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CIGUATERA, ME/CFS, ANESTHESIA AND ANTIEMETIC AWARENESS: SCIENTIFIC OVERVIEW

By The National CFIDS Foundation, December 2021 – Copyright 2021



Introduction - Brief overview of the pathophysiology of ciguatera poisoning [1,2]: Ciguatoxins (CTX) have been shown to bind to voltage-gated sodium channels. At the resting membrane potential of axons, sodium channels are closed. CTX molecules induce the opening of these channels at resting membrane potential, leading to an influx of sodium, a process that depolarizes the axonal membrane and triggers spontaneous and repetitive action potentials. Normally, gated influx of sodium is accompanied by an efflux of potassium, which maintains electroneutrality within the axon and mediates the water movement across the membrane. When the dynamic process of influx/efflux is interrupted due to CTX, it results in swelling at the nodes of Ranvier, the unmyelinated sections of axons exposed to extracellular fluid

in myelinated axons. The swelling of the nodes of Ranvier impairs the saltatory conduction along the axon and slows sensorimotor conduction velocities. Animal laboratory research shows that CTXs are rapidly absorbed from the gastrointestinal tract and distributed throughout the body. Moreover, because CTX-sensitive voltage-gated sodium channels have been found in all of the systems affected by ciguatera poisoning (i.e., brain, skeletal muscle, heart, peripheral nervous system, sensory neurons), these channels may mediate the symptomatology of ciguatera poisoning. (In fact, ciguatera poisoning can cause ME/CFS) As an example, cold allodynia may be attributable to a CTX-induced modification of the voltage-gated sodium channels in A-delta and

C fibers, which carry thermal and pain impulses through the spinal cord to the brain. Of note, nerve conduction studies of patients with acute ciguatera poisoning reveal a disturbance in both sensory and motor conduction. With regard to the central nervous system, one animal study showed that CTX administered orally and intraperitoneally was detected four days after exposure in the liver, muscle, and brain, suggesting that CTX crosses the blood–brain barrier. This supports the observation of central nervous system involvement in human clinical cases of ciguatera poisoning.

Basic mechanism and importance of ciguatoxin [3,4]: Ciguatoxins act on the neuronal voltage-dependent sodium (Na) channel NaV1.5. Dr. Yoshitsugi Hokama's monoclonal antibody for CTX (Mab-CTX) directly detects alterations to NaV1.5 and this specific antibody was previously identified to react with ME/CFS patient blood as reported in numerous studies. NaV1.5 is an integral membrane protein involved in the initiation and conduction of action potentials. Alterations to NaV1.5 have been associated with a variety of arrhythmic disorders, including long QT, Brugada, and sick sinus syndromes as well as progressive cardiac conduction defect and atrial standstill. Changes in the NaV1.5 expression level and/or sodium current density have been frequently noticed in acquired cardiac disorders such as heart failure.

Some commonly used anesthetics interact directly with NaV1.5 [5]: Propofol and dexmedetomidine are very commonly used sedative agents. Several case reports have demonstrated cardiovascular adverse effects of these two sedatives. Both substances have been found to potently inhibit the neuronal voltage-gated Na⁺ channel NaV1.5. Dexmedetomidine was generally more potent as compared to propofol.

Some commonly used antiemetics interact directly with NaV1.5 [6]: Prokinetic and antiemetic agents are substances that are commonly used in daily clinical practice of anesthetists, notably for the treatment of gastroparesis, nausea, and vomiting. Two often used antiemetic agents are metoclopramide and domperidone. Several case reports accuse both substances for inducing cardiac adverse reactions. Metoclopramide can induce torsade de pointes arrhythmias, cardiac arrest and sudden cardiac death. Other case reports refer to cardiotoxic effects of domperidone that range from ventricular arrhythmias to sudden cardiac death. Domperidone and Metoclopramide have been found to inhibit NaV1.5.

Summary: NaV1.5 is often an unrecognized molecular component of some cardiovascular side effects of several commonly used sedatives as well as antiemetic agents. Since CTX poisoning can have long-term side effects, the use of anesthetics that utilize the same sodium channel (NaV1.5) may affect their sedative use and therefore patients and physicians (anesthesiologists) should be made aware of this potential interaction. Likewise, the use of antiemetics that utilize this same sodium channel (NaV1.5) may affect their use and have potential for interaction like the anesthetics mentioned above. Therefore, it is recommended that patients discuss this matter with their physicians (anesthesiologists) prior to any surgeries.

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PRESIDENT'S MESSAGE

By Gail Kansky – Copyright 2021

The National CFIDS Foundation has, for decades, been adamant about both GET and CBT being not only wrong for those with ME/CFIDS but absolutely detrimental. The majority of physicians who continue to advocate graded exercise and cognitive behavioral therapy are mainly in the U.K. although there are a few who continue to practice this in the U.S. despite scientific discoveries about CFIDS/ME that shows the illness to be in the chronic immune area. One of the very first physicians to spend decades not only documenting this disease but discovering new scientific evidence, Paul R. Cheney, M.D., Ph.D. was one of the leading forces who died this past June but is remembered and missed by thousands of patients who have welcomed his intelligence and his clinical work to try to help the disease that had stolen their normal lives away.

Dr. Cheney graduated from Duke University in 1975 and, two years later, received his doctorate degree from Emory University School of Medicine. He worked at the CDC's Division of Immunology and then at a USAF Hospital in Idaho before going into private practice in Nevada along with Dr. Daniel Peterson. Both Dr. Peterson and Cheney documented a large cluster outbreak of CFS patients in Lake Tahoe. He then moved to Charlotte, NC and opened a private

practice for ME/CFIDS patients while continuing clinical research. His research found evidence of specific T-cell activation which showed much higher elevation than the control group. His clinical practice saw him spend hours treating individual patients and he had dozens of papers published in peer-reviewed medical journals. He was the founding director of what now is called the International Association of CFS/ME which began as the American Association of CFS. He went against the CDC that downplayed ME/CFIDS.

The insightful and knowledgeable and fearless Dr.Cheney had a heart transplant several years ago. At an international ME/CFIDS conference held a few years before he died, he said, “The whole idea that you can take a disease like this and exercise your way to health is foolishness. It is insane.”

RIP, Dr. Cheney. We will never forget you.

“My father (Dr. Paul Cheney), an MD/PhD who we lost this year, withstood decades of professional ridicule for specializing in CFS. He once said, ‘Western medicine is great at emergency care, but horrible at chronic disease.’”

~ Kate Cheney Davidson (Daughter)

NCF EXCERPT FROM: RADIATION EXPOSURE AND MITOCHONDRIAL INSUFFICIENCY IN CHRONIC FATIGUE AND IMMUNE DYSFUNCTION SYNDROME

[Rusin A et. al; Med Hypotheses. 2021 Sep;154:110647.]

Human exposure to radiation and CFIDS: The connection between radiation exposure and the development of CFIDS was originally proposed by Loganovsky et al. [11,85]. The Chernobyl liquidators were the group of workers responsible for the cleaning efforts following the Chernobyl nuclear disaster in 1986. This was a diverse team made up of firefighters, civil defence, police, civilians, custodians, and military personnel. Some of these liquidators were subsequently studied for health effects following radiation exposure. Among a sample of 100 Chernobyl liquidators with fatigue as a symptom, 26 met the diagnostic criteria for CFIDS; their absorbed radiation doses were estimated to be less than 0.3 Sv. The authors noted Chernobyl accident victims displayed persistent fatigue, immune, cognitive, emotional and other disorders characteristic of CFIDS

