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Review Article

What Causes ME/CFS: The Role of the Dysfunctional Immune System and Viral Infections

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Abstract

Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) remains an enigmatic highly disabling and complex long-term condition with a wide range of aetiologies and symptoms. A viral onset is commonly mentioned by patients and several bodily systems are ultimately disturbed. The parallel with long-covid is clear. However, immune dysregulation with impaired NK cell dysfunction and tendency to novel autoimmunity have been frequently reported. These may contribute to reactivation of previous acquired viruses/retroviruses accompanied by impaired endocrine regulation and mitochondrial energy generation. The unpredictable nature of seemingly unconnected and diverse symptoms that are poorly responsive to several allopathic and alternative therapies then contributes to an escalation of the illness with secondary dysfunction of multiple other systems. Treatment of established ME/CFS is therefore difficult and requires multi-specialty input addressing each of the areas affected by the illness.

Keywords: Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS); Immune system; Viruses; Retroviruses; Cytokines; NK cells; Mitochondria.

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Background and hypothesis

Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) is a long-term condition with a wide range of symptoms, but extreme fatigue affects all patients. There are no specific biomarkers, diagnostic tests or

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effective treatments for ME/CFS reflecting the inability to define the underlying cause(s) of the disorder. In June 2021 the InvestinME Research charity convened a meeting organized by The European ME Research Group (EMERG) that included ME/CFS researchers from across the world to discuss ME/CFS research both past and current that tests popular hypotheses that explain the aetiology of ME/CFS. These included: immunogenetics and dysfunctional immune responses; an abnormal autonomous nervous system and autoimmunity; mitochondrial metabolic dysfunction; and altered host-microbe (commensal and pathogen) interactions. This article summarizes discussions focusing on the immune system and addressing the hypothesis that immune dysfunction and viral factors may drive the development and progression of ME/CFS. Collectively, the variable patterns of immune dysfunction in ME/CFS may explain the specific combinations of symptoms experienced by patients and their propensity for improvement. Unravelling the details of these changes will not only help patients understand the nature of their illness and its multiple symptoms but also provide important clues as to how it is best treated. This understanding may ultimately help the increasing number of people suffering fatigue and cognitive dysfunction following SARS-CoV-2 infection as part of long-covid.

Introduction

The clinical phenotype of ME/CFS reflects a combination of symptoms and pathologies that are either instigated by an initiating illness, or by factors associated with on-going neuro-immuno-endocrine disruption [1] and perpetuated and aggravated by the severity and multiplicity of never-ending inexplicable symptoms and extreme fatigue. This is illustrated in Figure 1, which shows the multiple pathways by which unfavorable interaction between the several bodily systems known to be impaired in CFS/ME can perpetuate and aggravate overall ill health.

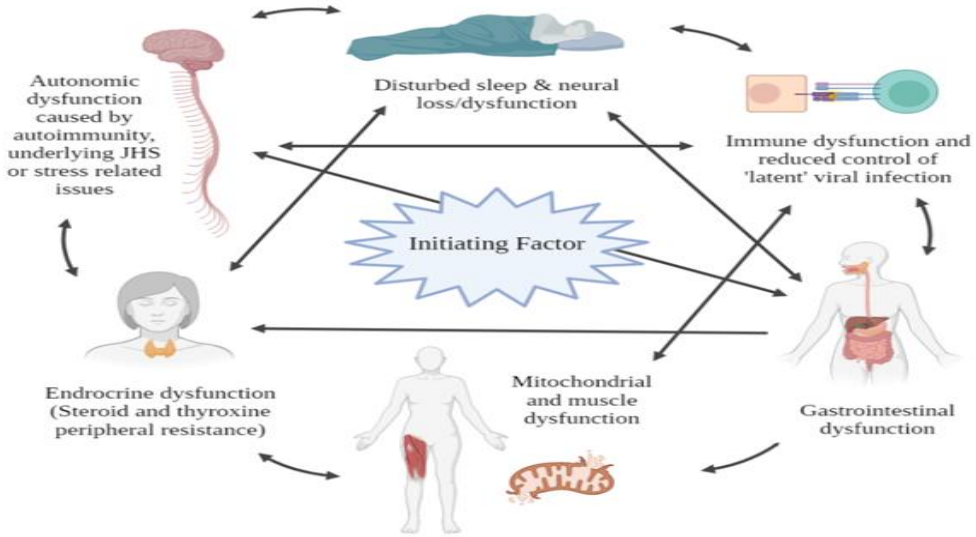

Figure 1: Factors causing or perpetuating ME/CFS.

