infectolab AMERICAS

Chronic Fatigue Long Haul Viral Panel

Introducing a new panel to monitor ME/CFS and PASC (post-acute SARS-COV-2). This panel is designed to identify viral reactivation in patients presenting with chronic fatigue or other post-viral symptoms.

The Long Haul Viral panel utilizes Elispot T-cell testing to identify reactivation of chronic viruses, such as EBV and CMV and quantifies 3 key pro-inflammatory cytokines, plus serum cortisol. These three pro-inflammatory cytokines (IL-1β, IL-6, TNF-α) have been shown to be elevated in PASC by recent retrospective studies but not reliably elevated in ME/CFS[1,2,3,4]. Recent studies show that the timing of the ME/CFS is a better predictor of which cytokines elevate in the course of the disease progression[5]. Therefore, the search for reactivation versus chronic, controlled infection will help the clinician determine treatment protocols specific for the infection and the patient. Clinical signs and symptoms must ultimately be used for diagnosis as there are no definitive diagnostic labs for ME/CFS or PASC, according to current CDC guidelines. Utilizing a functional analysis of antigen specific responses to chronic viruses and quantifying the amount of inflammation provides the clinician with tools to assess and treat.

PASC and ME/CFS share similar symptomatology and etiology. Persistent fatigue, post-exertional malaise, and brain fog represent the striking similarities between PASC and ME/CFS, along with both syndromes being preceded by viral illness[3]. EBV, CMV, HHV-6, Lyme, and enteroviruses are examples of viral infections that transition into chronic, complex viral syndromes. Post-viral syndrome is a complex set of conditions that may be physical, emotional, or neurological. The signs and symptoms tend to vary from mild to severe and can continue for weeks to months. Fatigue, malaise, muscle pain, muscle weakness, headaches and difficulty sleeping are all common symptoms of post-viral syndromes. These symptoms tend to linger even after the viral infection has cleared, making diagnosis and treatment difficult. Examples of common post-viral syndromes are ME/CFS, PASC, POTS (postural orthostatic tachycardia), EDS (Ehlers-Danlos syndrome), and MCAS (mast cell activation syndrome). Post-viral syndrome is thought to be triggered by a reaction to a virus which does not resolve in a normal way and is noted by sustained inflammation. Post-viral syndrome is common following infection with EBV, CMV, HHV-6, enteroviruses, and Lyme. Immune suppression increases the risk for post-viral syndrome.

A survey by the National Center for Health Statistics in 2022 reported that 1 in 5 was experiencing long COVID symptoms, 3 months post-acute infection. As of June 2022, the CDC estimates that there are more than 22 million cases of long covid. Recently, Mancini et al showed that 46% of patients with PASC meet the criteria for ME/CFS[6,7,8]. According to data from SolveME.org, 22-43 million cases of PASC were expected in 2022. These numbers are expected to increase in 2023, according to data from the CDC, as of June 2022. This reveals a true need that is best met by functional medicine and naturopathic doctors. It is a holistic, patient centered approach that can effectively treat and manage chronic post-viral syndromes, along with functional T cell testing for the clinical monitoring of post-viral syndromes. Why a person gets post-viral syndrome is unclear, but inflammation plays a central role in its development. Therefore, investigating inflammatory cytokines may support diagnosis and treatment protocols.

Cytokines are central to the body's response to injury and infection. The response to injury is a complex system that involves both pro and anti-inflammatory cytokines.

Immune system cells communicate with other immune cells via cytokines and they in turn impact inflammation, hematopoiesis, neurogenesis, embryogenesis, and oncogenesis. The key pro-inflammatory cytokines are IL-1, IL-6, and TNF-α. These key pro-inflammatory cytokines are secreted from Th1 cells, CD4+ cells, macrophages, and dendritic cells. They are crucial for coordinating cell mediated immune response and play a critical role in modulating the immune system. Pro-inflammatory cytokines generally regulate growth, cell activation, differentiation, and homing of the immune cells to the sites of infection in order to control and eradicate intracellular pathogens, including viruses.

Cytokine balance is key to responding to and eliminating a viral pathogen. Excess and uncontrolled inflammation resulted in the "cytokine storm" seen in acute, severe SARS-COV-2 infection[9] A disturbance in cytokine balance, leading to chronic inflammation is suspected to play a role in the pathogenesis of PASC, as with other post-viral syndromes. Initial screening of IL-1 b, IL-6, and TNF-α allows one to interpret the balance of cytokine production and to affect the course of symptom progression and may hold the key to resolving post-viral syndromes.

IL-1β plays a role in acute inflammation, chronic inflammation, metabolic diseases, autoimmune disease, and malignancy[10]. IL-1β is a pro-inflammatory cytokine that is induced mainly by lymphocytes, macrophages, and monocytes in response to microbial molecules. In viral infection, the pattern recognition receptors (PPR) and toll-like receptors (TLRs) are expressed. This leads to an enhanced expression of IL-1β. IL-1β stimulates CD4+ cells and differentiates them towards Th17 cells. Th17 cells are a subset of effector CD4+ cells that induce inflammation in mucosal tissues. They play a critical role in host defense against bacteria and fungi and have been implicated in the pathogenesis of several T cell–mediated autoimmune disorders[10].