likely as a consequence of exposure to low doses of radiation in combination with short term stressors such as infection, physical trauma, or psychological stress. A second study by Loganovsky et al. identified markers associated with functional brain damage which may result in cognitive symptoms of a CFIDS following the exposure to ionizing radiation [11]. Among liquidators, CFIDS prevalence significantly decreased from 65.5% (1990 to 1995) to 10.5% (1996 to 2001). CFIDS in these patients could be indicative of forthcoming neurodegeneration [86], cognitive impairment [87–89], and neuropsychiatric disorders [90,91], as is the case with other CFIDS patients. The deterioration of mental health in the Chernobyl personnel was found to be related to their estimated dose as well as their duration of work in the exclusion zone, thereby pointing to a potentially cumulative radiation effect. One report concluded that “[CFIDS] may therefore be one of the most widespread consequences of the catastrophe for liquidators” [92]. Other survivors of radiation accidents (such as Chernobyl and Fukushima), Atomic and Gulf War Veterans, and radiotherapy patients have similarly experienced symptoms following ionizing radiation exposure that are consistent with CFIDS [6–15]. However, the lack of a clear dose-dependence, deterministic radiation effects, and objective measures has resulted in the dismissal of the chronic illness as a psychological issue [24–27] or radiophobia [93]. The low induction threshold (2–5 mGy) of NTEs and low saturation point (under 0.5 Gy of gamma radiation) [94–97], yet tendency to be expressed over time across generations [98–101] could lead to immune compromise and inflammatory responses seen in CFIDS patients and explain the observed doseindependent effects. On a molecular level, low doses of ionizing radiation can activate a series of signals leading to chronic oxidative stress, inflammation, and the symptoms observed in CFIDS patients [102–105]. Kennedy et al. reported elevated levels of oxidative stress biomarkers (isoprostane, oxidized LDL, and isoprostaglandin) and reduced antioxidant levels in CFIDS patients compared to healthy controls [70]. Significantly, the severity of symptoms correlated with ROS levels in normotensive and non-obese CFIDS patients. Thus, this provided a possible connection between radiation exposure and chronic fatigue by means of excessive free radical generation. CFIDS has also been linked to post-radiation syndrome (PRS). According to Pall [106], considering the similarity between CFIDS- and PRS-initiating stressors, corresponding cellular signaling pathways involving oxidative stress and inflammatory cytokines, and complex yet similar chronic symptoms in both diseases, CFIDS may share the same etiological mechanism as PRS through the nitric oxide / peroxynitrite (NO/ONOO⁻) cycle. Nevertheless, continued investigation of the mechanisms involved in the radiation response in CFIDS patients is needed.

“I did, too, as a doctor, believe ME/CFS was psychosomatic...until I became ill with ME! We desperately need better education about ME in universities.”

~ Caroline Gregoire, MD, Canada

THE NICE GUIDELINES REVISION

By Kathy Collett – Copyright 2021

The long-awaited NICE (National Institute for Health and Care Excellence) Guidelines review due for release on August 18th was upheld with just 24 hours' notice creating a distressing time for patients. The process of updating began in 2017 and the draft eliminated graded exercise (GET). While no official reason was given for the delay at the time, there was pressure from some doctors who intervened.

The outdated version included CBT/GET (cognitive behavioral therapy/graded exercise therapy) as treatment options. If deleted, it would have created a void for those doctors endorsing CBT/GET and they would not have anything to offer their patients. Some doctors were seemingly unaware the PACE Trial had been revealed as flawed and left many patients who tried it bedridden for years. Patients were expecting that both treatments would be dropped from the revised guidelines. It would mean that the bio-psychosocial lobby, who have been anti ME science, would lose their control over the illness and patients would feel free of their damaging influence.

The reaction to the pause of the NICE Guidelines was felt in other countries, too. Petitions were arranged and letters written to NICE indicating their disappointment and despair. A protest was arranged outside the NICE London headquarters on September 20th. Some felt it was time to bring in lawyers to combat any further detrimental information outlines in the revision.

The PACE trial recommendations had been implemented in not only the UK, but in the USA, Europe, and Australia too and had far-reaching consequences following the publication in the Lancet. The coauthors have used the media to promote its recommendations and to counteract patient disapproval. Even the Science Medical Centre, a press center where events are held to inform journalists of medical research and information in the UK, didn't provide credible ME research and the journalists followed with what they were provided with and investigative journalism was sadly lacking. Professor Sir Simon Wessely is known to have contributed to the SMC wielding his influence.

I, like a lot of other patients, have been aware of the PACE Trial since the paper was published. I heard the interview promoting the trial when Dr. Norman Swan interviewed Professor Sharpe on the Australian Broadcasting Commission Radio National's Health Report and am appalled at the long-term damaging impact PACE has had on patients by suggesting they could exercise their way out of their illness. Prof. Sharpe has blocked many patients on Twitter because they have voiced their concerns about CBT/GET and the damage done to those who tried it. Some doctors blindly accepted it and haven't looked beyond it since its release ten years ago. It's no wonder patients felt concerned.

Following the revised NICE Guidelines pause, Dame Carole Black was chosen to chair the roundtable meeting. It disappointed patients as she wasn't considered neutral, and they felt she would appease the Royal College of Physicians who wanted CBT/GET to continue. Many of Twitter directed their frustrations at NICE because of her appointment. Just two days before the meeting, Dame Carole Black tweeted her support of GET for Long Covid patients who experience some of the same symptoms as ME.

During the pause, a legal challenge was investigated by a patient who hired lawyer Peter Todd*. The male patient was made worse by GET. The lawyer stipulated the revised Guidelines be released by October 6th and before the roundtable meeting to be held on October 20th--- otherwise, a High Court challenge would occur. The deadline was not met although NICE acknowledged his letter and they invited Prof John Edwards to take part in the roundtable meeting. That pleased patients. After the lawyer's letter to NICE, the claimant was successful in getting legal aid.

Finally, on October 29th, NICE released the final guidelines to various media outlets in the UK. GET was removed while CBT was retained as a support mechanism.

*Peter Todd, the lawyer, decided to defer issuing the claim until after a decision was reached at the roundtable meeting so that they can show that the issues raised were previously considered at the developmental stage.

Ed. Note: Both Trudie Chalder and Sir Simon Wessely were professors of cognitive behavioral psychotherapy at the Institute of Psychiatry, Kings College, London. Wessely was removed from the Science Medical Centre in 2019.

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HOW RADIATION HARMS CELLS

What happens when cells are exposed to radiation?

In this case, an electron is emitted from the atom. Let's take a look at the structure of an atom. In the center of the atom is a nucleus. Traveling around the nucleus are electrons. If the atom were the size of a baseball field, the nucleus would be smaller than a golf ball. Electrons can be forced from their orbit by energy from radiation. This process is called ionization or electrolytic dissociation.

Different from electron exchange in typical chemical reactions, predicting which electrons will be emitted by exposure to radiation is impossible. Ions, also called radicals, generated in this way are extremely unstable chemically. They have very high levels of chemical reactivity, and therefore generate indiscriminate chemical reactions.

Radiation and electrons bombarded by radiation move haphazardly inside the cell, resulting in damage to the various molecules forming the cell. Chromosomal DNA inside the cell nucleus can also be damaged.

What ultimately becomes of cells harmed by radiation?

When radiation dose is large: Because of damage to DNA and resulting cell death, white blood cells can decrease and mucosa of the digestive tract may become injured, resulting in diarrhea, among other symptoms.

When radiation dose is smaller: The acute symptoms described above do not appear in exposure to lower radiation doses, but there is damage to cells, which attempt to repair themselves. Very rarely, however, mistakes do occur in the repair process, resulting in genetic abnormality (mutation). It is believed that inside such cells, certain developments may cause cancer in the future.

Radiation is harmful to health because radiation exposure can damage cellular DNA mostly in the form of DNA breaks. When part of a DNA break is repaired incorrectly, chromosome aberrations occur. DNA damage from radiation exposure causes various kinds of disease.

Recap:

- When the human body (its cells) is exposed to radiation (X-rays, gamma rays, etc), electrons are emitted from atoms and molecules.
 - These electrons bounce around, dispersing energy into surrounding areas.
 - This results in the formation of radicals.
 - These radicals react immediately with surrounding atoms, causing abnormal chemical reactions or minor damage to localized areas of cells.
 - Cell membrane damage can cause cell death (apoptosis), and breaks in cellular DNA, occurring either directly or indirectly by radicals of H₂O molecules attacking DNA, can cause cell death or mutations.
 - Mutations arise from mistakes in DNA repair - several hours or several days later
 - Tissue recovers from injury - several weeks later
 - Leukemia incidence increases - several years later
 - Cancer incidence increases - several decades later
- * This is why long-term studies are important.

Reference: Radiation Effects Research Foundation;

https://www.rerf.or.jp/en/about_radiation/how_radiation_harms_cells_e/

WHAT'S OLD IS NEW AGAIN – CFIDS SALIVARY MARKER

By Alan Cocchetto, NCF Medical Director – Copyright 2021

A number of years ago the NCF reported on a salivary test for CFIDS. More recently, this exact same test came up again in a paper titled, “Saliva fatigue biomarker index as a marker for severe myalgic encephalomyelitis/chronic fatigue syndrome in a community-based sample.” As a blast from the past, here is our previous report on this saliva marker and its link to ionizing radiation taken from the Spring 2014 Forum:

In 2011, a San Antonio news page reported on a very intriguing marker [1]. A bio-based company, known as Hyperion Biotechnology, had developed a saliva test for measuring fatigue. It sounded interesting to the NCF, so we did some checking and found several answers that appear to potentially link saliva fatigue markers to ionizing radiation exposure.