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Here the central initiating factor contributes to worsening ill health by disturbance of one or more of the peripheral systems. If left unchecked the primary and secondary disruption leads to adverse activation or impairment of the other systems. This ultimately produces a clinical disorder with multiple, seemingly unrelated, symptoms and which defies a unifying known physical aetiology and which are now recognize to be CFS/ME. In respect to the factors which can initiate CFS/ME, persistent disabling fatigue is not unusual after viral and bacterial infections and is particularly common in rheumatological conditions [2-4]. In ME/CFS a significant immunological component is suggested by the nature of the symptoms (recurrent sore throats, lymph gland enlargement, flu-like sensations, arthralgia and myalgia) and by subtle abnormalities observed in the immune system [5]. In the clinical setting, however, the majority of routine immune based blood tests are normal although low level anti-nuclear antibodies, mildly raised IgM and atypical lymphocytes can be seen in a small proportion of patients. However, despite mildly reduced levels of IgG3 and IgG4 and possible prevalence of reduced mannose binding lectin, an overt clinical immune deficiency and autoimmunity that can be demonstrated in routine blood tests is rarely evident in ME/CFS [6]. Indeed, antibody deficiency warranting replacement therapy was evident in only one of over nine thousand CFS/ME patients seen in our clinic and a systemic connective tissue disorder in the form of Sjogrens syndrome was seen in only two people. Additionally, there many studies reporting inconsistent or contradictory findings from cytokine analyses. However, subtle dysregulation in Natural Killer [7], T cells [8] and B cells [9,10] associated with the generation of specific autoantibodies is a hallmark of disease in a significant proportion of CFS/ME sufferers [11] although there are conflicting reports for each cell type [12]. These abnormalities can be accompanied by distinct transcription changes and epigenetic signatures involving genes that regulate cellular immunity, inflammation, mitochondrial energy generation and autoantibodies targeting autonomic system hormones and receptors [13-14]. However, it remains unclear whether these defects are the cause or the result of ME/CFS because the immune system is significantly influenced by stress, mood and sleep disturbance, all of which are affected by diverse aetiologies of ill health [15]. Alongside this, there is evidence for reactivation of one or more previously-acquired conventional viruses and retroviruses which would normally be kept in check by an optimally functioning immune system [16-17]. Viral or retroviral reactivation caused by illness initiated immune paresis and contributing to inflammation and mitochondrial dysfunction has been considered important in precipitating and perpetuating ME/CFS symptoms [18].

Collectively, variable patterns in immune dysfunction may explain the specific combinations of symptoms experienced by patients and their likelihood of improvement. Unravelling the details of these changes will not only help patients understand the nature of their illness and its multiple symptoms, but also provide important clues as to how it is best treated.

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Confounding factors in previous immune research in ME/CFS

Previous investigations of biochemical, microbiological and immunological abnormalities in subjects with ME/CFS have often considered this to be a single disorder with clinical and immune changes associated with particular stages of the disease and aetiological factors [19-21]. This may explain the absence of any consistent set of immune system related abnormalities in groups of patients for whom diagnosis is primarily achieved by exclusion as there are no specific diagnostic tests. Furthermore, the nature and timing of sample collection as well as the assays used for immune analysis may have an influence as differences in sample processing and cryopreservation can impact significantly on the expression of cellular markers and function [22].

