Guildford ME/CFS Support Group
(& West Surrey)

Newsletter

June 2020

Baby Flying Squirrel

Future dates

Due to the Covid-19 Pandemic we are unable to offer monthly meetings until further notice.

A never-ending immune battle in ME/CFS? the regulatory T-cell / Herpesvirus hypothesis

Source: http://simmaronresearch.com/2020/05/immune-battle-chronic-fatigue-syndrome-herpesviruses-regulatory-t-cell

5th May 2020

The failed Rituximab trial might seem like the death knell for autoimmunity in chronic fatigue syndrome (ME/CFS) but it's not – not by a long shot. While the B-cells that Rituximab targeted are at the heart of much autoimmunity, T-cells can also cause autoimmune diseases. They also play a very important role in stopping infections.

This interesting paper, conceived and led by a Portuguese researcher named Nuno Sepúlveda, PhD suggests that both options are on the table in ME/CFS. He proposes that a battle between a subset of T-cells called regulatory T cells (Tregs) and herpesviruses may be causing ME/CFS. Nuno Sepúlveda's PhD is in theoretical immunology, and he's on the faculty of the London School of Hygiene and Tropical Medical.

The study, the third Sepúlveda has co-authored on ME/CFS, is the tale of both a new hypothesis and a new researcher entering the field. I asked Sepúlveda how he got involved.

> "My interest in ME/CFS and the conception of this research came a bit by chance as most things in life. I am a statistician by training but I did a PhD project on theoretical immunology in Gulbenkian Institute for Science in the outskirts of Lisbon. In my PhD theory (supervised by Dr Jorge Carneiro, second author of the paper), I developed mathematical theories on how regulatory T cells regulate autoimmunity throughout life; these cells are thought to be master regulators of the adaptive immune system.
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> In my post-doctoral research, I was a statistical geneticist and a biostatistician doing research in genetics, immunology and epidemiology of tropical and infectious diseases. Along the way I met Luis Nacul and Eliana Lacerda (we are all from the same faculty/institution) who asked me to help them with the statistical analysis of UK biobank data.
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> One day I came across a review paper about autoimmunity and ME/CFS, and I got amazed that no one had done a comprehensive assessment of the role of regulatory T cells on ME/CFS. So I thought to resuscitate my old work on regulatory T cells and give it a go. Then I got hooked up in the field."

We can see how this field widens. Luis Nacul PhD, the senior author of the study, has spent much of his career deeply embedded in ME/CFS. The former leader of the CureME team at the London School of Hygiene and Tropical Medicine, as well as the UK ME/CFS biobank, Nacul is now the Medical and Research Director of the Complex Chronic Diseases Program at BC Women's Hospital in Vancouver, Canada. He enrolled Sepulveda in taking on ME/CFS.

The model

> "Given this observation, one can hypothesise that these (ME/CFS) patients might be healthy individuals who, by chance, were infected with a microorganism with a strong molecular mimicry to a human protein." Sepúlveda et. al.

Nuno Sepúlveda 1 2, Jorge Carneiro 3, Eliana Lacerda 4, Luis Nacul 4 Myalgic Encephalomyelitis/Chronic Fatigue Syndrome as a Hyper-Regulated Immune System Driven by an Interplay Between Regulatory T Cells and Chronic Human Herpesvirus Infections. Frontiers in Immunology. 2019 Nov 21 eCollection 2019

The story begins with the infectious onset that many people with ME/CFS experience. The ferocious immune response that pathogens evoke puts a strain on the immune system's regulatory processes. The "policeman" of the immune system – the regulatory T or Treg cells – are tasked with ensuring that the immune system in its frenzy doesn't run amok and start attacking the human body.

It's an inexact science. As with any complex system, the immune system walks a fine line between too much and too little regulation. Too much suppression by the Tregs will impair the immune system's ability to fight off invaders, while too little suppression could result in autoimmunity. Each of us is genetically predisposed one way or the other.

People genetically predisposed to more Treg activity would be better at suppressing autoimmunity, but they might also be more prone to letting infections flourish when their Treg cells mistake the pathogenic antigens as self – and call off the immune response.

Other individuals predisposed to less Treg activity might be more effective at wiping our pathogens, but more prone to developing autoimmunity. (Since infections, evolutionarily speaking, are more destructive, the authors believe this subset might be more prevalent.)