According to this news page, Hyperion has developed a simple test for measuring specific peptides in an individual's saliva to determine the level of fatigue. How did this company develop this technology? Here is where this gets very interesting. Hyperion does biomedical research for the military. In fact, Hyperion's Fatigue Biomarker Index, known as FBI, was developed through two Army grants totaling \$875,000. According to the article, the Army wanted to improve the way it assessed fatigue in trainees. It took Hyperion five years to complete product development, which included tests involving about 500 people, mostly in the military, and 4,000 saliva samples.

Well, the NCF's research had identified additional information because of Hyperion's patent applications [2,3]. In the 2011 patent application, Hyperion's work was sponsored by both the US Army as well as the US Air Force. Two amino acid peptides are identified that represent the fatigue biomarkers used for testing. These peptides are part of the basic proline-rich protein genes known as PRB1 and PRB2. PRB1's gene product is known as Basic Salivary Proline-rich Protein 1 while PRB2's gene product is known as Basic Salivary Proline-rich Protein 2.

It turns out that Hyperion's FBI test results are a measure of physical performance capability and are used to predict success in Special Operations Forces members. As compared to controls, a decrease in the levels of FBI are indicative of excessive fatigue in normal people.

If we now fast forward a bit, Hyperion has completed work with the CDC and have published their results associated with the testing of CFS/ME patients [3,4]. In September 2012, Hyperion had won a Distinguished Abstracts Award for Chronic Fatigue Syndrome Research at the American Association for Clinical Chemistry (AACC) annual meeting. Their abstract was titled "Search for a novel salivary biomarker candidate for chronic fatigue syndrome."

As we look at the 2014 patent application, there are many interesting details here especially since it is all about CFS. First, a staggering 21,165 subjects were screened to determine inclusion/exclusion criteria! This was ultimately dwindled down to just 45 controls and 46 CFS patients! We would suggest that this effort was completed with the mighty help of the CDC since their name is on the AACC Annual Meeting abstract and because patient selection involved telephone screening methods typical of other CDC based CFS studies!

According to this document, "The present invention also provides a method of identifying a subject as having chronic fatigue syndrome or having an increased likelihood of having or developing chronic fatigue syndrome, comprising: a) measuring the amount of 1) human basic proline-rich protein 1 (PRB1), 2) human basic proline-rich protein 2 (PRB2), and 3) human basic proline-rich protein 4 (PRB4) in a biological sample from a test subject; and b) calculating the amount of the proteins relative to the total amount of protein in the sample of (a) to determine a biomarker index for the test subject, wherein a biomarker index of the test subject that is higher than a threshold biomarker index identifies the subject as having chronic fatigue syndrome or having an increased likelihood of having or developing chronic fatigue syndrome."

Although the description above is just a short excerpt from the entire document, the key point is that these human basic proline-rich proteins (PRB1, PRB2 and/or PRB4), or their associated amino acid peptides, are used to identify not only normal fatigue in healthy subjects but also the likelihood of CFS in ill subjects.

To get to the point that we are trying to make here, according to the published medical literature, is that these proline-rich proteins are modulated by radiation effects [5,6]. In 2006, the NCF had published an article in *The Forum* that served to remind patients about some of the key characteristics from the Lake Tahoe outbreak as outlined in Hillary Johnson's book, *Osler's Web* [7]. Dr. Paul Cheney along with Dr. Dan Peterson had identified numerous B-cell lymphomas in the salivary or parotid glands in their CFS patients. These glands are very sensitive to radiation effects and this observation from the outbreak is in total agreement with the implications of Hyperion's research.

The salivary glands make as much as a quart of saliva each day. Saliva is important to lubricate your mouth, help with swallowing, protect your teeth against bacteria, and aid in the digestion of food. The three major pairs of salivary glands are (A) the parotid glands on the insides of the cheeks; (B) the submandibular glands at the floor of the mouth; and (C) the sublingual glands under the tongue. In addition, there are also several hundred minor salivary glands throughout the mouth and throat. Alterations to proline-rich proteins are associated with the development of dental problems, dry mouth, etc. Many patients are plagued with these problems.

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CBT

By Robert Huntington – Copyright 2021

The man who developed CBT died on November 1st. Dr. Aaron T. Beck's work as a psychiatrist treated people with anxiety, depression and all kinds of mental distress using cognitive behavioral therapy (CBT). He would have patients with mental disorders focus on their distortions in thinking which, after using this method in psychotherapy, would lead them to circumvent their depression. Yes, CBT is used to counter their depression, addictions, anxiety, insomnia, delusions, panic attacks and other mental illnesses.

Yes, ME/CFIDS is considered a mental illness that not only will be helped by psychiatric therapy sessions but, eventually will cure you! That's false. There is no cure for ME/CFIDS. Now that we know the cause, we know why nobody can recover. We have been irradiated and nothing can turn that around despite shrinks telling you that CBT will help. The other helpful measure

that we're told is GET (graded exercise therapy) which is actually harmful. No patient with ME/CFIDS should ever begin an exercise regime unless they want to end up lying in bed for days, weeks or years. But we will continue to have the medical profession tell us the only helpful things we can do to get better is to practice CBT and GET. Going to the Beck Institute for Cognitive Behavior Therapy won't do us one iota of good.

I do not have any faith for help via CBT or GET. That's why I've tried to help other volunteers at the National CFIDS Foundation, Inc. They're looking for ways to treat this illness by actually funding scientific research themselves with every penny that is donated to them. They're determined to find a treatment that will help and be able to shut down their charity. Look for my name under the Donations page of this newsletter online and see if I'm telling the truth. I just hope, as we all do, that that day comes faster than we think.

JUST ASK!

By Alan Cocchetto, NCF Medical Director – Copyright 2021



The “Just Ask” column is intended to act as a means for patients to inquire about issues related to the NCF’s research activities. This column is NOT intended to act as medical advice in any way, shape or form. The National CFIDS Foundation assumes no responsibility for any action or treatment undertaken by readers. For medical advice, please consult your own personal healthcare providers.

Q: Dear NCF, please allow me to vent as I recently hit a new milestone in my disease. I have been ill for forty years of my life on this earth. I must admit out loud that this totally sucks although I personally know of other patients who have had it longer and are sicker than I am.

Still, it really stinks. As I now look back, I had underestimated both the duration as well as the magnitude of this damn disease to disrupt my life.

Like most patients, I long to live again freely and to be unencumbered by constant health problems that have continually worn me down. For so long, I felt like I haven't lived and though I've survived and existed, I certainly haven't thrived. Sometimes I think something inside me died in this long process and perhaps I've lost myself. I'm well aware of the many losses that patients suffer.

What I want to know is this: Is there really any hope out there regarding actual help for patients like me? Will we ever get a targeted therapy? Will there ever be a definitive test for this disease? Thanks.

A: Let me first say that I hear and feel your pain. We here at the NCF are just like you....patients. Like you, we all know firsthand about this disease because we're living it daily, so please realize that you are not alone on this journey. Likewise, we recognize that your feelings are your own and applaud you for expressing them openly. We can certainly empathize with you in your situation and like you, we long for freedom.

Though I'm probably preaching to the choir here given that you are a long-term patient, there are numerous resources that span the range from mental health support to local or regional support groups to online (internet) support groups. You can look into these yourself or you can give us a call here at the NCF to discuss these options. As a seasoned patient, this is the best advice that I have to give you: As a fellow patient had reminded me, no matter what, never give up your personal empowerment to anyone. Furthermore, remember that although your body is at war, your spirit is limitless.

You asked me one of the toughest questions that can be asked. Though I don't have a crystal ball, do I truly believe that patients will one day, in the not too distant future, have an actual meaningful lab test for this disease.... yes I do. Do I truly believe that patients will also have at last a meaningful therapy in the same time frame....yes I do. The NCF will not give up the ship! Thank you for your question.

“Unsurprisingly, the arguments for considering to recommend such discredited practices turn out to be as poor as the practices themselves.”

~ Dr. Steven Lubet, Northwestern Law

MY PERSPECTIVE

By Helen M. Reynolds – Copyright 2021

Here we are, more than a year and a half since the start of COVID-19, and a large number of COVID patients have not returned to their pre-illness levels of health. Instead, they work with great difficulty or not at all, have trouble caring for themselves and their children, and are sick with new symptoms, including post-exertional malaise (PEM).

