated that the toxin produces neuropathology at levels that occur in water-damaged buildings [237]. Trichothecenes and many other mycotoxins can bind to ribosome subunits generating "ribotoxic stress" which leads to the p38, c-Jun N-terminal kinase (JNK), ERK, and MAPK activation [238–240]. This mycotoxin-induced activation of MAPK mediates increased levels of pro-inflammatory cytokines and, in certain circumstances, cellular apoptosis [241–243].

Patients subjected to chronic mold exposure develop a wide range of immune abnormalities, including inflammatory responses. These abnormalities include increased levels of CD19+B, CD20+B, CD8+T, and CD4+T cells [244, 245]. Other abnormalities include elevated numbers of natural killer cells that have reduced killing capability [244, 245]. Such patients also display an elevated CD4/CD8 ratio and T and B cell responses to mitogenic stimulation, which can be

suppressed, elevated, or grossly elevated [246]. People suffering from chronic mold exposure also display a range of autoantibodies that generate a range of substances associated with muscle damage and can also activate the classical complement pathway [245–247]. Exposure to mold antigens and toxins, frequently found in the air in water-damaged buildings, are a well-documented source of inflammation, oxidative stress, and subsequent inflammatory reactions in animal and human studies [248–253]. Oxidative stress, indexed by elevated ROS/RNS is a significant mechanism underpinning the development of pathology [251, 254–256]. It is also worthy of note that inflammation, initially generated by chronic mold exposure, appears to play a major role in illness even after exposure to water-damaged, mold-rich, environments is terminated [252, 253, 257]. Numerous studies also report the existence of mitochondrial damage and compromised bioenergetic function in people subjected to chronic mold exposure [246, 258, 259]. Elevated levels of ROS/RNS are likely to be partly responsible for the existence of mitochondrial pathology, but various mycotoxins can compromise the function of these organelles directly by a range of mechanisms involving inhibition of translation, promotion of calcium dyshomeostasis, inhibition of mitochondrial membrane potential, and inhibiting the transcription of cytochrome oxidase and reduced nicotinamide adenine dinucleotide (NADH) dehydrogenase [250, 260, 261]. Individuals with a documented history of chronic mold exposure also display a wide range of immune abnormalities.

Inflammatory responses following mold exposure or infection can be mediated via engagement of TLR4 or TLR2 [262]. There is also considerable evidence that polymorphisms in TLR4 or other immune cell receptors makes an individual more susceptible to mold-induced pathology [262, 263]. Immune activation following mold exposure can also be mediated by TLR9 [264]. Engagement of these receptors on dendritic cells following aerial exposure to SC can lead to increased IFN (production by activated Th1 cells [265]). However, in other tissues, activation of these receptors by SC leads to the production of IL-23 and IL-17 and the development of pathogenic Th17 cells [265]. Other mycotoxins such as aflatoxin increase the production of forkhead box P3 (FoxP3) and regulatory T cells and promote a T helper 2 (Th2)-biased immune system [266].

Chronic exposure to mycotoxins may cause injury to the gastrointestinal tract [236, 250]. For example, vomitoxin (deoxynivalenol or DON) provokes intestinal inflammation in vivo [267], and its presence drives the immune system in the intestine toward a Th17 bias involving the presence of the pathogenic group of activated Th17 cells [268, 269]. Ingestion of this toxin induces significant increases in the levels of pro-inflammatory cytokines and chemokines, e.g., IL-8, IL-1β, TNFα, and IL-6 [270, 271]. DON activates ERK1/2 thereby activating MAPK signaling cascades that consequently up-regulate COX-2, NF-κB, and PGE-2 which are major drivers of the inflammatory response [241, 268, 272]. DON also significantly induces the expression of several genes that play a role in driving the differentiation of Th17 cells including signal transducer and activator of transcription 3 (STAT3), IL-17A, and suppresses the production of T regulatory cells and the transcription of FoxP3 [269]. Furthermore, this trichothecene stimulates IL-23A, IL-22, and IL-21 production at the expense of IL-10 producing Th17 lymphocytes [269]. It is also possible that the inflammation generated in intestinal epithelial cells could result in the activation of a population of DCs and Th17 cells by eliciting communication with lymphocytes and antigen presenting cells situated in the lamina propria, ultimately leading to the initiation of the classical immune response [269].