The big question is where do people with ME/CFS fit in? On the one hand, many of their symptoms mimic those found in autoimmune diseases – suggesting they may be immunologically predisposed to have an overly strong immune response to pathogens but are poor regulators of that response.

On the other, many people come down with ME/CFS in response to an infection – which suggests they weren't all that good at fighting off pathogens.

The third way – the ME/CFS way?

There is a third way, though – a kind of a worst of both worlds way – and that's what this group's mathematical modelling, the first of its kind done in ME/CFS, uncovered. If the authors are right it could explain why people with ME/CFS are in such a fix.

The Herpesviruses

The authors demonstrated how such a situation could happen by modelling the effect of herpesviruses on the T regulatory cells in ME/CFS in different immunological contexts.

HHV-6

Using HHV-6, the authors proposed that an ME/CFS state could occur when a **smouldering** infection is responded to by a T-cell clone with **a high potential for producing an autoimmune state.**

T-cell clones are populations of T-cells which contain both T regulatory cells and T effector (helper) cells. Because their composition reflects the immune milieu around them, a T-cell clone with a high autoimmune potential reflects a T-cell clone existing in an environment loaded with self-antigens; i.e. antigens from a pathogen which look like they come from humans. In this example, an HHV-6 infection producing many self-like antigens is present.

Because the infection is smouldering and the viral load is low, though, the full T-helper immune response which would serve to stop the infection is not initiated. Nor do the T regulatory cells fully step in to ward off an autoimmune response.

Instead, the virus, replicating slowly, triggers **both responses.** As the Treg cells tamp down the chronic immune response, they also shut down the cytotoxic NK cells. With the immune system not geared up in either direction, the smouldering infection continues in perpetuity causing high energy costs as well as inflammation and fatigue, and there you have it – a metabolically exhausting state of inflammation and fatigue; i.e. ME/CFS.

Epstein-Barr Virus

A similar situation may occur with EBV when a Treg clone with a high autoimmune potential co-occurs with a low T-cell killing rate. Instead of a blatant autoimmune response that racks the body, or an effective response to the pathogen, you get partial amounts of both: you get both a sucky immune response to a pathogen AND an autoreactive reaction. If the authors are right it's no wonder ME/CFS is such a puzzle and so difficult to treat.

How do the authors believe this shows up biologically? In a high density of and increased percentage of Treg cells in ME/CFS patients compared to healthy controls and people with autoimmune diseases. That's actually what they see in their ME/CFS patients in their lab.

Different roads taken

Interestingly, the authors believe both autoimmune diseases and ME/CFS start off the same path – both are triggered by the cumulative effects of an autoreactive response to a common viral infection – but then both flit off on different paths.

Herpesviruses may be setting off autoimmune reactions in both autoimmune diseases and ME/CFS, but in ME/CFS the Treg cells kick in to dampen down the autoimmune response.

Unfortunately, as they're doing that, they're also bollixing up the immune response to the pathogen – leaving ME/CFS patients in the strange state of both defending against a pathogen and trying to dampen down an autoimmune response at the same time – a metabolically exhausting situation.

The authors believe that a genetic predisposition affecting T-cells would probably be present in ME/CFS, and pointed to genetic polymorphisms that have been found. Defective T-cell responses to Epstein-Barr Virus have also been found in ME/CFS. Further study of the T-cell repertoires in ME/CFS are needed, though, as well as studies to validate whether Treg density and percentages are increased in ME/CFS.

T-cells – perhaps the single most impactful immune cell in the body – have become the focus of interest of a number of other ME/CFS researchers including Derya Unutmaz at the Jackson Labs, and Mark Davis at Stanford.

Smouldering viral infections have also become a hot topic in ME/CFS. Bob Naviaux and Bhupesh Prusty propose a smouldering HHV-6 infection, and Marshall Williams proposes a smouldering Epstein-Barr infection may be present in ME/CFS, as well.

A further widening field
The "widening" of the ME/CFS field is continuing with Sepúlveda. When I asked him what he's working on next he reported he was bringing new researchers (and new funders) into the field as well. His research into this possible aspect of ME/CFS is continuing full-bore.

Currently I have a PhD student working full time on a project extending some ideas about the role of regulatory T cells on ME/CFS. This project is funded by the Portuguese Foundation for Science and Technology and my student is doing his research in the Molecular Medicine Institute in Lisbon. I am also trying to find/identify candidate molecular mimicries between viruses and human proteins that could explain ME/CFS.