In the spring, I contacted the Department of Health to see what materials were available about long-COVID. There was nothing. The department was awaiting directives from the CDC. I am most concerned about the children who may have long-COVID and hoped there was material for educators. The thought of a family going through what we experienced with a school system is frightening, and our situation was not the most extreme. Why didn't those with long-COVID, health care workers, and schools have information? Websites existed in Great Britain and Canada. They both included information on COVID and Long Covid.

In May 2020, CNN's Chris Cuomo reported on his ongoing struggle with lasting symptoms from COVID. About the same time, Dr. Anthony Fauci mentioned that the continuation of COVID symptoms reminded him of Myalgic Encephalomyelitis (ME) and Chronic Fatigue Syndrome (CFS). Another name for ME/CFS is Post-Viral Fatigue Syndrome (PVS). Physicians can find it included with ME and CFS in the Internal Classification of Diseases (ICD). The three share one diagnostic code. They also share a symptom not reported in other diseases: post-exertional malaise (PEM). Interestingly, this symptom was mentioned by Mr. Cuomo, not by name but by description, when he said he couldn't come back from exercise as he had previously.

Enter the parallel universe. I always believed that if it looked like a duck and quacked like a duck, you'd call it a duck. Apparently, I am wrong. What I call long-COVID is now named post-acute sequelae SARS-CoV-s (PASC) with its own diagnostic code. In February 2021, the National Institutes of Health (NIH) announced that it received \$1.15 billion to study PASC. Suddenly it is "new" information that a post-viral illness has so many symptoms, that there are neurological manifestations, or that the symptoms are different from the original virus, and that the organ systems are affected. So why wasn't it called Post-Viral Fatigue Syndrome?

Meantime, patients are begging for answers. Social media carries story after story of going to 10 or more doctors looking for help. Several mentioned they had to prove they had a positive COVID test to be seen. Are these doctors unaware there were long periods of complete absence of testing equipment and supplies? Medical Professionals dismiss patients due to too many symptoms or because blood tests are in the normal range. Patients are being told they

should exercise because their muscle pain is due to deconditioning. Does this sound familiar? It does to those with ME/CFS.

History is repeating itself, and some of the original players are still present. Had the CDC not failed in its mission to “detect and respond to new and emerging health threats” over thirty years ago, today’s situation might be unfolding differently. Over thirty years ago, Stephen Strauss was head of clinical investigation at the National Institute for Allergy and Infectious Diseases (NIAID). His boss was Dr. Anthony Fauci. Together, they led a misinformation campaign against what would come to be known as Chronic Fatigue Syndrome (CFS). That is the same Anthony Fauci whose efforts, during the pandemic as the public face of COVID, I wholeheartedly support.

Their campaign, devoid of science, informed the medical community and the public that those with CFS had a psychiatric illness even before becoming ill. Moreover, as a result of their respective positions, they served on the boards that reviewed grant proposals and submissions to medical journals. Thus, they effectively controlled all research funding and information about a very serious physical illness. Interestingly, at the time, CFS was reportedly only second to AIDS in the number of inquiries received every month at NIAID.

The only positive I can glean from all this is ME/CFS folks are trying to help long-COVID patients. They are calling themselves long-haulers and adding the number of years (long-hauler 20 years). The goal is to warn new patients against “exercise makes everything better” and provide a space to speak with others who truly understand. As a result, a strange but rather lovely alliance has formed. Twitter and Facebook can now be considered the most extensive support groups, as thousands of people flock to these sites.

Prevalence studies of children with long-COVID are in short supply and what is available is not encouraging. A neuroinfectious disease specialist at Boston Children’s Hospital reports patients who were not severe enough to be hospitalized with COVID reporting symptoms that never go away. They also see patients whose COVID seems to have resolved develop post-viral symptoms a couple of weeks to months later.

With 30 years to “get it right”, there cannot be negative repercussions within the education system for these children. Yet, when I asked a couple of teachers in the area if they had any students with long-COVID, believe it or not, they didn’t know what I was talking about.

P.S. I wrote this before school openings in the South, where there us so much more at stake for the children than their education. Historical information can be found in Osler’s Web.

ASK BERNIE THE ATTORNEY

By Bernard A. Kansky, Esq. – Copyright 2021

Q. What effect if any will the Covid Pandemic have upon the treatment and diagnosis of CFIDS i.e. Chronic Fatigue and Immune Dysfunction Syndrome?

A. It should greatly help the medical profession to have a much better understanding as to the similarities between victims of Covid who are considered “long haulers,” and the victims of CFIDS who in a similar manner are also “long haulers.” In either case, one of the best and most accurate ways of proving inability to engage in substantial gainful employment activity, in my opinion, is taking a two (2) successive day Cardiopulmonary Exercise Test, i.e. a CPET, by a professional tester such as but not only Workwell Foundation which will test a patient for evaluation of metabolic, cardiovascular and pulmonary function. This test usually takes the form of a fixed bicycle riding test-retest and as indicated, over a two (2) successive day period. By many, it is considered the gold standard for measuring and evaluating functional capacity and fatigue where fatigue is involved as a major disabling symptom. The test measures metabolic responses, cardiovascular responses, recovery responses and more. The test also has a method for evaluating malingering. The results of such a test accompanied by an affidavit as to when the condition first began and continues to the present, as well as accompanying fasting blood tests showing multiple irregularities should satisfy the Social Security Administration and/or your long-term disability carrier that you are totally disabled and entitled to disability benefits.

In addition, if you are indebted for student loans, they may be forgiven if you are totally and permanently disabled.

If you have any questions for Bernie, please send them to: “Ask Bernie The Attorney,” c/o The National CFIDS Foundation, Inc. 103 Aletha Road, Needham, MA 02492- 3931, or email gailronda@aol.com. For Better Health Always!

“A win for Medical Education by Doctors with M.E. Prof. Trudie Chalder’s webinar gone. She is ignorant about Post Exertional Malaise and advises GET for Long Covid patients who crash after exercise. Get educated, Trudie!”

~ Dr. Hng & Friends at Doctors with ME

NEW CELL PHONE HEALTH RISKS

By Devra Lee Davis, PhD, MPH, Environmental Health Trust

While the coming of 5G cellular service sounds exciting, the health risks of this fifth-generation wireless technology and the radiation this emits are concerning. Cell-phone companies warn shareholders that they may be sued for cancer and other health impacts from 5G and other wireless devices, while at the same time aggressively marketing these same devices to consumers.

Talking about the risks of cell-phone radiation is not new – Environmental Health Trust has been warning about it for many years. But 5G and wireless dramatically increase the risk. These new networks rely on 4G connections and use the same wireless frequencies we have now but with new, higher frequencies. More than a million new “short” cell towers are being built, bringing microwave-radiating antennas closer than ever before and more than tripling exposure. You have no say at all about antenna location – one could be right outside your bedroom wall! And you’re at risk of exposure whether or not you have a 5G phone.

One of the most ironic things about 5G is that it actually doesn’t improve reception for voice calls. What it does do is create a new, faster way for wireless devices to communicate with one another, such as in a smart home. It also boosts download speeds for data, movies and video games.

How to reduce your exposure:

To protect yourself and your family from radiation associated with 5G – as well as from 4G and 3G – follow these guidelines. These steps are more important than ever...

Don’t carry your cell phone in your pocket, bra or against your body unless it is turned off.

When you are not using the phone, power it off or set it to Airplane/Flight mode. Also turn off Wi-Fi and Bluetooth.

When talking on the cell phone, use speaker mode or a plug-in earpiece to keep your phone away from your brain and body. Or, even better, send texts rather than make phone calls.

Don’t use your cell phone when you have only one or two bars or when you are between cell towers. A cell phone sends signals to a tower up to 900 times a minute, and each time, some of that radiation is absorbed into your body.

Don’t sleep with your cell phone nearby. If you use your phone as an alarm, set it to Airplane/Flight mode and turn off Wi-Fi and Bluetooth before putting it on your nightstand. Better: Purchase a battery powered alarm clock (plug-in digital clocks can emit EMF radiation).

Keep your corded-phone landline, which is free of wireless radiation and works in an emergency. Cordless home phones emit the same type of radiation as cell towers.

Use a wired mouse, keyboard, and printer to avoid unnecessary radiation, and don't buy smartphone wireless devices.

Get engaged in your community and at the state and federal levels to prevent cell-phone towers from being built near your home and schools.