Cytokine analyses in ME/CFS

Cytokine dysregulation has been documented frequently in ME/CFS but the findings have often been contradictory [23-25]. Early studies suggested increased levels of pro-inflammatory cytokines despite normal levels of C-reactive protein [26] while others have found no difference [27] or only increases in specific cytokines such as TGF-β [28,21]. A systematic review showed that patients had significantly elevated TNF-α, IL-2, IL-4, TGF-β and CRP [29]. Using a proteomics approach and aptamers able to detect 4797 human protein abundances [30], found the levels of IL18 binding protein and TNF-α receptor to be raised in 20 female patients with CFS/ME. The results suggested immune dysregulation with efforts to control inflammation. Notwithstanding, lipopolysaccharide (LPS)-induced IL10 secretion in whole blood cultures that was highly sensitive to suppression by dexamethasone, was significantly increased in patients with ME/CFS compared with controls [31]. In a later study [32], noted significant glucocorticoid suppression of LPS induced IL10 production by PBMCs but this was no different to health controls. In addition to raised inflammatory cytokines, other factors have been reported, specifically: lowered overall plasma anti-oxidant activity; increased N-terminal pro-brain derived natriuretic factor; increased fibroblast growth factor 21 [33]. Positive correlations between some of these variables has also been reported [33]. Interestingly, serum levels of IL4, IFN and soluble CD23 in monozygotic (MZ) and dizygotic (DZ) twins discordant for chronic fatigue [34] were similar while persistent fatigue was more frequently concordant in the MZ versus the DZ twins. To reduce the variability of individual variations in cytokine levels, the use of cytokine signatures unique to ME/CFS have been reported and used to distinguish the early stages of ME/CFS [35] and were shown to be correlated with disease severity [21]. More recently attention has been focused on correlating psychological variables and sleep disturbance with cytokine levels [36]. This suggested an association between executive function and IL-1 and IL-6, interpersonal function and IL-6 and TNF-α and sleep with IL1, IL2, IL6 and TNFa [36]. Further correlative studies have shown IL17 levels to be raised in CFS/ME patients in whom IL4, IL10, IL18 and IFNg were normal and there was no correlation with tryptophan metabolites [37].

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Natural Killer cell analyses in ME/CFS

The only immune abnormality consistently demonstrated in the majority of reports on ME/CFS is a reduction in the number [38-39] or function [40] or both of NK cells [41]. However, a recent report based on data from large numbers of well characterized ME/CFS patients (some with severe disease) showed no significant differences in NK cell numbers or cytotoxicity [8] compared with healthy subjects and patients with Multiple Sclerosis. However, they did note an interesting reduction in terminally differentiated effector CD8 T cells and an increase in effector memory CD8 T cells and mucosal associated invariant T cells [8]. Regardless, [42] confirmed reduced NK cell numbers in ME/CFS patients and increased numbers of adhesion (CD11b, CD11c and CD54) and activation (CD38) markers on those NK cells. However, others have found NK cells numbers to be higher in subjects with ME/CFS but that NK cell cytotoxicity was reduced compared with healthy controls [43]. Functionally, NK cells recognize their targets by the absence of classical HLA class I proteins and by binding NK stimulatory and inhibitory receptors of the killer immunoglobulin-like receptor (KIR) superfamily. Findings have been variable with some studies showing no change in expression of CD94, numerous inhibitory killer immunoglobulin–like receptors (KIRs) and activating receptors (NKG2D) [44] while others in severely affected ME/CFS patients reported KIR3DL1 to be significantly increased and NK cytotoxicity reduced compared with healthy controls [45,46]. As further evidence of the disarray in NK results in CFS/ME, Rivas et al in 2018 [7] reported a lower expression of NKG2C, an activating receptor that recognizes Human Leucocyte Antigen E (HLA-E), in contrast to an earlier study where no differences were observed and with the differences attributed to frozen PMBC used in one study and whole blood in the other [47]. Importantly, altered expression of activating and inhibitory NK cell receptors are evident in chronic cytomegalovirus (CMV) infections and in co-infections with other viruses, notably Epstein-Barr virus (EBV) [48]. In patients with severe ME/CFS, defects in protein kinase gene expression in NK cells has been reported [49]. Thirty-seven genes showed increased expression while 55 showed significantly reduced expression, with a significant reduction in calcium-dependent protein kinases, lymphocyte-specific protein kinase (Lck) and Zeta-chain-associated protein kinase 70 (ZAP 70). The authors concluded that this dysregulation could contribute to impaired NK cell function as these kinases play critical roles in intracellular signaling and could disrupt NK responses to its environment. Defects in the mitogen activated protein kinases (MAPK) pathway were observed in ME/CFS patients, such as a reduction in ERK1/2 in cytolytic NK cells while the cytokine producing NK cells showed a significant increase in MEK 1/2 and p38 expression [50]. ERK 1/2 has been identified as having an important role in cytotoxicity and furthermore, phosphorylation of ERK1/2 induces a conformational change that is required for NK cell cytotoxic activity. Thus, aberrant signaling through ERK 1/2 could interfere with the release of lytic proteins and thus