One consequence of the production of pro-inflammatory cytokines is the modulation of the intestinal tight junction barrier, potentially favoring an increased translocation of luminal antigens including commensal bacteria, a mechanism that plays a role in some patients with chronic fatigue syndrome [273, 274]. DON exposure provokes increases in intestinal permeability allowing passage of pathogenic and commensal bacteria from the gut lumen into the systemic circulation [275, 276]. This is caused by a suppressed transcription of claudin hence impairing the effectiveness of endothelial tight junctions [276, 277]. DON-induced MAPK and ERK activation suppresses claudin expression in a manner that correlates with reduced intestinal barrier function [278]. It is noteworthy that DON augments pro-inflammatory stimuli, such as TLR4 ligands on immune cells potentially providing an indirect mode of pathogenicity [252, 279].

Individuals who have developed symptoms stemming from chronic exposure to mycotoxins and mold particles may present with “classical” neurological abnormalities including movement disorders, pain syndromes, neurocognitive defects, and impaired coordination and balance [280]. Abnormalities in standardized neurocognitive tests are also frequently apparent [281, 282]. Disturbances of balance, a positive Romberg, tandem gait, and computerized sway balance testing are commonplace [226, 282]. Interestingly, these symptoms often worsen on repeated testing months or years following initial mold exposure [226]. Exposure to mycotoxins and mold may cause significant abnormalities in single-photon emission computed tomography and quantitative electroencephalogram testing [224, 281, 283]. Interestingly, intranasal glutathione may improve neurocognitive symptoms stemming from exposure to such environments [227].

There are a number of elements involved in driving such neuropathology. T2 toxins bind to ribosomal subunits triggering ribotoxic stress activating JNK/MAPK [284]. This mycotoxin also impedes membrane phospholipid metabolism producing lipid peroxidation [285]. Chronic exposure, even at very low levels, induces undesirable changes in brain

monoamine turnover and the permeability of the blood–brain barrier to amino acids [286, 287]. T2 toxins suppress the transcription of enzymes in the detoxification of xenobiotics such as glutathione transferases leading to dysfunctional mitochondria [288, 289]. Dermal and subcutaneous exposure to these trichothecenes leads to increased production of ROS, protein carbonyls, lipid peroxidation, and depletion of reduced glutathione [290]. This class of mycotoxin is also known to induce increased permeability, or even frank disruption, of the blood–brain barrier in animal subjects even at nanomolar concentrations [291, 292]. Macrocyclic trichothecenes, such as those produced by SC [293], can also activate p38, JNK, ERK, and MAPK kinases simultaneously, once again via the induction of ribotoxic stress [239, 294]. When compared to T2 toxins, however, macrolytic thrichothecenes are up to a hundred times more potent at activating MAPKs and inhibiting the proliferation of leucocytes [250, 294].

Another mycotoxin found in the dust and air within water-damaged buildings is ochratoxin A [295]. Chronic exposure to this toxin leads to increased oxidative stress, with elevated levels of lipid peroxidation and oxidative damage to DNA in brain tissue in vivo [296, 297]. Furthermore, ochratoxin exposure leads to mitochondrial impairment and bioenergetics compromise and a secondary increase in the production of ROS [296, 298]. Such diminished mitochondrial performance is in part likely to be due to chronic oxidative stress, but the toxin also inhibits complex 1 of the electron transport chain and directly impairs mitochondrial membrane potential [299, 300]. It is also of interest that exposure to ochratoxin A provokes atypical responses in microglia and astrocytes compromising their neuroprotective function and positively promotes neuroinflammation via the up-regulation of for example NF-κB [301, 302].

Fumonsin B1 is yet another mycotoxin found in the atmosphere of water-damaged buildings with data demonstrating neurotoxic properties [303]. These properties include the generation of oxidative stress and subsequent lipid peroxidation and DNA damage within brain tissue [250]. This toxin also appears to transverse the blood–brain barrier leading to the activation of microglia and astrocytes with the subsequent secretion of pro-inflammatory cytokines and other neurotoxic substances [250].

Finally, we return to a consideration of specific macrocyclic trichothecenes produced by SC, in part because SC is the organism most implicated in causing the neurological sequelae seen in people with a history of chronic mold exposure, and in part because these mycotoxins are known to produce neurotoxicity in humans [227, 246, 270]. These mycotoxins are known as Saratoxin G and Saratoxin H, respectively [250] and we now turn to a consideration of their pathogenic capability.

