Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) is a disease with unknown etiology, no validated specific and sensitive biomarker, and no standard approved effective treatment. ME/CFS has a profound impact on the quality of life of both patients and caregivers and entails high costs for society. The severity varies among patients who are able to participate to some extent in social life (mild), those who are mainly housebound (moderate) or bedridden (severe), and the very severely ill who are completely dependent on assistance for all daily living tasks, such as feeding or turning around in bed. Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) often starts in previously healthy individuals after an infection, the most common being infectious mononucleosis (EBV). It is more frequent in women and influenced by genetic predisposition. The main symptoms are postexertional malaise (PEM), fatigue, orthostatic intolerance, cognitive disturbances, sleep problems with inadequate restitution after rest, sensory hypersensitivity with pain, and symptoms related to autonomic and immune dysfunction. The prevalence is 0.1% to 0.8%, and ME/CFS must be distinguished from general fatigue, which is much more common in the population. Historically, there has been limited scientific interest in ME/CFS. However, research efforts have increased in the last decade. Although this has led to different hypotheses, a firmly established pathomechanism is lacking. Herein, we suggest a framework model for the initiation and […]
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Herein, we suggest a framework model for the initiation and maintenance of ME/CFS consisting of three principal steps: (a) an initial aberrant immune response; (b) an effector system for symptom generation and maintenance; and (c) compensatory adaptations. The model and possible therapeutic opportunities are summarized in Figure 1.

**Immune response**

Our interest in ME/CFS started in 2007 in our cancer ward, when we observed patients with long-standing ME/CFS who got cancer and who independently reported that the cancer treatment had beneficial effects on their ME/CFS. The treatments included the cytotoxic drug cyclophosphamide and/or the monoclonal B cell–depleting anti-CD20 antibody rituximab. Our observations led to the working hypothesis that ME/CFS in a subgroup could be a variant of an autoimmune disease, often with a postinfectious onset and with a role for B cells/plasma cells and antibodies. Consequently, we decided to test relevant immunomodulatory drugs in clinical trials for ME/CFS patients.

Several findings support an autoimmune disease mechanism in ME/CFS. These include a marked female preponderance, a high frequency of autoimmunity among first-degree family members (40%-55% in our trials), and enriched HLA risk alleles. Among patients with an infectious onset, associations with autoimmunity-related gene variants (1) and skewed B cell receptor gene usage (2) have been demonstrated. Furthermore, elderly ME/CFS patients have an increased risk of B cell lymphoma, especially the low-grade marginal zone lymphomas often associated with autoimmunity or chronic infections (3). Serum B cell activating factor (BAFF) increase and gene expression studies suggesting antigen-driven B cell clonality (4) or altered B cell differentiation (5) may point to B cell involvement. Beneficial clinical effects have been reported after immunoadsorption to remove plasma IgG (6).

Despite promising results from our early phase II trials evaluating rituximab in ME/CFS, the subsequent multicenter, double-blind, and placebo-controlled phase III trial was negative for the outcome measures (ref. 7; additional references therein). Factors that may have influenced the outcome of the phase III trial include heterogeneity among patients, placebo mechanisms, natural symptom variation, and nonoptimal outcome measures. However, our pooled experience supports that some ME/CFS patients do respond to rituximab and B cell depletion. As rituximab targets CD20-positive cells, patients whose autoantibody production occurs in CD20-positive plasmablasts would be likely responders. In the majority of patients, however, autoantibodies may be produced in CD20-negative, long-lived plasma cells not targeted by rituximab (Figure 1). These are known mechanisms in several established autoimmune diseases. However, other parts of the immune system may play important pathomechanistic roles in other subgroups of ME/CFS patients.