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explain the reduced NK cytotoxicity. More recently it has been suggested that the cause of NK cell dysfunction is due to a loss in function of Transient Receptor Potential Mela statin ion channel-3 (TRPM-3) activity which is critical for NK cytotoxicity [51] and could be improved by naltrexone, an opioid receptor antagonist mitigating its inhibitory function on TRPM3 [52]. Interestingly, the latter used in low doses has been found helpful by patients with ME/CFS and also in fibromyalgia.

Immunodeficiency and disturbed immunological memory in ME/CFS

While a reduction in the numbers of CD19/IgM+ B cells has been observed [53], ME/CFS has never been linked to symptomatic antibody immunodeficiency with recurrent bacterial infections. Conversely, B cell depletion using a monoclonal anti-CD20 antibody, Rituximab, was initially found to markedly improve clinical symptoms in three patients with ME/CFS [54] and then in a double-blind placebo-controlled trial with 30 CFS patients [55]. However, no significant benefit was reported by the same group in a more recent report using 12 months of Rituximab [56].

Recently, B cell subsets were examined and no differences found between ME/CFS patients and healthy controls for classical B cell markers, immunoglobulin D (IgD), CD27 and CD38 as well as CD5, CD21, CD23, B cell activating factor (BAFF) receptor and IgM [57]. Intriguingly, a significant increase in CD24 expression on IgD positive B cells in ME/CFS was evident but there was no correlation with disease duration. Interestingly, CD24 is a glycoprotein expressed on most B cells and is a marker for transitional B cells that are at an intermediate stage in their development between immature bone marrow cells and peripheral mature B cells. These are highly pleomorphic with some polymorphisms associated with autoimmune disease [58] and possibly also with altered mitochondrial function [57].

In ME/CFS the function of both memory CD4 and CD8 T cells may be affected and associated with impaired mitochondrial function [59]. T cell memory is complex and based partly on the strength of the initial antigenic stimulus with viral infections providing a very strong stimulus. For all T cells long-lived memory is maintained most significantly by continued antigen stimulation or cross-reactive antigen stimulation. This is evident in persistent viral infections such as those caused by EBV and HHV6 and both HHV6 [60] and EBV can cause major alterations in T cell memory function. In the case of EBV, acute mononucleosis was accompanied by loss of IL-7R expression by all CD8+ T cells, including EBV epitope-specific populations [61]. While expression was rapidly regained in total CD8+ cells it was only slowly and incompletely regained in EBV-specific memory cells [61] permitting bouts of viral reactivation. Therapeutically this could lead to treatments that would involve using agents active against EBV. T regulatory cells and Th17 cells have been studied in ME/CFS and the results showed that regulatory T cells are either increased in number in ME/CFS patients [62,63] or reduced [7]. These findings

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need to be confirmed as do the associated increases in Th2 cells [64] which have central roles in immunity to viruses and the immune response and could be dysregulated in ME/CFS. Regardless, increased Treg function may hypothetically suppress CD4 and CD8 T cells having anti-EBV and HHV6 activity if the prevailing clones manifested virus induced cross reactive immunity to a self-antigen [65].