Hang onto your non-5G phone as long as possible. Newer phones usually have more antennas, and you can't always turn them off.

Ed. Note: This article was originally printed in Bottom Line Personal in July and reprinted with the author's permission.

“Health Education England have removed Trudie Chalder’s training video on Long Covid where she dismissed a patient’s relapse after an exercise test as health anxiety and recommended graded exercise therapy.”

~ Adam

PALPABLE

By Lorraine V. Legendre* – Copyright 2021

I know

the taste of fear

the texture of trama

the voice of stress

I know

one hundred percent

I know

the adage insists:

‘knowledge is power.’

not today

not here
not enough
not with this illness
it is mighty powerful
unbelievable force

I know
EVERY DAY
I hear
I taste
I see
I smell
I touch
All my senses are on high alert
I feel fear and trauma
apprehension casts
a dark shadow
“This illness is stronger
than we are!”
Prophetic words!

This Forum is working
At changing that.
The Forum is the real deal!
Let us ever be supportive!

* If anyone has information on Lorraine or her son,
please let us know.



MEDICAL JOURNAL SUMMARIES



Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: A Neurological Entity?

Gandasegui IM et. Al; Medicina (Kaunas) 2021 Sep 27;57(10):1030.

Abstract: Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) is a disorder of unknown physiopathology with multisystemic repercussions, framed in ICD-11 under the heading of neurology (8E49). There is no specific test to support its clinical diagnosis. Our objective is to review the evidence in neuroimaging and dysautonomia evaluation in order to support the neurological involvement and to find biomarkers serving to identify and/or monitor the pathology. The symptoms typically appear acutely, although they can develop progressively over years; an essential trait for diagnosis is "central" fatigue together with physical and/or mental exhaustion after a small effort. Neuroimaging reveals various morphological, connectivity, metabolic, and functional alterations of low specificity, which can serve to complement the neurological study of the patient. The COMPASS-31 questionnaire is a useful tool to triage patients under suspect of dysautonomia, at which point they may be redirected for deeper evaluation. Recently, alterations in heart rate variability, the Valsalva maneuver, and the tilt table test, together with the presence of serum autoantibodies against adrenergic, cholinergic, and serotonin receptors were shown in a subgroup of patients. This approach provides a way to identify patient phenotypes. Broader studies are needed to establish the level of sensitivity and

specificity necessary for their validation. Neuroimaging contributes scarcely to the diagnosis, and this depends on the identification of specific changes. On the other hand, dysautonomia studies, carried out in specialized units, are highly promising in order to support the diagnosis and to identify potential biomarkers. ME/CFS orients towards a functional pathology that mainly involves the autonomic nervous system, although not exclusively.

Turning a Corner in ME/CFS Research

Pheby DFH et. al; *Medicina (Kaunas)* 2021 Sep 25;57(10):1012.

Abstract: This collection of research papers addresses fundamental questions concerning the nature of myalgic encephalomyelitis/ chronic fatigue syndrome (ME/CFS), the problem of disbelief and lack of knowledge and understanding of the condition among many doctors and the origins of this problem, and its impact on patients and their families. We report briefly the growing knowledge of the underlying pathological processes in ME/CFS, and the development of new organizations, including Doctors with ME, the US ME/CFS Clinical Coalition and EUROMENE, to address aspects of the challenges posed by the illness. We discuss the implications of COVID-19, which has much in common with ME/CFS, with much overlap of symptoms, and propose a new taxonomic category, which we are terming post-active phase of infection syndromes (PAPIS) to include both. This collection of papers includes a number of papers reporting similar serious impacts on the quality of life of patients and their families in various European countries. The advice of EUROMENE experts on diagnosis and management is included in the collection. We report this in light of guidance from other parts of the world, including the USA and Australia, and in the context of current difficulties in the UK over the promulgation of a revised guideline from the National Institute for Health and Care Excellence (NICE). We also consider evidence on the cost-effectiveness of interventions for ME/CFS, and on the difficulties of determining the costs of care when a high proportion of people with ME/CFS are never diagnosed as such. The Special Issue includes a paper which is a reminder of the importance of a person-centred approach to care by reviewing mind-body interventions. Finally, another paper reviews the scope for prevention in minimizing the population burden of ME/CFS, and concludes that secondary prevention, through early detection and diagnosis, could be of value.

Caring for the Patient with Severe or Very Severe Myalgic Encephalomyelitis/Chronic Fatigue Syndrome

Montoya JG et. al; Healthcare (Basel) 2021 Oct 6;9(10):1331.

Abstract: Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) can cause a wide range of severity and functional impairment, leaving some patients able to work while others are homebound or bedbound. The most severely ill patients may need total care. Yet, patients with severe or very severe ME/CFS struggle to receive appropriate medical care because they cannot travel to doctors' offices and their doctors lack accurate information about the nature of this disease and how to diagnose and manage it. Recently published clinical guidance provides updated information about ME/CFS but advice on caring for the severely ill is limited. This article is intended to fill that gap. Based on published clinical guidance and clinical experience, we describe the clinical presentation of severe ME/CFS and provide patient-centered recommendations on diagnosis, assessment and approaches to treatment and management. We also provide suggestions to support the busy provider in caring for these patients by leveraging partnerships with the patient, their caregivers, and other providers and by using technology such as telemedicine. Combined with compassion, humility, and respect for the patient's experience, such approaches can enable the primary care provider and other healthcare professionals to provide the care these patients require and deserve.

A Comprehensive Examination of Severely Ill ME/CFS Patients

Chang CJ et. al; Healthcare (Basel) 2021 Sep 29;9(10):1290.

Abstract: One in four myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) patients are estimated to be severely affected by the disease, and these house-bound or bedbound patients are currently understudied. Here, we report a comprehensive examination of the symptoms and clinical laboratory tests of a cohort of severely ill patients and healthy controls. The greatly reduced quality of life of the patients was negatively correlated with clinical depression. The most troublesome symptoms included fatigue (85%), pain (65%), cognitive impairment (50%), orthostatic intolerance (45%), sleep disturbance (35%), post-exertional malaise (30%), and neurosensory disturbance (30%). Sleep profiles and cognitive tests revealed distinctive impairments. Lower morning cortisol level and alterations in its diurnal rhythm were observed in the patients, and antibody and antigen measurements showed no evidence for acute infections by common viral or bacterial pathogens. These results highlight the urgent need of developing molecular diagnostic tests for ME/CFS. In addition, there was a striking similarity in symptoms between long COVID and ME/CFS, suggesting that studies on the mechanism and treatment of ME/CFS may help prevent and treat long COVID and vice versa.

Network Analysis of Symptoms Co-Occurrence in Chronic Fatigue Syndrome

Kujawski S et. al; *Int J Environ Res Public Health* 2021 Oct 13;18(20):10736.

Abstract: Chronic fatigue syndrome (CFS) is a heterogenous disorder of multiple disabling symptoms with complex manifestations. Network analysis is a statistical and interrogative methodology to investigate the prevalence of symptoms (nodes) and their inter-dependent (inter-nodal) relationships. In the present study, we explored the co-occurrence of symptoms in a cohort of Polish CFS patients using network analysis. A total of 110 patients with CFS were examined (75 females). The mean age of the total sample was 37.93 (8.5) years old while the mean duration of symptoms in years was 4.4 (4). Postexertional malaise (PEM) was present in 75.45% of patients, unrefreshing sleep was noted in 89.09% and impaired memory or concentration was observed in 87.27% of patients. The least prevalent symptom was tender cervical or axillary lymph nodes, noted in 34.55% of the total sample. Three of the most densely connected nodes were the total number of symptoms, sore throat and PEM. PEM was positively related with impairment in memory or concentration. Both PEM and impairment in memory or concentration presence are related to more severe fatigue measured by CFQ and FIS. PEM presence was positively related with the presence of multi-joint pain and negatively with tender lymph nodes and muscle pain. Sore throat was related with objective and subjective autonomic nervous system impairment. This study helps define symptom presentation of CFS with the pathophysiology of specific systems and links with multidisciplinary contemporary molecular pathology, including comparative MRI.