Gene-Eden-VIR and Novirin

Sources:
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Our ME group aims to bring its newsletter readers interesting insights that may be useful. Including, supplements, but we are not doctors and any supplements are explored at your own risk. The Epstein-Barr-Virus is famously associated with ME/CFS as demonstrated by numerous articles in our previous newsletters and the article at the beginning of this newsletter. Therefore, supplement options for tackling a smouldering EBV infection may be of interest.

Gene-Eden-VIR/Novirin is a natural treatment designed to help the immune system target the latent Epstein Barr Virus (EBV). A post marketing clinical study showed that Gene-Eden-VIR/Novirin decreased symptoms of an EBV infection. The study followed the FDA guidelines for clinical studies.

Infants become susceptible to EBV as soon as maternal antibody protection (present at birth) disappears. Many children become infected with EBV, and these infections usually cause no symptoms or are indistinguishable from the other mild, brief illnesses of childhood. In the United States and in other developed countries, many persons are not infected with EBV in their childhood years. When infection with EBV occurs during adolescence or young adulthood, it causes infectious mononucleosis 35% to 50% of the time.

Although the symptoms of infectious mononucleosis usually resolve in 1 or 2 months, EBV remains in a latent state in a few cells in the throat and blood for the rest of the person's life. Periodically, the virus can reactivate and is commonly found in the saliva of infected persons. This reactivation usually occurs without symptoms of illness. Persons with infectious mononucleosis may be able to spread the infection to others for a period of weeks. However, no special precautions or isolation procedures are recommended, since the virus is also found frequently in the saliva of healthy people. In fact, many healthy people can carry and spread the virus intermittently for life.

Ingredients
Novirin:
contains five natural ingredients: Selenium, Camellia Sinesis Extract, Quercetin, Cinnamomum Extract, and Licorice Extract. Scientists at polyDNA, the company that invented and patented the formula, scanned thousands of scientific and medical papers published in various medical and scientific journals, and identified the safest and most effective natural ingredients against latent viruses.

Gene-Eden-VIR:
Contains almost the same ingredients as Novirin, but instead of Camellia Sinesis Extract, contains green tea extract. A capsule of Gene-Eden-VIR includes: 100mg of quercetin, 150mg of green tea extract, 50mg of a cinnamon extract, 25mg of a licorice extract, and 100mcg of selenium.

What drug treatments are available for EBV infections?
A few antiviral drugs are available that were shown to inhibit EBV replication in cell culture. These drugs include the acyclic nucleoside analogues aciclovir, ganciclovir, penciclovir, and their respective prodrugs valaciclovir, valganciclovir and famciclovir, the acyclic nucleotide analogues cidofovir and adefovir, and the pyrophosphate analogue foscarnet. However, clinical studies have shown that these drugs are mostly ineffective in humans.

Where to source Novirin and Gene-Eden-VIR
Orders can be placed at the following website: https://novirin.com/ebv.php
From looking at the ordering pages it looks like delivery to the UK is possible. If however it is not possible the ingredients have been listed above which should be available from Amazon UK.
Please refer to the source links provided at the beginning of this article for further information.

Researchers expect Covid-19 will cause surge of chronic illness, including ME

Source: www.meaction.net/2020/05/10/researchers-expect-covid-19-will-cause-surge-of-chronic-illness-including-me

Since a new coronavirus emerged from Wuhan, China late in 2019, some 3.8 million cases and 265,000 deaths have been reported world-wide. Governments are focused on treating patients acutely sick with COVID-19, the disease caused by the new virus SARS-CoV-2, and slowing the spread of the virus. However, a second crisis of long-term disability is looming.

A large body of research shows that long-term illness and disability can be triggered by viral infections. Some of these illnesses include postural orthostatic tachycardia syndrome (POTS), myasthenia gravis, multiple sclerosis, Guillain-Barré syndrome, and type I diabetes. Some patients in Italy have developed Guillain-Barré after COVID-19.

ME/CFS (myalgic encephalomyelitis/ chronic fatigue syndrome) is a common but less well-understood neurological disease with notable effects on cognitive and muscular function. Up to 80% of cases of ME/CFS are initiated by infection but may also arise in the wake of a surgery or traumatic injury, similar to Guillain-Barré.