Gene immune-signature analysis in ME/CFS

Several studies have sought to identify diagnostic biomarkers for ME/CFS, with varying results. Using whole blood gene expression in 29 adolescent ME/CFS patients [10] found that 176 genes were differentially expressed, including CD79a, which is involved in B cell differentiation, activation and signaling; Tumor necrosis factor receptor superfamily 13C, which is involved in B cell homeostasis; and FLT3 (fms-related tyrosine kinase 3) which has effects on numerous aspects of the immune system including B and pro B cell survival, proliferation, differentiation and responses to cytokines. Collectively, these findings suggest that abnormal B cell differentiation and survival is related to ME/CFS and linked to an altered hypothalamus–pituitary-adrenal (HPA) axis. These B cell abnormalities were also significantly linked to post exertional malaise. Interestingly they also found evidence of an up-regulated antiviral response. Presson [66] used weighted Gene Co-expression Network Analysis (WGCNA) to integrate gene expression and trait data for ME/CFS. They initially noted 299 genes correlating with chronic fatigue of which 20 candidate genes showed special prominence. Amongst the latter FOXN1, PRDX3 and SUCLA2 were noteworthy as they were involved in thymic T cell development and maturation, mitochondrial energy generation and apoptosis and mitochondrial function. Combining both mRNA expression and DNA methylation data of ME/CFS and healthy controls, [67] performed recursive ensemble feature selection (REFS) on publicly available mRNA expression and DNA methylation data in peripheral blood mononuclear cells. They found a signature of 23 genes capable of distinguishing between ME/CFS patients and controls (AUC of 0.92), ten of which were indicative of a 'derailed immune system in ME/CFS' associated with downregulated IL2, CCR4 and MHC class II receptor function as well as proteoglycan 4, an immune cell receptor ligand, and intracellular signaling molecules important for anti-viral immunity.

ME/CFS and viral infection

Consistent evidence of specific viral infections causing ME/CFS remains elusive. However, several investigators have reported increased 2'5'OA synthetase (2-5A) activity in the mononuclear cells of patients with ME/CFS and with levels correlating with disease severity [68-70]. As 2-5A is induced by IFN-? and IFN-? and is important in combating viral proliferation [71], the raised levels appear to suggest chronic viral infection in ME/CFS. Intriguingly, increased 2-5A dimers compared to the normal oligomers that inhibit the proteolytic breakdown of RNase L, an important ribonuclease part of anti-viral innate immune

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defense, [72] may be responsible for elevated RNase L levels in ME/CFS and were significantly linked to exercise tolerance [73]. However, the detection of several herpes viruses (HHV), enteroviruses and Borna viruses in patients with ME/CFS by serology and PCR have provided conflicting results. Thus, [74] suggested HHV-6 reactivation after detecting a raised frequency of anti-HHV-6 IgM and detection of HHV-6 antigen in short term PBMC cultures from their patients with ME/CFS. In marked contrast, [75] in their co-twin study detected no serological evidence of HHV-8, cytomegalovirus, herpes simplex virus 1 and 2 or hepatitis C virus in MZ twins discordant for ME/CFS.

Moreover, there was no PCR evidence of infection with HHV-6, HHV-7, HHV-8, CMV, EBV, herpes simplex virus, varicella zoster virus, JC virus, BK virus and parvovirus B19. This was also noted in an earlier study by in 1996 [76] of 548 chronically fatigued patients using serological techniques for rubella, coxsackie B viruses and adenovirus. Similar negative results for increased viral prevalence in those with ME/CFS was presented by [8]. In contrast, others found serological evidence of an increased frequency of previous EBV and Coxackie viruses B1 and B4 in patients with ME/CFS [77]. IgM antibodies to non-structural genes in human CMV have also been detected in a subset of ME/CFS patients [78]. This group also found IgM antibodies to EBV in a subset of ME/CFS patients indicating that a defect in the immune system could be permitting chronic infection by viruses. More recently salivary samples from patients with CFS/ME have shown increased DNA for HHV6 and HHV7 which in many patients correlated with fatigue and symptom severity [79].