IL-6 is a cytokine that affects the immune system, but also regulates cell growth, proliferation, survival, gene activation and differentiation. IL-6 is produced by a variety of cell types including monocytes, fibroblasts, and endothelial cells. Upon stimulation, IL-6 is secreted by many additional cell types including macrophages, T cells, B cells, mast cells, glial cells, eosinophils, keratinocytes, and granulocytes. IL-6 stimulates several types of leukocytes and the production of acute phase proteins in the liver. It is particularly important in inducing B-cells to differentiate into antibody-forming cells (plasma cells)[11,12].

TNF-α is a pro-inflammatory cytokine. Like other Th1 pro-inflammatory cytokines, TNF-α has an important role comprised of the inflammatory response locally and peripherally in the circulation. TNF-α triggers the expression of vascular endothelial cells as well as enhances the leukocyte adhesion molecules that stimulate immune cell infiltration. It has a crucial role in early response against viral infection by enhancing the infiltration of lymphocyte to the site of infection[13]. In summary, TNF-α, IL-1β, and IL-6 are considered major pro-inflammatory cytokines that protect the body from pathogens but exist within a complex system that strives towards balance. The loss of homeostasis leads to chronic diseases and the emergence of new disease states[14].

Myalgic Encephalitis or Chronic Fatigue Syndrome is a condition that historically has been difficult to diagnose, difficult to treat, and has had little acceptance from mainstream medicine[15].

There are estimates that less than 16% of patients are accurately diagnosed. According to a study by Valdez et al, there are 1.7-3.8 million Americans who suffer with ME/CFS[8]. It tends to affect women more than men, but no difference in infection rates is seen with respect to age, race, ethnicity, or socioeconomic level. Symptoms of ME/CFS are post-exertional malaise, persistent fatigue for more than 6 months, non-restorative sleep, brain fog, joint pain, sore throat, lymph node swelling, and neurologic abnormalities. Neurologic symptoms may be sensitivity to light, sound, odors, chemicals, food, or medications. Additionally, patients can experience migraines and gastrointestinal issues such as gas, bloating, stomach pain, and nausea. ME/CFS is thought to be preceded by a viral infection, such as EBV, CMV or some other stressor to the immune system[4]. EBV has been shown to establish latency in lymphocytes and can reactivate under certain conditions, such as diminished cell-mediated immunity[16].

Because there are currently no FDA approved treatments for ME/CFS many patients feel unheard, go untreated and often end up fully disabled and out of the workforce. It is a condition that ranges from mild to severe, but often results in poor quality of life due to mismanagement and misdiagnosis. Elispot T cell testing for EBV and CMV, along with inflammatory cytokines can help guide treatment and support your patients' overall wellness by ruling out co-infections and other stressors to the immune system. Ultimately, the diagnosis of ME/CFS is a clinical diagnosis but the treatment of ME/CFS can be supported by managing chronic or reactivated viral infections[17].

In conclusion, PASC and ME/CFS share similar symptomatology and etiology, along with lacking a definitive laboratory diagnosis as defined by the CDC. The utilization of the Long Haul Viral panel provides the tools necessary to assess chronic versus reactivation of CMV and EBV, assess inflammation via pro-inflammatory cytokines, and a serum cortisol to begin assessing adrenal function. Add-ons of HHV-6 and Lyme can expand the surveillance into other viruses that often evolve into chronic, complex infections. Additionally, it is wise to consider neurotransmitters, common serum inflammatory markers, and microbiome testing to support the development of treatment protocols that support these challenging syndromes.

Guidance for Next Steps

Work-up for fatigue, utilizing Infectolab-Americas functional T cell testing

- Rule out: EBV, CMV, HHV-6, Lyme (chronic or reactivation)
- Basic cytokine panel to assess inflammation
- Neurotransmitter panel
- Microbiome testing
- Serum tests to consider: ferritin, hs-CRP, SED rate, CBC w/ diff, metabolic panel, auto-immune panel
  - The CDC recommends using EBV antibody panels (IgA, IgG, IgM) to determine susceptibility to infection, recent or past infection. Anti-VCA IgM appears early in the infection and usually disappears after 4-6 weeks. Anti-VCA IgG appears at 2-4 weeks in the acute infection and then decreases but persists for one's lifetime. The early antigen, Anti-EA IgG appears in the acute phase of the infection and is usually not detectable after 6 months. Anti-EA IgG is usually a sign of an active infection. Antibodies to the EBV nuclear antigen are not seen in the acute phase. They appear 2-4 months after the appearance of symptoms and persist for life.
- Infectolab-Americas offers T cell testing with antigen specific EBV Elispot, which allows one to determine if the infection is chronic or reactivated. This gives a functional approach to testing for reactivation as it measures the patient's own T cell response to the specific antigen

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