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Gut Infection Could Underlie Symptoms in Chronic Fatigue Syndrome

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> "We are cautiously optimistic regarding these results because, if confirmed, we may have identified a contributing factor to the innate immune issues associated with ME/CFS and a molecular target for potential treatment strategies." – Lombardi et al.

Over the past couple of years the Whittemore-Peterson Institute has been quietly digging into the human gut. They found that the duodenum – the first section of the small intestine – of many people with ME/CFS is inflamed and has become infiltrated with lymphocytes (disease-fighting white blood cells) – a clear sign that the immune system is on the attack.

Plasmacytoid dendritic cells in the duodenum of individuals diagnosed with myalgic encephalomyelitis are uniquely immunoreactive to antibodies to human endogenous retroviral proteins. De Meirleir KL, Khaiboullina SF, Frémont M, Hulstaert J, Rizvanov AA, Palotás A, Lombardi VC. In Vivo. 2013 Mar-Apr;27(2):177-87.

Further investigations indicated that innate immune cells called plasmacytoid dendritic cells (pDCs) were present in higher than normal levels. The first part of the immune system on the scene of a pathogen attack, the innate immune system initiates a kind of a broad inflammatory attack against pathogens. It's the innate immune system that's behind those flu-like symptoms you experience when you get a cold.

Dendritic Cells

Swarming the tissues in our body (skin, nose, lungs, stomach and intestines) that pathogens first come into contact with, dendritic cells (DCs) are an important part of our immune response. If they find an invader, they snatch a piece of it (an antigen) and then dash back to the lymph nodes where they present it to T-cells for inspection.

The type of DCs the WPI found in ME/CFS patients – plasmacytoid dendritic cells (pDC's) – are a bit different, however. Much more than just messenger cells, pDCs are actually important virus-fighting cells that produce huge amounts of antiviral cytokines such as type-1 interferons (IFNs) when activated. Both the pDCs and the interferon they produce activate natural killer cells – which tend to be dysfunctional in ME/CFS. Usually quite rare, they typically make up just 0.4% of the lymphocytes in the blood.

Dysregulated pDC's dendritic cells have been associated with the some autoimmune disorders.

HERVs The WPI found higher than normal levels of pDCs in the duodenums of ME/CFS patients. When the WPI took a deeper look at the pDC's they found them to be infected with endogenous retroviruses called human endogenous retroviruses or HERVs.

Endogenous retroviruses are ancient bits of retroviruses that have made their way into our DNA. Almost all are now benign bits of degraded DNA; a few retain enough of the original viral DNA to become partially active. Some HERVs able to initiate destructive immune responses have been associated with autoimmune disorders such as Sjogren's Syndrome, multiple sclerosis, and lupus.

Autoimmunity and the Gut

What do autoimmune disorders have to do with the gut? There's a good chance the gut may play an important role in the development of some autoimmune disorders. The idea goes something like this: first, leaky gut linings allow massive amounts of gut material to leak into the bloodstream. That gut material then triggers a a massive immune response that overwhelms the immune system's ability to keep itself in check and it begins mistakenly attacking the body – resulting in autoimmunity. Several studies have associated celiac disease – which can impair gut linings – with an increased risk of autoimmune disorders.

pDCs also play an important role in triggering B-cells to produce immunoglobulins to commensal (non-harmful) gut bacteria. Damaged pDC cells could result in bacterial overgrowth, intestinal dysbiosis, and other gut issues. The symptoms associated with all of these problems, of course, are common in both ME/CFS and FM.

Digging Deeper!

The WPI found pDCs with HERVs; then, in rather impressive fashion, they set out to determine why they were there.

First, they created a laboratory model of pDCs producing HERVs. When they analyzed those pDCs they found they were producing high levels of certain proteins. Then they looked to see if those proteins were present in the guts of ME/CFS patients with pDCs, and they were.

That means that HERVs they found were indeed active – a key finding. Whether or not they've causing gut and other issues is another question, but the potential is definitely there for these infected pDCs to produce bacterial overgrowth (believed common in both chronic fatigue syndrome and fibromyalgia), altered bacterial flora, and other gut issues.

Obviously quite intrigued by that finding the WPI then looked to see if a genetic weakness could explain the presence of the HERVs in the ME/CFS patients. A gene polymorphism study identified a set of gene polymorphisms (alterations) more commonly found in ME/CFS patients with gastrointestinal (GI) issues. An in-depth analysis of genes associated with the innate immune response found significant differences in these patients as well. The findings are preliminary, but they could be describing a patient population that's genetically at risk for innate immune system derived issues (pDCs) in the gut – and perhaps autoimmune issues as well.