The ME/CFS community, researchers, clinicians, advocates and patients are deeply concerned about the potential for COVID-19 to develop into ME/CFS and other post-infectious diseases and disorders. With an estimated 25% of people with ME/CFS housebound or bedbound, patients suffering from the lowest quality of life of any disease to which it has been compared, including multiple sclerosis, and only ~13% of patients are able to return to full-time work, the potential for many new cases of ME/CFS in the wake of COVID-19 is no small matter.

The National Institutes of Health (NIH) agrees. Dr. Walter Koroshetz, Director of the National Institute for Neurological Disorders and Stroke (NINDS) at NIH, stated that "this idea of a viral infection — infectious mono, Lyme disease, for instance — triggering an immune response that then goes on to [initiate] ME/CFS is front and centre in [researcher's] minds." The NIH is currently studying post-infectious ME/CFS at their Clinical Centre in Maryland.

There is a lot of evidence that when a severe infection sweeps through the population, ME/CFS will often follow. The Institute of Medicine's (NAM) 2015 report concluded that ME/CFS may be triggered by a number of acute viral infections, including herpesviruses such as EBV or HHV-6, enteroviruses, and echoviruses. A study on Epstein-Barr virus, Q Fever, and Ross River virus showed that ~12% of subjects across the board met ME/CFS criteria at 6 months after clearing the infection; and another study of people with mononucleosis (Epstein-Barr virus) produced identical numbers. 20% of patients with West Nile Virus (n=140) met the criteria for CFS six months after tests first returned negative for West Nile. There are also a handful of highly-publicized outbreaks leading to ME/CFS: some of the biggest ones include the Epstein-Barr Viral outbreaks in New York; the Lake Tahoe outbreak in Nevada; and the Royal Free Outbreak in London.

SARS-CoV-2 would not be the first coronavirus to result in documented ME/CFS. Studies have shown that long-lasting disabling symptoms commonly occur in people who contracted two other coronaviruses that cause SARS and Middle East Respiratory Syndrome (MERS). In one study, 27% of SARS survivors were found to meet CFS criteria several years after developing SARS.

That a wide variety of different infectious organisms can lead to the same disease-state may seem surprising – but ME/CFS may be caused by the body's unexpectedly uniform reaction to any number of assaults. Dr. Ian Lipkin, the Director of the Centre for Infection and Immunity and a coronavirus and ME/CFS expert, stated in an interview with #MEAction, "I wouldn't suggest that coronavirus is the cause of ME; rather, innate immune mechanisms in response to a virus may cause it, meaning that many viruses can probably [initiate ME/CFS]." One study that he was a co-author of found that getting H1N1 doubles a person's risk of developing ME/CFS.

Doctors are starting to see many emerging long-term effects of COVID-19 and in Italy, neurologists have already created a separate neuro unit for COVID-19 patients, who are being treated for "stroke, delirium, epileptic seizures, and non-specific neurologic syndromes that look very much like encephalitis," according to Neurology Today. Professor Chris Ponting, Chair of Medical Bioinformatics at University of Edinburgh, explained to #MEAction that he would "expect that [of the] people who have COVID-19 symptoms quite severely… about 10% [would] have fatigue-like syndromes after 6 months, given current evidence."

In an interview with #MEAction, Dr. Alain Moreau of Université de Montréal, Montréal, Québec, concurred. "Coronavirus leading to more cases of ME will happen for sure, unfortunately. A previous study in which ~200 people who survived the ICU in a previous outbreak of a coronavirus infection, close to 1/3 developed ME/CFS-like symptoms and were unable to get back to work over a year later… there are some preliminary reports of the same from COVID-19. This should not be a surprise, given that other cases [of ME/CFS] are reported to be post-viral, the classic being EBV. The question is not 'will this happen' but how many will suffer."

Infectious Diseases and Epidemiology professor at Harvard University, Dr. Marc Lipsitch, predicted in February that 40-70% of the world's population will contract SARS-CoV-2 within a year. Using his most conservative estimate of 40%, over 3.12 billion people world-wide may contract SARS-CoV-2 by March of next year. Based on the myriad studies showing that a wide range of infections can trigger ME/CFS and the many early case reports of people continuing to have neurological symptoms months after first getting COVID-19, it is likely that there will soon be a flood of new ME/CFS patients that medical systems around the world are woefully unprepared to treat.