Further dysregulation of the immune system is suggested by the detection of antibodies to mitochondrial components and also to serotonin, microtubule-associated protein 2 and muscarinic cholinergic receptor 1 [80]. Similar endocrine receptor auto-antibodies were also subsequently reported by [81] and more recently against G-protein coupled receptors by [11]. Furthermore, auto-antibodies against alpha 1 adrenergic and muscarinic M3 receptor was positively correlated with soluble CD23 in patients with an infective onset to their CFS/ME [82]. In each case, infection stimulated autoimmunity has been proposed as an explanation for many of the symptoms in ME/CFS [83]. In this respect, active EBV and HHV6, infection does not appear necessary for the development of autoimmunity [84,85] and several viral proteins can aid the persistence of immune cells with autoimmune tendency. In respect to CFS/ME, stress has been reported to reactivate EBV [16,86] and it is possible that the increased stress suffered by patients with ME/CFS may contribute to recurrent relapses in ME/CFS. For HHV6, however, reactivation may be necessary, and this has been shown to induce mitochondrial degeneration and impaired ATP generation which could theoretically at least contribute to fatigue symptoms [87].

Regarding other viruses, enterovirus particles in gastric biopsies of patients with confirmed ME/CFS have been reported [88] and supporting previous work suggesting

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enteroviral persistence in patients with ME/CFS [89]. Previous negative associations between enteroviruses and ME/CFS have recently been attributed to sampling issues, methodological inadequacies using serological, tissue culture and molecular technologies and 'incomprehensive' detection panels for each method [90]. Active lytic infection is also not necessary for clinical illness as many enteroviruses are capable of disrupting cellular homeostasis and mitochondrial energy production by several means [90].

Endogenous retroviral activation in ME/CFS

A non-excluding possibility to explain ME/CFS symptoms and their relationship with immune dysregulation, is as result of aberrant activation of human endogenous retrovirus (HERVs). HERVs are dormant viral sequences incorporated in our genome through evolution which actually represent about 8% of our genome (~four times the size of protein-coding sequences)) [91-93]. Acquired through ancient exogenous infections they provide essential functions and the main source for human evolution [94,95].

Although most elements appear permanently silenced in adult cells [96,97], environmental factors, including exogenous infections, may compromise their restriction [98-100]. Importantly, differential expression of HERVs in fibromyalgia and ME/CFS has been evidenced by several groups [101,102]. Furthermore, HERV activation has been found in lymphocytes of COVID patients correlating with inflammatory markers and pneumonia´s severity [98]. Thus, the possibility that Long-COVID, a post-viral syndrome with symptoms that overlap those of ME/CFS [103,104], derives from the incapacity of some patients to re-silence HERVs seems to deserve interrogation. Symptomatically, HERV activation may translate into infection-like symptoms, such as pain, fatigue, immune and metabolic disturbances [105,106] which are common in ME/CFS.

In multiple sclerosis and amyotrophic lateral sclerosis HERV activation can lead to demyelination, inflammation and cognitive problems [107]. HERVs detection and targeting opens up new diagnostic and therapeutic avenues [107,108].

Conclusion

Is the immune dysregulation hypothesis proven?

After over 20 year of attempting to identify specific immune defects and infectious agents that cause ME/CFS, clear pathways are still not evident. However, a complex interaction between the immune system and viruses/retroviruses is now emerging and manifesting subtle changes in cytokines, NK cells and T cells which directly or via autoimmunity may be responsible for the plethora of symptoms seen in ME/CFS. Combined with immune and pathogen-induced mitochondrial dysfunction now being dissected by several research groups it is quite possible that it will gain real insight into the cause of this enigmatic and highly disabling illness.

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