Potential Implications of Mammalian Transient Receptor Potential Melastatin 7 in the Pathophysiology of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: A Review

Du Preez S et. al;

Abstract: The transient receptor potential (TRP) superfamily of ion channels is involved in the molecular mechanisms that mediate neuroimmune interactions and activities. Recent advancements in neuroimmunology have identified a role for TRP cation channels in several neuroimmune disorders including amyotrophic lateral sclerosis, multiple sclerosis, and myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS). ME/CFS is a debilitating disorder with an obscure aetiology, hence considerable examination of its pathobiology is warranted. Dysregulation of TRP melastatin (TRPM) subfamily members and calcium signalling processes are implicated in the neurological, immunological, cardiovascular, and metabolic impairments inherent in ME/CFS. In this review, we present TRPM7 as a potential candidate in the pathomechanism of ME/CFS, as TRPM7 is increasingly recognized as a key mediator of physiological and pathophysiological mechanisms affecting neurological, immunological,

cardiovascular, and metabolic processes. A focused examination of the biochemistry of TRPM7, the role of this protein in the aforementioned systems, and the potential of TRPM7 as a molecular mechanism in the pathophysiology of ME/CFS will be discussed in this review. TRPM7 is a compelling candidate to examine in the pathobiology of ME/CFS as TRPM7 fulfils several key roles in multiple organ systems, and there is a paucity of literature reporting on its role in ME/CFS.

Impact of Life Stressors on Myalgic Encephalomyelitis/Chronic Fatigue Syndrome Symptoms: An Australian Longitudinal Study

Cassandra Balinas et. al; Int J Environ Res Public Health 2021 Oct 11;18(20):10614.

Abstract: (1) **Background:** Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) is a complex, multifaceted illness. The pathomechanism, severity and progression of this illness is still being investigated. Stressors have been implicated in symptom exacerbation for ME/CFS, however, there is limited information for an Australian ME/CFS cohort. The aim of this study was to assess the potential effect of life stressors including changes in work, income, or family scenario on symptom severity in an Australian ME/CFS cohort over five months; (2) **Methods:** Australian residents with ME/CFS responded to questions relating to work, income, living arrangement, access to healthcare and support services as well as symptoms experienced; (3) **Results:** thirty-six ME/CFS patients (age: 41.25 ± 12.14) completed all questionnaires (response rate 83.7%). Muscle pain and weakness, orthostatic intolerance and intolerance to extreme temperatures were experienced and fluctuated over time. Sleep disturbances were likely to present as severe. Work and household income were associated with worsened cognitive, gastrointestinal, body pain and sleep symptoms. Increased access to healthcare services was associated with improved symptom presentation; (4) **Conclusions:** life stressors such as work and financial disruptions may significantly contribute to exacerbation of ME/CFS symptoms. Access to support services correlates with lower symptom scores.

Pain-related post-exertional malaise in Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) and Fibromyalgia: A systematic review and three-level meta-analysis

Barhorst EE et. al; Pain Med 2021 Oct 20;pnab308.

Abstract: Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) and Fibromyalgia (FM) are two debilitating, moderately comorbid illnesses in which chronic musculoskeletal pain symptoms are prevalent. These individuals can experience post-exertional malaise (PEM), a phenomenon where symptom severity is worsened 24hr or longer following

physical stress, but the pain-related component of PEM is not well characterized. Results: Forty-five effects were extracted from 15 studies involving 306 patients and 292 healthy controls. After adjusting for nesting effects, we observed a small-to moderate effect indicating higher post-exercise pain in patients than controls (Hedges' $d=0.42$; 95% CI:0.16, 0.67). The mean effect was significantly moderated by pain measurement timepoint ($b = -0.19$, $z = -2.57$, $P = 0.01$) such that studies measuring pain 8-72hr post-exercise showed larger effects ($d = 0.71$, 95% CI = 0.28-1.14) than those measuring pain 0-2hr post-exercise ($d = 0.32$, 95% CI = 0.10-0.53). Conclusions: People with ME/CFS and FM experience small-to-moderate increases in pain severity following exercise which confirms pain as a component of PEM and emphasizes its debilitating impact in ME/CFS and FM. Future directions include determining mechanisms of pain-related PEM and developing exercise prescriptions that minimize symptom exacerbation in these illnesses.

Cerebral blood flow remains reduced after tilt testing in myalgic encephalomyelitis/chronic fatigue syndrome patients

van Campen CLMC et. al; Clin Neurophysiol Pract 2021 Sep 23;6:245-255.

Abstract: Orthostatic symptoms in myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) may be caused by an abnormal reduction in cerebral blood flow. An abnormal cerebral blood flow reduction was shown in previous studies, without information on the recovery pace of cerebral blood flow. This study examined the prevalence and risk factors for delayed recovery of cerebral blood flow in ME/CFS patients. Methods: 60 ME/CFS adults were studied: 30 patients had a normal heart rate and blood pressure response during the tilt test, 4 developed delayed orthostatic hypotension, and 26 developed postural orthostatic tachycardia syndrome (POTS) during the tilt. Cerebral blood flow measurements, using extracranial Doppler, were made in the supine position pre-tilt, at end-tilt, and in the supine position at 5 min post-tilt. Also, cardiac index measurements were performed, using suprasternal Doppler imaging, as well as end-tidal PCO₂ measurements. The change in cerebral blood flow from supine to end-tilt was expressed as a percent reduction with mean and (SD). Disease severity was scored as mild (approximately 50% reduction in activity), moderate (mostly housebound), or severe (mostly bedbound).

Results: End-tilt cerebral blood flow reduction was -29 (6)%, improving to -16 (7)% at post-tilt. No differences in either end-tilt or post-tilt measurements were found when patients with a normal heart rate and blood pressure were compared to those with POTS, or between patients with normocapnia (end-tidal PCO₂ ≥ 30 mmHg) versus hypocapnia (end-tidal PCO₂ < 30 mmHg) at end-tilt. A significant difference was found in the degree of abnormal cerebral blood flow reduction in the supine post-test in mild, moderate, and severe ME/CFS: mild: cerebral blood flow: -7 (2)%, moderate: -16 (3)%, and severe : -25 (4)% (p all < 0.0001). Cardiac index declined

significantly during the tilt test in all 3 severity groups, with no significant differences between the groups. In the supine post-test cardiac index returned to normal in all patients.

Conclusions: During tilt testing, extracranial Doppler measurements show that cerebral blood flow is reduced in ME/CFS patients and recovery to normal supine values is incomplete, despite cardiac index returning to pre-tilt values. The delayed recovery of cerebral blood flow was independent of the hemodynamic findings of the tilt test (normal heart rate and blood pressure response, POTS, or delayed orthostatic hypotension), or the presence/absence of hypocapnia, and was only related to clinical ME/CFS severity grading. We observed a significantly slower recovery in cerebral blood flow in the most severely ill ME/CFS patients.

Significance: The finding that orthostatic stress elicits a post-stress cerebral blood flow reduction and that disease severity greatly influences the cerebral blood flow reduction may have implications on the advice of energy management after a stressor and on the advice of lying down after a stressor in these ME/CFS patients.

Cortical autonomic network connectivity predicts symptoms in myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS)

Zinn MA et. al; Int J Psychophysiol 2021 Oct 15;170:89-101.

Abstract: Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) represents a significant public health challenge given the presence of many unexplained patient symptoms. Research has shown that many features in ME/CFS may result from a dysfunctional autonomic nervous system (ANS). We explored the role of the cortical autonomic network (CAN) involved in higher-order control of ANS functioning in 34 patients with ME/CFS and 34 healthy controls under task-free conditions. All participants underwent resting-state quantitative electroencephalographic (qEEG) scalp recordings during an eyes-closed condition. Source analysis was performed using exact low-resolution electromagnetic tomography (eLORETA), and lagged coherence was used to estimate intrinsic functional connectivity between each node across 7 frequency bands: delta (1-3 Hz), theta (4-7 Hz), alpha-1 (8-10 Hz), alpha-2 (10-12 Hz), beta-1 (13-18 Hz), beta-2 (19-21 Hz), and beta-3 (22-30 Hz). Symptom ratings were measured using the DePaul Symptom Questionnaire and the Short Form (SF-36) health survey. Graph theoretical analysis of weighted, undirected connections revealed significant group differences in baseline CAN organization. Regression results showed that cognitive, affective, and somatomotor symptom cluster ratings were associated with alteration to CAN topology in patients, depending on the frequency band. These findings provide evidence for reduced higher-order homeostatic regulation and adaptability in ME/CFS. If confirmed, these findings address the CAN as a potential therapeutic target for managing patient symptoms.

Reduced Parasympathetic Reactivation during Recovery from Exercise in Myalgic Encephalomyelitis/Chronic Fatigue Syndrome

Oosterwijk JV et. al; J Clin Med 2021 Sep 30;10(19):4527.