In addition, COVID-19 is hitting racial and ethnic minorities and those of low socioeconomic status the hardest; yet this demographic is also the least likely to be diagnosed with ME/CFS even when they meet the diagnostic criteria. The crisis of care will be magnified in these communities.
If we wait to address post-COVID as a separate issue, the pandemic apparatus and the research and clinical funding for COVID-19 will have long since dissolved, leaving millions ill. Many will be undiagnosed or misdiagnosed, and at risk of being given treatment recommendations that will worsen their condition. We will only truly know how many people with COVID-19 develop ME/CFS if the NIH, CDC, and national health organizations worldwide begin tracking post-viral illness now. In many ways, we have thus far failed our coronavirus responses: we have the opportunity, now, to do better for post-COVID patients who face long-term disability.

"We need to be ready for the next wave," Moreau says. "We are not out of the woods, but we also need to be ready for what is coming next."

The great split? Are post-infectious ME/CFS patients fundamentally different?

Source: www.healthrising.org/blog/2020/06/13/split-post-infectious-chronic-fatigue-syndrome

The findings are tentative and need to be validated, but if they hold up they could signal a fundamental split between people whose chronic fatigue syndrome (ME/CFS) was triggered by an infection and those who came down with ME/CFS some other way. If your ME/CFS was triggered by an infection, your immune system may have been tilted in an autoimmune direction. If your ME/CFS was triggered in another way, it may have been tilted towards inflammation.

Time will tell.

Autoimmunity and ME/CFS
Chronic fatigue syndrome (ME/CFS) has long been thought to be a possible autoimmune disease. The infectious onset, the gender imbalance (almost 80% of people with autoimmune diseases are female), the age of onset, even the wide variety of symptoms, all suggest autoimmunity might be present.

One might ask why infectious mononucleosis, which was recently linked to no less than seven autoimmune diseases, would not – given that it's a common trigger for ME/CFS – also have produced an autoimmune disease in ME/CFS?

Establishing that a disease is autoimmune in nature is not easy, however – and while we're not nearly there yet – the evidence and interest appears to be growing. Dr. Scheibenbogen was the senior author of a Euromene paper, "Myalgic Encephalomyelitis/Chronic Fatigue Syndrome – Evidence for an autoimmune disease'', which argued that a startling array of immune findings in ME/CFS pointed toward some sort of autoimmunity.

The review paper – which was published prior to the publication of the failed Rituximab trial in ME/CFS – asserted "there is compelling evidence that autoimmune mechanisms play a role in ME/CFS", while warning that subgroups of patients likely have different "pathomechanisms". Recently, a hypothesis paper suggested that people with ME/CFS are caught in a kind of weird limbo state between autoimmunity and pathogen persistence.

• A never-ending immune battle in ME/CFS? The regulatory T-cell / Herpesvirus hypothesis

Given the heterogeneous immune findings found in ME/CFS, the authors of the review paper concluded that it was critical to "identify clinically useful diagnostic markers"; in this case very small genetic changes – a shift in just one nucleotide – called single nucleotide polymorphisms as well as immune factors.

The polymorphism story
Polymorphisms have been looked at before. A fascinating 2017 review paper which examined no less than 50 studies on the genetic polymorphisms found in ME/CFS, cancer-related fatigue and other fatiguing diseases. It suggested that slightly altered forms of TNFα, IL1b, IL4 and IL6 genes put people at risk for high levels of fatigue.

The connections found between ME/CFS and polymorphisms in HLA, IFN-γ, 5-HT (serotonin) and NR3C1 (glucocorticoid) genes, in particular, were cited in that paper. Several of these altered genes could be tied to autoimmunity or other immune dysfunction. The link between the HLA genes tasked with spotting an invader and autoimmunity is well known. Given the role the HPA axis plays in regulating the immune system, the glucocorticoid polymorphism documented in ME/CFS could play a role as well.

The COMT gene that appears to play a big role in fibromyalgia, and perhaps ME/CFS, breaks down catecholamines like norepinephrine. Both it and the beta 2 adrenergic receptors that are under investigation in ME/CFS modulate the immune response. All in all, it appears that ME/CFS patients' genetic makeup provides plenty of opportunity for their immune systems to go awry.