We also performed an open-label phase II trial with intravenous cyclophosphamide, in which half the patients reported clinical responses lasting several years (8). Cyclophosphamide has broad effects on several subsets of lymphocytes, and the mechanism for benefit in ME/CFS could involve the antiproliferative effects inhibiting B cell activation to plasmablasts (Figure 1). Although there were no severe side effects, cyclophosphamide can induce infertility, and a broader use in ME/CFS patients is problematic due to toxicity concerns. Further, we have seen symptom improvement in ME/CFS patients using...
with PEM as the cardinal symptom? We believe that the clinical symptoms in ME/CFS suggest inadequate autoregulation of blood flow according to the demands of tissues, resulting in tissue hypoxia. This is associated with lactate accumulation from limited exertion, in some patients even at rest.

There is growing evidence for endothelial dysfunction in ME/CFS, affecting large arteries, assessed by flow-mediated dilation (FMD), and small arteries, assessed by postocclusive reactive hyperemia (refs. 9, 10, and Figure 1). FMD mainly reflects the release of nitric oxide (NO) from endothelial cells in response to shear stress in vessel walls. However, patients had intact ability to dilate adequately from endothelium-independent vasodilation when given sublingual nitroglycerin. The endothelial dysfunction was not associated with laboratory markers of endothelial dysfunction seen in cardiovascular disease, which argues for a different mechanism, possibly related to an abnormal immune response (10).

Head-up tilt testing using extracranial Doppler measurements of carotid and vertebral arteries has shown reduced cerebral blood flow (11), which may contribute to PEM and cognitive dysfunction. In a recent study assessing ME/CFS patients with upright cardiopulmonary exercise test (CPET) and invasive mon-
monitoring, a subgroup of the patients had reduced right atrial pressure and venous return (preload failure), with reduced cardiac output and reduced peak oxygen uptake on exertion (12). Other ME/CFS patients showed evidence of microcirculatory disturbances with impaired peripheral oxygen extraction, compatible with arteriovenous (AV) shunting and possibly related to neurovascular dysregulation and small fiber neuropathy (12). Impaired oxygen extraction in muscles during exercise tests has also been demonstrated by noninvasive measurements (13). According to the CPET test results, the circulatory disturbances could not be explained by deconditioning in patients with orthostatic intolerance and reduced cerebral blood flow upon head-up tilt testing (14) nor in patients with exercise intolerance and low biventricular filling pressures or impaired AV oxygen extraction (12). It would, however, be expected that physical deconditioning and other effects of long-lasting disease may contribute to symptom worsening.

Endothelial dysfunction with inadequate flow regulation to meet the demands of tissues, reduced venous tone and return, and reduced cardiac output on exertion as well as AV shunting with reduced peripheral oxygen extraction would all result in tissue hypoxia, which we believe may be a common pathomechanistic denominator in ME/CFS (Figure 1). Several two-day CPET studies have shown that ME/CFS patients have ventilatory anaerobic threshold at a lower workload compared with healthy subjects, especially on day two (15), which is a manifestation of PEM. PEM often occurs with a time lag after exertion and may be sustained for days and weeks. One may speculate that some symptom-generating factors are physiologically reinforced by exercise. Moreover, patient reports of transient symptom improvement from oxygen inhalation, from nitroglycerin-mediated vasodilation (briefly alleviating the “brain fog”), or from saline infusions (to increase volume and venous pressure) may correspond with poor vasoregulation. Alternatively, in some patients, there could be a primary autonomic pathomechanism with increased sympathetic tone.

Several studies have reported metabolic changes in ME/CFS patients, e.g., A. Germain et al. (19) and Ø. Fluge et al. (20). The results suggest altered utilization of substrates for energy metabolism, such as increased use of amino acids and fatty acids for tricarboxylic acid cycle (TCA) fueling, with reduced glucose and pyruvate oxidation. Impaired pyruvate dehydrogenase (PDH) function due to increased expression of PDH kinases (PDKs) (20) may indicate chronic activation of physiological metabolic programs that normally protect cellular energy (ATP) supply under demanding conditions, such as endurance exercise, hypoxia, or starvation. Metabolic adaptations, aiming to maintain and restore energy supply, may be caused by an underlying tissue hypoxia on exertion in ME/CFS. This restriction will compromise homeostasis and promote energy strain and corresponding metabolic responses.

Variant of autoimmune mechanism?