Abstract: Although autonomic nervous system (ANS) dysfunction in Myalgic Encephalomyelitis / Chronic Fatigue Syndrome (ME/CFS) has been proposed, conflicting evidence makes it difficult to draw firm conclusions regarding ANS activity at rest in ME/CFS patients. Although severe exercise intolerance is one of the core features of ME/CFS, little attempts have been made to study ANS responses to physical exercise. Therefore, impairments in ANS activation at rest and following exercise were examined using a case-control study in 20 ME/CFS patients and 20 healthy people. Different autonomous variables, including cardiac, respiratory, and electrodermal responses were assessed at rest and following an acute exercise bout. At rest, parameters in the time-domain represented normal autonomic function in ME/CFS, while frequency-domain parameters indicated the possible presence of diminished (para)sympathetic activation. Reduced parasympathetic reactivation during recovery from exercise was observed in ME/CFS. This is the first study showing reduced parasympathetic reactivation during recovery from physical exercise in ME/CFS. Delayed HR recovery and/or a reduced HRV as seen in ME/CFS have been associated with poor disease prognosis, high risk for adverse cardiac events, and morbidity in other pathologies, implying that future studies should examine whether this is also the case in ME/CFS and how to safely improve HR recovery in this population.

Neurochemical abnormalities in chronic fatigue syndrome: a pilot magnetic resonance spectroscopy study at 7 Tesla

Godlewska BR et. al; Psychopharmacology (Berl) 2021 Oct 5.

Abstract: Chronic fatigue syndrome (CFS) is a common and burdensome illness with a poorly understood pathophysiology, though many of the characteristic symptoms are likely to be of brain origin. The use of high-field proton magnetic resonance spectroscopy (MRS) enables the detection of a range of brain neurochemicals relevant to aetiological processes that have been linked to CFS, for example, oxidative stress and mitochondrial dysfunction.

Methods: We studied 22 CFS patients and 13 healthy controls who underwent MRS scanning at 7 T with a voxel placed in the anterior cingulate cortex. Neurometabolite concentrations were calculated using the unsuppressed water signal as a reference.

Results: Compared to controls, CFS patients had lowered levels of glutathione, total creatine and myoinositol in anterior cingulate cortex. However, when using N-acetylaspartate as

a reference metabolite, only myo-inositol levels continued to be significantly lower in CFS participants.

Conclusions: The changes in glutathione and creatine are consistent with the presence of oxidative and energetic stress in CFS patients and are potentially remediable by nutritional intervention. A reduction in myo-inositol would be consistent with glial dysfunction. However, the relationship of the neurochemical abnormalities to the causation of CFS remains to be established, and the current findings require prospective replication in a larger sample.

Inflammation plays a causal role in fatigue-like behavior induced by pelvic irradiation in mice

Wolff BS et. al; Brain Behav Immun Health 2021 May 19;15:100264.

Abstract: Fatigue is a persistent and debilitating symptom following radiation therapy for prostate cancer. However, it is not well-understood how radiation targeted to a small region of the body can lead to broad changes in behavior. In this study, we used targeted pelvic irradiation of healthy male mice to test whether inflammatory signaling mediates changes in voluntary physical activity levels. First, we tested the relationship between radiation dose, blood cell counts, and fatigue-like behavior measured as voluntary wheel-running activity. Next, we used oral minocycline treatments to reduce inflammation and found that minocycline reduces, but does not eliminate, the fatigue-like behavioral changes induced by radiation. We also used a strain of mice lacking the MyD88 adaptor protein and found that these mice also showed less fatigue-like behavior than the wild-type controls. Finally, using serum and brain tissue samples, we determined changes in inflammatory signaling induced by irradiation in wildtype, minocycline treated, and MyD88 knockout mice. We found that irradiation increased serum levels of IL-6, a change that was partially reversed in mice treated with minocycline or lacking MyD88. Overall, our results suggest that inflammation plays a causal role in radiation-induced fatigue and that IL-6 may be an important mediator.

Complement Component C1q as a Potential Diagnostic Tool for Myalgic Encephalomyelitis/Chronic Fatigue Syndrome Subtyping

Castro-Marrero J et. al; J Clin Med 2021 Sep 15;10(18):4171.

Abstract: Routine blood analytics are systematically used in the clinic to diagnose disease or confirm individuals' healthy status. For myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS), a disease relying exclusively on clinical symptoms for its diagnosis, blood analytics only serve to rule out underlying conditions leading to exerting fatigue. However, studies evaluating complete and large blood datasets by combinatorial approaches to evidence ME/CFS condition or detect/identify case subgroups are still scarce.

Methods: This study used unbiased hierarchical cluster analysis of a large cohort of 250 carefully phenotyped female ME/CFS cases toward exploring this possibility.

Results: The results show three symptom-based clusters, classified as severe, moderate, and mild, presenting significant differences ($p < 0.05$) in five blood parameters. Unexpectedly the study also revealed high levels of circulating complement factor C1q in 107/250 (43%) of the participants, placing C1q as a key molecule to identify an ME/CFS subtype/subgroup with more apparent pain symptoms.

Conclusions: The results obtained have important implications for the research of ME/CFS etiology and, most likely, for the implementation of future diagnosis methods and treatments of ME/CFS in the clinic.

Evaluation of Immune Dysregulation in an Austrian Patient Cohort Suffering from Myalgic Encephalomyelitis/Chronic Fatigue Syndrome

Lutz L et. al; *Biomolecules* 2021 Sep 14;11(9):1359.

Abstract: Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) is a severe multi-systemic disease characterized by debilitating fatigue that is not relieved by rest. The causes of the disease are still largely unexplained, and no causative treatment is currently available. Changes in the immune response are considered as fundamental in the development of ME/CFS. Thus, we aimed to evaluate the immunological profile of ME/CFS patients in a retrospective data analysis. As part of the routine workup for ME/CFS patients, a differential blood count, leukocyte subtyping, and quantification of immunoglobulins and IgG subclasses, as well as a complement analysis, was performed. Out of 262 ME/CFS patients, 64.9% had a reduction or deficiency in at least one of the listed immune parameters. In contrast, 26.3% showed signs of immune activation or inflammation. A total of 17.6% of the ME/CFS patients had an unclassified antibody deficiency, with IgG3 and IgG4 subclass deficiencies as the most common phenotypes. Reduced MBL (mannose-binding lectin) levels were found in 32% of ME/CFS patients, and MBL deficiency in 7%. In summary, the present results confirmed the relevance of immune dysfunction in ME/CFS patients underlining the involvement of a dysfunctional immune response in the disease. Thus, immune parameters are relevant disease biomarkers, which might lead to targeted therapeutic approaches in the future.

Induced pluripotent stem cells as suitable sensors for fibromyalgia and myalgic encephalomyelitis /chronic fatigue syndrome

Monzón-Nomdedeu MB; World J Stem Cells 2021 Aug 26;13(8):1134-1150.

Abstract: Background: Fibromyalgia (FM) and myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) are devastating metabolic neuroimmune diseases that are difficult to diagnose because of the presence of numerous symptoms and a lack of specific biomarkers. Despite patient heterogeneity linked to patient subgroups and variation in disease severity, anomalies are found in the blood and plasma of these patients when compared with healthy control groups. The seeming specificity of these "plasma factors", as recently reported by Ron Davis and his group at Stanford University, CA, United States, and observations by our group, have led to the proposal that induced pluripotent stem cells (iPSCs) may be used as metabolic sensors for FM and ME/CFS, a hypothesis that is the basis for this in-depth review.

Aim: To identify metabolic signatures in FM and/or ME/CFS supporting the existence of disease associated plasma factors to be sensed by iPSCs.

Methods: A PRISMA (Preferred Reported Items for Systematic Reviews and Meta-analysis)-based systematic review of the literature was used to select original studies evaluating the metabolite profiles of FM and ME/CFS body fluids. The MeSH terms "metabolomic" or "metabolites" in combination with FM and ME/CFS disease terms were screened against the PubMed database. Only original studies applying omics technologies, published in English, were included. The data obtained were tabulated according to the disease and type of body fluid analyzed. Coincidences across studies were searched and P-values reported by the original studies were gathered to document significant differences found in the disease groups.

