General Medicine

Short Communication

Unifying Hypothesis on The Pathogenesis of ME/CFS, LongCOVID, Chronic Lyme Disease, and Q-fever Fatigue Syndrome (QFS)

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Abstract

Patients suffering from any of the "invisible diseases", namely myalgic encephalomyelitis/chronic fatigue syndrome, long COVID, chronic Lyme disease, or Q-fever fatigue syndrome, present similar symptoms and prognosis. So far they also bear the burden that they cannot heal. The most probable reason for this is that these diseases occur in persons carrying a specific genetic composition, who have been victim of a viral (Epstein-Barr virus or Cytomegalovirus) or bacterial (Borrelia burgdorferi or Coxiella burnetii) infection, initiating a cascade of immune and inflammatory processes. Aside from causing oxidative stress–associated cellular damage and membrane receptor dysfunction, these processes deregulate the concentration and activity of several kinases, such as the pyruvate dehydrogenase kinase, phenylalanine- and tyrosine hydroxylases. Impaired glucose metabolism resulting from pyruvate dehydrogenase deficiency causes poor energy production by the mitochondria, with fatigue and post-exertional malaise. Deficient conversion of phenylalanine to tyrosine and dopamine results in neurological and cerebral problems, such as brain fog, poor concentration and memory, and depressive mood. Local hypothalamic inflammation may cause adrenal and gonadal endocrine dysfunctions. Whereas particular steps of the pathogenesis of these diseases may be improved by treatment, it is currently impossible to restore the entire process.

Considerations

For any disease to develop a trigger should initiate the pathological process occurring in a suitable environment ("le grain et le terrain", Louis Pasteur 1822–1895).

The environment that allows ME/CFS, but probably also Long COVID, chronic Lyme disease, and Q-fever Fatigue Syndrome (QFS), to develop is the characteristic composition of eight genes [1]. These genes are related to the defense mechanism against viruses, or are associated with post-exertional malaise (PEM) or chronic multisite pain.

On the other hand, a trigger should be present in the form of an infection, such as by respectively the Epstein-Barr virus, the coronavirus, or the bacteria Borrelia burgdorferi or Coxiella burnetii [2]. These infectious agents will, however, initiate the respective diseases only in persons carrying the characteristic genetic composition [3]. In addition, a case report suggests that intestinal infestation with Giardia intestinalis, or with amoebae, may also serve as a trigger.

It remains doubtful whether vaccination with weakened viruses may trigger ME/CFS, since it also results in the activation of immunity, and it may possibly initiate the pathogenic cascade of pathological events. It has been proposed, but remains unproven, that severe emotional or physical stress, or so-called burnout or exhaustion, may deregulate the immune system, provoking ME-like symptoms.

In fact, the trigger provokes an immune response and elevated production of, among other substances, specific IgG immunoglobulins, that bind to complement C3, composing the cytotoxic [IgG-C3] complex. This complex damages the cell membranes. The reactive inflammation generates cytokines (interleukins 7 and 8), which are commonly found elevated in the blood of the patients [4]. The inflammatory reaction generates reactive oxygen species (ROS), altering the fatty acid composition and the fluidity of the cell membrane, as well as the inlaying three-dimensional structure of the receptors and the pump functions. This may cause insulin resistance, reducing glucose metabolism. Also, the potassium–chloride ion transporter may be deregulated, resulting in abnormal signal transmission in postsynaptic neurons [5].

The interleukins activate the intracellular Janus kinase (JAK). As a result, rheumatic-like symptoms appear, such as arthralgia, tenosynovitis, and enthesitis. But also, the

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activity of pyruvate dehydrogenase (PDH) is inhibited by the increased pyruvate dehydrogenase kinase (PDK) induced by the elevated JAK-STAT [6]. Both the relative insulin resistance and the impaired activity of pyruvate dehydrogenase, the rate-limiting step in aerobic glucose metabolism, reduce the production of adenosine triphosphate (ATP) by the Krebs cycle in the mitochondria. As the latter becomes deficient, the anaerobic glycolysis and Cori cycle metabolic systems take over in producing ATP. This, however, results in excessive generation of lactate and lactic acid.

In summary, the disturbance of glucose metabolism causes chronic lack of energy, hence fatigue, whereas the overproduction of lactic acid may explain post-exertional malaise and poor recovery. Also, the concentration of lactic acid in the cerebrospinal fluid of patients with ME/CFS is elevated [7], explaining brain fog and mental dysfunction.

In parallel, the metabolism of phenylalanine, via tyrosine to the neurotransmitter dopamine, is impaired, because the activity of the phenylalanine- and the tyrosine hydroxylase is inhibited by inflammatory cytokines [8] and, possibly, elevated JAK. In agreement with the rules of Michaelis–Menten, important alterations of the enzyme affinity or catalytic power may occur, since the phenylalanine concentration is elevated [9], inducing substrate inhibition. In patients with established ME/CFS, the decreased concentration of tyrosine [10] and synthesis of dopamine may lead to mental disturbance, including brain fog, difficulty memorizing, and depressive mood.

Aside from the proven metabolic aspects of ME/CFS and similar conditions, alterations of the endocrine regulations may occur. Local inflammation in the hypothalamus could result in disturbed homeostasis [11], and deregulation of the hypothalamo–pituitary–adrenal axis. It may also deregulate the gonadotropic stimulation of ovarian function, altering the menstrual cycle. Men may suffer late-onset hypogonadism (LOH). These conditions require appropriate substitution treatment. Alternatively, dysfunction of the neuroendocrine cells may be involved because of kinase effects on the enzymatic processes, though there are no hard data proving such mechanisms.

Conclusion

In conclusion, it is suggested that ME/CFS and similar diseases are the result of the sequence of infection and immunological dysfunction related to genetic factors, followed by inflammation and metabolic alterations, both at the level of glucose metabolism and neurotransmission. Treatments directed to any of these aspects separately can probably improve particular symptoms [12], but may not be adequate in curing the patients. Psychological assistance by cognitive behavior therapy (CBT) may be recommended, but does not correct the pathogenic processes. In addition, treatment that aims at improving the protective and nutritional function of microglial cells may be helpful. The latter should be included into a more holistic approach, addressing residual infection, abnormal immune response, oxidative stress, and the disturbed processes of inflammation and cellular metabolism.

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