Exposure to Saratoxin G, or its surrogate, produces apoptosis of sensory neurons leading to the olfactory bulb combined with atrophy of that structure in animal subjects. Moreover, the same animal subjects developed encephalitis accompanied by chronically elevated levels of pro-inflammatory cytokines in the frontal brain [304, 305]. Saratoxin H exposure leads to the activation of MAPKs, JNK p38, and capase-3 together with the predictable development of oxidative stress, increased levels of reactive oxygen species, and the depletion of reduced glutathione [250]. There is evidence that the constant presence of Saratoxin H with subsequent self-amplifying neuroinflammation and chronic immune activation renders an individual more susceptible to the effects of other neurotoxic species in the environment and more susceptible to the presence of such species in the environment thereafter [237, 306]. This would be consistent with evidence demonstrating temporal exacerbation of neurotoxicity via microglial priming [21]. There is also evidence that mycotoxins act synergistically, so that a combination of mycotoxins could induce toxicity at very low levels where a single mycotoxin would not [307].

There may, however, be additional elements underpinning the development of neurological pathology in patients chronically exposed to mycotoxins in water-damaged buildings. LPS once again present at high concentrations in water-damaged buildings potentiates trichothecene toxicity exacerbating any mycotoxin-induced damage [227, 308, 309]. Co-exposure to otherwise sub-toxic doses of deoxynivalenol and LPS significantly induces apoptosis in the thymus, Peyer's patches, and the bone marrow of laboratory animals via the up-regulation of pro-inflammatory cytokine transcription [305, 310]. Equally, bacterial translocation as a result of mycotoxin-induced damage to the intestinal endothelium is another source of LPS which is known to provoke neurotoxicity and is the cause of chronic immune activation in patients with HIV [311, 312]. Finally, the presence of nanoparticulate matter in such environments may also be a source of neuropathology per se whether coated in mycotoxins or not [313, 314]. These authors have demonstrated that such nanoparticles passage into the brain via the olfactory epithelium and the olfactory bulb lead to increased production of inducible nitric oxide synthase (iNOS), NF-KB, and TNFα and the deposition of beta amyloid plaques highly reminiscent of the pattern seen in Alzheimer's disease [314, 315]. These authors also reported the results of a disturbing study examining the effects of the polluted air of Mexico City on the brains of local children. These children had clinically significant deficits on neurocognitive testing, and over half displayed prefrontal white matter hyperintense lesions indicative of chronic neuroinflammation [314] (Fig. 1).

Conclusion

It must be remembered that chronic fatigue syndrome is a diagnostic label afforded to individuals with apparently idiopathic fatigue, with or without a few additional non-specific