In established autoimmune diseases, pathogenic IgGs often associate with complement activation, inflammation, and tissue injury. These features are not characteristic of ME/CFS. We suggest that a variant of an autoimmune mechanism affects the autonomic control of blood vessel tone and flow autoregulation. ME/CFS overlaps clinically with postural orthostatic tachycardia syndrome (POTS), orthostatic intolerance, fibromyalgia, and complex regional pain syndrome. We speculate that these illnesses could be associated with a pattern of autoantibodies occurring after triggers such as systemic infections (21), but not resolving properly over time. In ME/CFS, a persistent functional autoantibody pattern could disturb blood vessel autoregulation and lead to secondary metabolic and autonomic adaptations (Figure 1).

To this end, functional GPCR autoantibodies may be involved (22). Agonistic autoantibodies to β2 adrenergic receptors (β2ARs) and muscarinic 3 receptors have been demonstrated in orthostatic hypotension (23). In POTS, an autoimmune basis has been suggested by the presence of several functional autoantibodies toward GPCRs affecting blood pressure and heart rate regulation, such as antibodies to α1AR, β1AR, and β2AR (24), and also toward angiotensin II type 1 receptor. Autoantibodies to GPCRs, including adrenergic and muscarinic receptors, have been investigated in ME/CFS (25), and anti-β2AR antibodies were proposed to have an important role (26). Although GPCR autoantibodies are also present in healthy individuals, it is possible that they contribute in regulatory networks associated with different physiological states and with disease (27).

A recent study using rapid extracellular antigen profiling (REAP) to assess autoantibodies against the “exoproteome” (secreted and extracellular proteins) after COVID-19 infection showed a myriad of autoantibodies with functional impairment of many important immune-related and receptor molecules (28). Similar broad autoantibody responses may possibly occur after other systemic infections that could trigger ME/CFS, such as infectious mononucleosis. In a study of CFS risk after infectious mononucleosis among adolescents, 13%, 7%, and 4% met the Fukuda diagnostic criteria for CFS after 6, 12, and 24 months, respectively (29). Such decreasing risk over time could be compatible with an initial pattern of diverse regulatory autoantibodies perturbing function, normally resolving over time, but in some patients persisting and contributing to ME/CFS.

Conclusions

Our proposed pathomechanistic model (Figure 1) is compatible with the lack of obvious histologic inflammation in tissue samples from ME/CFS, lack of overt organ damage, and the potential for recovery — sometimes spontaneous and without sequelae. Future research should focus on the natural course of ME/CFS over time to identify the mechanisms that induce and
maintain disease, find targets for intervention, and specifically aim to elucidate immune dysregulation and patterns of autoantibodies with mechanisms for circulatory disturbances.

In our model, clinical symptoms of ME/CFS are related primarily to the inadequate autoregulation of blood flow yielding tissue hypoxia on exertion, but are also influenced by the compensatory adaptations from increased sympathetic output and from metabolic shifts. We speculate that cognitive techniques, which are reported to help subgroups of patients, might act by modulating the sympathetic output. If so, one would expect a greater benefit for patients with less ongoing immune activation and less vascular dysregulation, but with main symptom contributions from the secondary autonomic adaptations. Conversely, patients with active immune disturbance and ongoing vascular dysregulation as the main symptom generators would have less impact from cognitive intervention, although psychosocial support and coping strategies may still have a beneficial impact on their quality of life.

In conclusion, we suggest that ME/CFS in a subgroup of patients is a variant of an autoimmune disease, with a role for B cells/plasma cells and a pattern of autoantibodies emerging after infection and persisting over time. Key symptoms may result from the consequent functional disturbance in blood flow autoregulation causing tissue hypoxia on exertion and associated autonomic and metabolic responses to maintain energy homeostasis.

Finally, there is growing concern for patients with “long COVID.” Research is needed to determine whether the symptoms, which may resemble those of ME/CFS, are caused by subtle organ damage from the viral infection or whether subgroups of “long haulers” actually have a postinfectious immune disturbance and pathomechanism similar to those in ME/CFS.

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