Gene Expression Differentials in CFS and COVID-19

There are two published articles on gene expression differences between controls and two very similar and perhaps identical models of chronic, post-viral illness, namely ME/CFS and Long-Haul COVID-19. The published gene expression data is specifically for cases of moderate-severe COVID-19 late in their course (see below link) and for moderate-severe cases of CFS (see link below). However, what strikes me is that the gene expression differences compared to controls in CFS and COVID-19 are very similar in regards to a disruption of the Renin-Angiotensin-System or RAS system and the activation of the Bradykinin system. This leads to vasodilation, increased vascular permeability, cardiac pre-load deficiencies, hypotension with POTS/NMH- orthostatic intolerance (OI) and salt wasting as well as low cardiac output. These features are clinically very apparent in CFS and explains the positive response I have seen to SQ Nexavir, a bradykinin inhibitor with anti-viral properties. There is a link between the RAS/Bradykinin system and the innate immune system which is also over-activated in long-haul COVID-19 and CFS/ME. The center of gravity of the innate immune system are the antigen processing cells or APC's (monocytes, macrophages, mast cells, dendritic cells and brain glial cells) and are all called APC's.

What is noteworthy and allows a direct comparison of these data sets on gene expression is that once a COVID-19 case gets past 7-10 days after symptom onset, their problem is excessive immune activation rather than a viral infection per se which is the problem during the first 7-10 days after symptom onset. When COVID-19 cases improve but remain dysfunctional we call it long-haul COVID-19 and is a chronic immune activation state that is clinically identical to CFS/ME.

Moderate-Severe COVID-19 – https://elifesciences.org/articles/59177

Moderate -Severe CFS -
https://www.sciencedirect.com/science/article/abs/pii/S0149291819300475

From the COVID-19 gene expression paper by Garvin et al (2020) out of Oak Ridge National Labs (see link above @ elifesciences.org):

ABSTRACT
Neither the disease mechanism nor treatments for COVID-19 are currently known. Here, we present a novel molecular mechanism for COVID-19 that provides therapeutic intervention points that can be addressed with existing FDA-approved pharmaceuticals. The entry point for the virus is ACE2, which is a component of the counteracting hypotensive axis of RAS. Bradykinin is a potent part of the vasopressor system that induces hypotension and vasodilation and is degraded by ACE and enhanced by the angiotensin1-9 produced by ACE2. Here, we perform a new analysis on gene expression data from cells in bronchoalveolar lavage fluid (BALF) from COVID-19 patients that were used to sequence the virus. Comparison with BALF from controls identifies a critical imbalance in RAS represented by decreased expression of ACE in combination with increases in ACE2, renin, angiotensin, key RAS receptors, kinogen and many kallikrein enzymes that activate it, and both bradykinin receptors.

This very atypical pattern of the RAS is predicted to elevate bradykinin levels in multiple tissues and systems that will likely cause increases in vascular dilation, vascular permeability and hypotension. These bradykinin-driven outcomes explain many of the symptoms being observed in COVID-19.

From the article published by Jeffrey et al in Clinical Therapeutics (2019) on gene expression if CFS/ME patients (see sciencedirect.com link above)

ABSTRACT:
Purpose

Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) is a debilitating multi-symptom illness impacting up to 1 million people in the United States. As the pathogenesis and etiology of this complex condition are unclear, prospective treatments are limited. Identifying US Food and Drug Administration–approved drugs that may be repositioned as treatments for ME/CFS may offer a rapid and cost-effective solution.

Methods

Here we used gene-expression data from 33 patients with Fukuda-defined ME/CFS (23 females, 10 males) and 21 healthy demographically comparable controls (15 females, 6 males) to identify differential expression of predefined gene-module sets based on nonparametric statistics. Differentially expressed gene modules were then annotated via over-representation analysis using the Consensus Pathway database. Differentially expressed modules were then regressed onto measures of fatigue and cross-referenced with drug atlas and pharmacogenomics databases to identify putative treatment agents.

Findings

The top 1% of modules identified in males indicated small effect sizes in modules associated with immune regulation and mitochondrial dysfunction. In females, modules identified included those related to immune factors and cardiac/blood factors, returning effect sizes ranging from very small to intermediate ($0.147 < \text{Cohen } \delta < 0.532$). Regression analysis indicated that B-cell receptors, T-cell receptors, tumor necrosis factor α, transforming growth factor β, and metabolic and cardiac modules were strongly correlated with multiple composite measures of fatigue. Cross-referencing identified genes with pharmacogenomics data indicated immunosuppressants as potential treatments of ME/CFS symptoms.

Implications

The findings from our analysis suggest that ME/CFS symptoms are perpetuated by immune dysregulation that may be approached via immune modulation–based treatment strategies.

When formulating a treatment plan that targets the core of CFS pathophysiology, those drugs or supplements or life-style issues such as diet and stressors all need to focus on immune dysregulation and metabolic dysregulation as well as cardiovascular issues, especially in females. Of particular interest to me appears to be the Bradykinin system which appears dysregulated in both CFS/ME and long-haul COVID-19. This alone could decrease cardiac pre-load and thus cardiac output and then there could be a downregulation of metabolic or energy demand not because of a primary energy problem but rather as a compensatory response to a lower cardiac output driven by reduced pre-load driven by Bradykinin excess. Broad-based reduction in cellular energetics is controlled by mTOR and lower mTOR activates the innate immune system which can magnify the vascular effects of Bradykinin and immune activation.

My top recommendations to do this are ordered from inexpensive to expensive.

1) Magnesium either as SQ shots or paste to reduce the impact of a low energy state
2) Zinc Liver Chelate (10 mg) along with Quercetin (250-500 mg BID) to reduce Bradykinin
3) Low dose prednisone at 1-2 mg QAM as an anti-inflammatory
4) Low dose Nalrexone @ 1.5 - 4.5 mg QD as an anti-inflammatory
5) Dietary constraints that reduce insulin resistance which is a potent immune activator.
6) Stress reduction which feeds into insulin resistance and can exhaust the HPA axis over time and impairs sleep.
7) Doxepin Elixir and Klonopin (Clonazepam) which both act to inhibit immune activation
8) Anabolic Paste QHS to down-regulate Bradykinin
9) VIP Nasal Spray to inhibit immune activation, regulate sleep and HPA axis stress responses and improve gut motility and function.
10) Nexavir which acts as a Bradykinin modulator and anti-viral @ 2 ml SQ daily

PRC