The study
Autoimmunity-Related Risk Variants in PTPN22 and CTLA4 Are Associated With ME/CFS With Infectious Onset. Sophie Steiner1, Sonya C. Becker1†, Jelka Hartwig1, Franziska Sotzny1, Sebastian Lorenz1, Sandra Bauer1, Madlen Löbel2, Anna B. Stittrich3,4, Patricia Grabowski1 and Carmen Scheibenbogen1,3* Front. Immunol., 09 April 2020 https://doi.org/10.3389/fimmu.2020.00578

This present study – another Carmen Scheibenbogen and company production from Germany – assessed whether small changes in immune genes (called polymorphisms) that have been associated with autoimmunity were present in ME/CFS. These polymorphisms usually affect the activation of T or B cells or the production of immune factors called cytokines.

This large study included 305 people with ME/CFS (205 female/100 male) and 201 (103 female/98 male) healthy controls.

The goal was to determine if the immune systems of ME/CFS patients were genetically skewed towards autoimmunity. This is not the be-all and end-all of genetic studies – it examined the frequency of just five polymorphisms in immune genes that have been associated with autoimmunity. They included:

- tyrosine phosphatase non-receptor type 22 (PTPN22) SNP rs2476601,
- cytotoxic T-lymphocyte-associated protein 4 (CTLA4) SNP rs3087243,
- interferon regulatory factor 5 (IRF5) SNP rs3807306,
- gene tumour necrosis factor (TNF) SNP rs1800629,
- gene rs1799724 (TNF) SNP Rs1799724

Two of these gene polymorphisms code for production of a key gene in the pathogen response – higher tumour necrosis factor – (TNF-a); one coded for higher IFN-y production, and two affected T and/or B cell activity or signalling.

Results
Given the limited search, any positive result probably would have been greeted with celebration. The study did better than that, though, as two of the five polymorphisms assessed were upregulated in ME/CFS patients compared to healthy controls.

Infectious subset stands out. There was a catch, though. The polymorphisms were only found with more frequency in the 2/3rds of patients with post-infectious onset.

Both of the polymorphisms (PTPN22 rs2476601, CTLA4 rs3087243) have been associated with several autoimmune diseases such as type I diabetes, lupus and rheumatoid arthritis.

The PTPN22 rs2476601 polymorphism is a major autoimmune factor. It is believed to make it more difficult to delete autoreactive T cells, to reduce the activity of the Treg cells in charge of ensuring autoimmunity does not occur, and to impair B-cell clonal regulation.

The form of CTLA4 found enhanced in the infectious onset group, on the other hand, makes it more difficult to turn off the activated T cells that can drive some autoimmune diseases.

The EBV Autoimmune ME/CFS Group?
Almost 20% of those with a post-infectious onset of ME/CFS reported that their illness was triggered in adolescence by an Epstein-Barr virus (EBV) infection (infectious mononucleosis, glandular fever). EBV, as was noted above, is a known for autoimmunity. A 2018 paper provided a reason why EBV may be so adept at turning an infection into an autoimmune disease.

Virtually everyone carries EBV in its latent state in their cells. It turns out that even in its latent state, when EBV isn't replicating, a transcription factor in EBV is still busy turning on and off genes that just happen to increase the risk of developing a host of autoimmune diseases (lupus, multiple sclerosis, rheumatoid arthritis, juvenile idiopathic arthritis, inflammatory bowel disease , celiac disease, type 1 diabetes.) Fully 50% of the gene regions associated with an increased risk for lupus, for example, appear to have been turned on by EBV.

- The autoimmune virus? Groundbreaking EBV finding could help explain ME/CFS

EBV or any other virus isn't the end of the story with autoimmunity. Most people who come down with infectious mononucleosis or another infection don't come down with an autoimmune disease but these stressors, perhaps like other significant stressors in childhood, adolescence or adulthood, can tilt the immune system in a direction which makes it susceptible to producing autoimmunity for some people.

A non-infectious onset inflammatory subset?
Interesting, two findings suggested that the immune systems of the non-infectious ME/CFS cohort may be tilted in the opposite direction of the post-infectious cohort. Instead of having higher frequencies of the of IRF5 and TNF risk variants, they had significantly lower frequencies compared to the infectious group.

Finding some genetic alterations in immune genes, the researchers took the next step to see if the unusual gene forms resulted in immune alterations as well.