They're attempting to confirm the polymorphism findings in a larger group of ME/CFS patients as well as in an additional group of ME/CFS patients from three different continents.

Making Progress – Under the Radar

The WPI is no longer in the news much. Instead they're moving cautiously and methodically to explore an intriguing finding. If it all works out, they may have a molecular target they could conceivably use to shut off the HERV production and perhaps help resolve gut issues and even autoimmune tendencies and immune activation in ME/CFS.

Gut Work on the Clinical Side

"There are multiple steps in my treatment protocol that appear to be working well for a majority of my patients, but we still have much more to learn before we can successfully treat all of those who are affected," – Dr. De Meirleir.

Dr. De Meirleir's statement that his treatment protocols are working well for most of his patients was borne out by a recent Norwegian ME/CFS survey that identified Dr. De Meirleir as a physician with good success rates (2/3 improved; 1/10 declined). Now, as the Medical Director of the WPI, Dr. De Meirleir may have been the first ME/CFS physician to focus heavily on the gut.

At a WPI lecture Dr. De Meirleir stated he generally begins healing the guts of his patients, a process that involves identifying dietary issues (including the removal of dairy, gluten, and fructose) and used fecal analysis to determine if a pulsed program of antibiotics, probiotics, and prebiotics and digestive enzymes will have a positive effect.

Dr. De Meirleir ended his lecture suggesting ME/CFS fits in a continuum of autoimmune diseases that includes lupus, RA, type 1 diabetes, and relapsing/remitting MS, all of which involve a dysregulation of the 2'-5'OA synthetase (RNase L pathway and Th1/Th2 immunity.

An Aside: the Gut – A Complicated Place

Since the gut with its millions of bacteria is one of the most complicated parts of the body, it's no surprise that the treatment picture is rather complicated.

The WPI's findings – if validated – could help simplify a complicated situation in the gut The fact that Audrey, for instance, had responded pretty well to dietary restrictions, then didn't respond to antibiotics/probiotics, and then responded very well to fermented foods simply demonstrates how individualized gut treatment plans can be (and really, how they must be to be effective).

We saw Esther find many ME/CFS symptoms get better or resolve with Xifaxin – an antibiotic focused on the gut. We covered a study suggesting that some herbal preparations were as effective as antibiotics. Dr. Rowe reports that ME/CFS patients with undiagnosed milk allergies will probably benefit little from other potentially beneficial treatments until milk is removed from their diet.
We've covered gluten-free diets, FODMAPS, and low glycemic and Mediterranean diets. We still have Paleo, anti-inflammatory diets and anti-histamine diets to go.

The gut is a complicated place – it's going to take quite a while to fit the right combinations of probiotics, prebiotics, antibiotics, fecal transplants, herbs, foods, etc. to help a particular patient. That kind of complication makes the WPI's gut studies all the more interesting. If infected immune cells in the gut are behind all this mess – and we're a long way from proving that – it makes the process of fixing the problem all the simpler.

Stay tuned. The last study the WPI published was in 2013. We should know much more about how this research is stacking up this year.

Chronic Fatigue Syndrome and Fibromyalgia Microbiome – Work Under Way

Multiple rejections to Dr. Lipkin's microbiome grant application notwithstanding, the gut in ME/CFS is getting some attention. Dr. Chia, of course, has presented his findings on enteroviral gut infections in ME/CFS. Besides his and the WPI's work several gut studies are underway or have been completed recently. Some promising gut work is underway but needless to say much more is needed to understand the guts effects on ME/CFS and FM.

We await the publication of the Solve ME/CFS Initiative's study of gut flora changes after exercise. Rebecca Hansen's large Microbiome and Inflammation (an NIH-funded study) examining bacterial composition in both the gut and blood as well as endotoxin and lactoferrin levels is due to finish up this year.

Dr. Pridgen's antiviral study grew out of a belief that herpes virus infections in the gut play a key role in fibromyalgia. The study included a pathological screen of herpes viruses in gut tissues and will be published this year. The Lipkin/Chronic Fatigue Initiative/Microbe Discovery project is identifying viruses, bacteria, and fungi in fecal samples as well as cytokines in the blood, taken from 100 ME/CFS patients and 100 carefully matched controls.

Finally, Fluge and Mella are using endoscopy, biopsys and ultrasound to assess gut functioning in ME/CFS patients receiving Rituxiimab.

About the author: *Cort Johnson has had ME/CFS for over 30 years. The founder of Phoenix Rising and Health Rising, Cort has contributed hundreds of blogs on chronic fatigue syndrome, fibromyalgia and their allied disorders over the past 10 years. Find more of Cort's and other bloggers' work at Health Rising.*