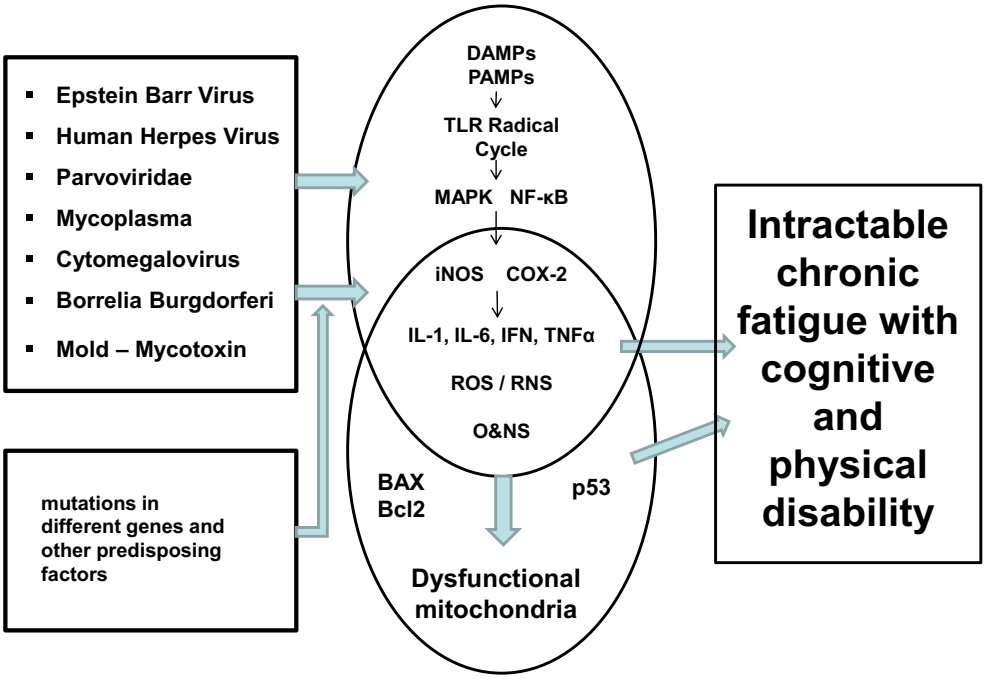

Fig. 1 This figure shows the role of viruses, bacteria, and chronic fungal biotoxin exposure in the genesis of intractable fatigue accompanied by cognitive and physical disability. Different microorganisms and biotoxins may activate the Toll-like receptor (TLR) cycle through pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs). Activation of the TLR cycle and other mechanisms may cause central and/or peripheral activation of intracellular signaling networks, e.g., nuclear factor (NF)-κB and mitogen-activated protein kinase (MAPK), leading to induction of cyclooxygenase (COX)-2 and inducible nitric oxide synthase (iNOS), the production of pro-inflammatory cytokines, interleukin (IL)-1, IL-6, interferons (IFN) and tumor necrosis factor (TNF)α, and reactive oxygen and nitrogen species (ROS/RNS) leading to damage by oxidative and nitrosative stress (O&NS). The above pathways may lead to mitochondrial dysfunctions and alterations in p53, Bcl2 (B cell lymphoma 2) and BAX (Bcl-2-associated X protein) functioning. It is argued that these (and other changes discussed in the text) may induce chronic fatigue

symptoms, and such a diagnosis likely does not represent a single disease entity with a unitary pathogenesis and pathophysiology. Given that pathological levels of fatigue are not even a mandatory requirement for most of the various selection criteria; the question of what causes CFS seems somewhat irrational and impossible to answer. The question of what might be the cause of severe, apparently idiopathic, fatigue together with profound levels of cognitive and or physical disability in an individual patient is a different matter, however, as we now have an objective descriptor. The role of functional polymorphisms in TLR or cytokine genes in the genesis and maintenance of such a presentation appears to be a promising avenue for research given that such genetic abnormalities are known to influence an individual's susceptibility to infection, the severity and duration of the immune response, and the development of chronic illness. Likewise, the role of chronic inflammation and oxidative stress, in driving chronic immune activation via DAMP formation and the consequent development of chronic illness, is well documented. Hence, a mechanism exists whereby patients with a genetic predisposition could go on to develop profound levels of disability accompanied by severe intractable fatigue. Such patients would be expected to display objective markers of systemic inflammation and elevated cytokine production. The presence of persistent active or periodically reactivating pathogens would also be a very likely cause of this symptom complex.

Active herpes virus infections are a well-known cause of fatigue and disability. Very recent research has demonstrated an increase in systemic inflammation and cytokine production following reactivation of HCMV and HHV6 in immunocompetent patients leading to increase in disease severity and, in the latter case, neuropathology. The reactivation of EBV even at very low levels is now known to provoke severe systemic inflammation and contribute to the development of serious pathology. Combined with the realization that this virus acts as a source of inflammation and immune dysregulation even in its latent state, this is likely to change the perception of EBV as a benign passenger following initial illness. The absence of active viral replication is no longer enough to dismiss the virus as a source of a person's symptoms. The presence of a persistent Mycoplasma infection would also be a rational explanation for the presence of disability and fatigue in any given patient, but is only detectable if very precise protocols are adhered to. The presence of Bf would also be an unproblematic explanation, but detecting this spirochete in patients who may have experienced these signs and symptoms for many years remains a significant challenge. The existence of a

persistent Parvovirus B19 infection with evidence of viral replication would also be a rational explanation for a patient's symptoms, but it may be present in tissues when absent in blood. The capacity of this virus and the herpes viruses to directly damage mitochondria and interfere with the biomechanics of p53 may well underpin their proven capability to induce profound levels of fatigue and disability. Finally, and perhaps somewhat paradoxically, a history of chronic mold exposure as a source of such symptoms is now well documented, and the science explaining the mechanisms involved is now increasingly delineated. This may also be the easiest presentation to treat given the potential utility of intranasal glutathione. In conclusion, the presence of any of the elements discussed in this paper could easily drive the production of severe fatigue and profound disability presented by any individual patient. The current practice of affording a diagnosis of chronic fatigue syndrome to such patients, if rudimentary tests fail to disclose the origins of their symptoms, is likely unhelpful and should, in our view, be discouraged.

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