They did. Several autoimmune-like factors jumped out. Reduced C4 levels in the infectious onset group were reminiscent of systemic lupus erythematosus (SLE), while reduced CD19+ B cells (B cell lymphocytopenia) are found in both SLE and rheumatoid arthritis (RA).

("Lymphocytopenia" refers to a count of less than 1,000 lymphocytes per microliter of blood in adults). CD19+ cells are the major immunoglobulin-secreting B-cell found in the blood, bone marrow, spleen and tonsils. Reduced CD19+ cells have been associated with an increased susceptibility to infection in animal studies.

Compare those findings to the increased c-reactive protein (CRP) levels in the non-infectious group of patients, suggesting a more pro-inflammatory profile. The authors suggested the disease in the non-infectious group may be more akin to that found in cancer-related fatigue.

No federal agencies funded this study – it was solely the result of your donation dollars. It was supported by a 2016 Ramsay Grant Program award, the Solve ME/CFS Initiative, as well as by several German foundations.

Cancer-related fatigue and the non-infectious ME/CFS group
HPA axis problems are present in ME/CFS and recent cancer-related fatigue studies have found a link between HPA axis problems and inflammation in post-cancer survivors with fatigue.

A 2020 study found that reduced sensitivity of the immune system to glucocorticoids (cortisol) resulted in increased levels of pro-inflammatory markers and cytokines (C-reactive protein, interleukin 6, and tumour necrosis factor α.) in the fatigued patients. Apparently, the HPA axis was having trouble tamping down inflammation in the fatigued cancer patients.

A head and neck cancer study uncovered a possibly revealing distinction between pathogen (papillomavirus) triggered and non-pathogen triggered cancer. The gene expression results suggested that the two types of cancers triggered different immune responses.

The non-pathogen triggered cancer triggered something called a "Conserved Transcriptional Response to Adversity (CTRA)" immune response. In this response, those beta adrenergic signalling pathways that we've been looking at lately in ME/CFS jacked up inflammation via the sympathetic nervous system. The CTRA response was diminished, on the other hand, in the infectious cancer cohort – and so was the fatigue.

While it's a bit of a stretch to compare infectious onset cancer and infectious onset ME/CFS, it's intriguing that in both cases the infectious onset was associated with less inflammation.

It brings up the question whether the fatigue in post-infectious onset and non-post-infectious onset ME/CFS patients could be coming from different places. Could the HPA axis/sympathetic nervous system-triggered inflammation be playing more of a role in ME/CFS patients with non-infectious onset?

A 2019 study suggested, though, that an infectious onset may not be so clear a trigger as one might think. Almost 40% of the participants reported that it took 7 months or more from whatever happened for ME/CFS to manifest itself. Twenty percent reported that it took more than two years. Eighty-eight percent, though, felt they could identify a specific triggering event.

While infectious onset seems like it would trigger a quicker decline into ME/CFS, people with infectious onset were no more likely to quickly come down with ME/CFS than people with other triggers. Only 14% of those citing an infectious onset said their ME/CFS developed within a month of the infection.

Conclusion

The study found that two gene variants – including one in "the archetypal non-HLA autoimmunity gene". found in autoimmune diseases were also increased in people with post-infectious ME/CFS. Plus, several immune factors associated with autoimmunity were increased as well. While autoimmunity hasn't been proven in ME/CFS, the study provided more evidence that autoimmune processes may be at play in a large subset of ME/CFS patients.

The story appeared quite different in people with ME/CFS who didn't have an infectious onset. Two of the polymorphisms associated with autoimmunity were significantly decreased in the non-infectious onset ME/CFS patients. Plus high levels of an inflammatory marker were found as well. That suggested that the pathology in the non-infectious group might be more akin to that which occurs in post-cancer fatigue.

Studies suggest that the post-cancer fatigue and non-infectious onset ME/CFS patients may have a balky HPA axis that has difficulty reigning in inflammation. Interestingly, given the focus on the sympathetic nervous system in ME/CFS, non-pathogen triggered cancer was associated with more sympathetic nervous system-induced inflammation than pathogen-triggered cancer.

While larger studies need to be done, these preliminary findings suggest that the kind of triggering event (or the absence of a triggering event) could have tilted the immune system in different directions in different sets of patients. With the Nath intramural study focusing on documented post-infectious ME/CFS cases underway, and his new study on post COVID-19 patients beginning, plus all the media attention being given to problems recovering from COVID-19, some real insights may be in store for the post-infectious group.