Results: Eighteen previous studies show that some metabolites are commonly altered in ME/CFS and FM body fluids. In vitro cell-based assays have the potential to be developed as screening platforms, providing evidence for the existence of factors in patient body fluids capable of altering morphology, differentiation state and/or growth patterns. Moreover, they can be further developed using approaches aimed at blocking or reversing the effects of specific plasma/serum factors seen in patients. The documented high sensitivity and effective responses of iPSCs to environmental cues suggests that these pluripotent cells could form robust, reproducible reporter systems of metabolic diseases, including ME/CFS and FM. Furthermore, culturing iPSCs, or their mesenchymal stem cell counterparts, in patient-conditioned medium may provide valuable information to predict individual outcomes to stem-cell therapy in the context of precision medicine studies.

Conclusion: This opinion review explains our hypothesis that iPSCs could be developed as a screening platform to provide evidence of a metabolic imbalance in FM and ME/CFS.

Acute Corticotropin-Releasing Factor Receptor Type 2 Agonism Results in Sustained Symptom Improvement in Myalgic Encephalomyelitis/Chronic Fatigue Syndrome

Pereira G; Front Syst Neurosci 2021 Sep 1;15:698240.

Abstract: Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) is a complex multi-symptom disease with widespread evidence of disrupted systems. The authors hypothesize that it is caused by the upregulation of the corticotropin-releasing factor receptor type 2 (CRFR2) in the raphé nuclei and limbic system, which impairs the ability to maintain homeostasis. The authors propose utilizing agonist-mediated receptor endocytosis to downregulate CRFR2. **Materials and methods:** This open-label trial tested the safety, tolerability and efficacy of an acute dose of CT38s (a short-lived, CRFR2-selective agonist, with no known off-target activity) in 14 ME/CFS patients. CT38s was subcutaneously-infused at one of four dose-levels (i.e., infusion rates of 0.01, 0.03, 0.06, and 0.20 µg/kg/h), for a maximum of 10.5 h. Effect was measured as the pre-/post-treatment g/kg/h, for a maximum of 10.5 h. Effect was measured as the pre-/post-treatment change in the mean 28-day total daily symptom score (TDSS), which aggregated 13 individual patient-reported symptoms.

Results: ME/CFS patients were significantly more sensitive to the transient hemodynamic effects of CRFR2 stimulation than healthy subjects in a prior trial, supporting the hypothesized CRFR2 upregulation. Adverse events were generally mild, resolved without intervention, and difficult to distinguish from ME/CFS symptoms, supporting a CRFR2 role in the disease. The acute dose of CT38s was associated with an improvement in mean TDSS that was sustained (over at least 28 days posttreatment) and correlated with both total exposure and pre-treatment symptom severity. At an infusion rate of 0.03 µg/kg/h, for a maximum of 10.5 h. Effect was measured as the pre-/post-treatment g/kg/h, mean TDSS improved by -7.5 ± 1.9 (or -25.7% , $p = 0.009$), with all monitored symptoms improving.

Conclusion: The trial supports the hypothesis that CRFR2 is upregulated in ME/CFS, and that acute CRFR2 agonism may be a viable treatment approach warranting further study.

Autoantibodies to Vasoregulative G-Protein-Coupled Receptors Correlate with Symptom Severity, Autonomic Dysfunction and Disability in Myalgic Encephalomyelitis/Chronic Fatigue Syndrome

Freitag H et. al; J Clin Med 2021 Aug 19;10(16):3675.

Abstract: Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) is an acquired complex disease with patients suffering from the cardinal symptoms of fatigue, post-exertional malaise (PEM), cognitive impairment, pain and autonomous dysfunction. ME/CFS is triggered by an infection in the majority of patients. Initial evidence for a potential role of natural regulatory

autoantibodies (AAB) to beta-adrenergic (AdR) and muscarinic acetylcholine receptors (M-AChR) in ME/CFS patients comes from a few studies.

Methods: Here, we analyzed the correlations of symptom severity with levels of AAB to vasoregulative AdR, AChR and Endothelin-1 type A and B (ETA/B) and Angiotensin II type 1 (AT1) receptor in a Berlin cohort of ME/CFS patients (n = 116) by ELISA. The severity of disease, symptoms and autonomic dysfunction were assessed by questionnaires.

Results: We found levels of most AABs significantly correlated with key symptoms of fatigue and muscle pain in patients with infection-triggered onset. The severity of cognitive impairment correlated with AT1-R- and ETA-R-AAB and severity of gastrointestinal symptoms with alpha1/2-AdR-AAB. In contrast, the patients with non-infection-triggered ME/CFS showed fewer and other correlations.

Conclusion: Correlations of specific AAB against G-protein-coupled receptors (GPCR) with symptoms provide evidence for a role of these AAB or respective receptor pathways in disease pathomechanism.

A map of metabolic phenotypes in patients with myalgic encephalomyelitis/chronic fatigue syndrome

Hoel F et. al; JCI Insight 2021 Aug 23;6(16):e149217.

Abstract: Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) is a debilitating disease usually presenting after infection. Emerging evidence supports that energy metabolism is affected in ME/CFS, but a unifying metabolic phenotype has not been firmly established. We performed global metabolomics, lipidomics, and hormone measurements, and we used exploratory data analyses to compare serum from 83 patients with ME/CFS and 35 healthy controls. Some changes were common in the patient group, and these were compatible with effects of elevated energy strain and altered utilization of fatty acids and amino acids as catabolic fuels. In addition, a set of heterogeneous effects reflected specific changes in 3 subsets of patients, and 2 of these expressed characteristic contexts of deregulated energy metabolism. The biological relevance of these metabolic phenotypes (metabotypes) was supported by clinical data and independent blood analyses. In summary, we report a map of common and context-dependent metabolic changes in ME/CFS, and some of them presented possible associations with clinical patient profiles. We suggest that elevated energy strain may result from exertion-triggered tissue hypoxia and lead to systemic metabolic adaptation and compensation. Through various mechanisms, such metabolic dysfunction represents a likely mediator of key symptoms in ME/CFS and possibly a target for supportive intervention.

Radiation exposure and mitochondrial insufficiency in chronic fatigue and immune dysfunction syndrome

Rusin A et. al; *Med Hypotheses* 2021 Sep;154:110647.

Abstract: Chronic fatigue and Immune Dysfunction Syndrome (CFIDS) is a heterogeneous disease that may be promoted by various environmental stressors, including viral infection, toxin uptake, and ionizing radiation exposure. Previous studies have identified mitochondrial dysfunction in CFIDS patients, including modulation of mitochondrial respiratory chain activity, deletions in the mitochondrial genome, and upregulation of reactive oxygen species (ROS). This paper focuses on radiation effects and hypothesizes that CFIDS is primarily caused by stressor-induced mitochondrial metabolic insufficiency, which results in decreased energy production and anabolic metabolites required for normal cellular metabolism. Furthermore, tissues neighbouring or distant from directly perturbed tissues compensate for this dysfunction, which causes symptoms associated with CFIDS. This hypothesis is justified by reviewing the links between radiation exposure and CFIDS, cancer, immune dysfunction, and induction of oxidative stress. Moreover, the relevance of mitochondria in cellular responses to radiation and metabolism are discussed and putative mitochondrial biomarkers for CFIDS are introduced. Implications for diagnosis are then described, including a potential urine assay and PCR test for mitochondrial genome mutations. Finally, future research needs are offered with an emphasis on where rapid progress may be made to assist the afflicted.

Skewing of the B cell receptor repertoire in myalgic encephalomyelitis/chronic fatigue syndrome

Sato W et. al; *Brain, Behavior, and Immunity* 95, 7/21, 245-255

Abstract: Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) is a debilitating condition characterized by fatigue and post-exertional malaise, accompanied by various signs of neurological and autonomic dysfunction. ME/CFS is often triggered by an infectious episode and associated with an aberrant immune system. Here we report that ME/CFS is a disorder characterized by skewed B cell receptor gene usage. By applying a next-generation sequencing to determine the clone-based IGHV/IGHD/IGHJ repertoires, we revealed a biased usage of several IGHV genes in peripheral blood B cells from ME/CFS patients. Results of receiver operating characteristic (ROC) analysis further indicated a possibility of distinguishing patients from healthy controls, based on the skewed B cell repertoire. Meanwhile, B cell clones using IGHV3-30 and IGHV3-30-3 genes were more frequent in patients with an obvious infection-related episode at onset and correlated to expression levels of interferon response genes in plasmablasts. Collectively, these results imply that B cell responses in ME/CFS are directed against an infectious agents or priming antigens induced before disease onset.

Limbic Perfusion Is Reduced in Patients with Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS)

Li X et. al; Tomography 2021, 7(4), 675-687

Abstract: Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) is an illness characterized by a diverse range of debilitating symptoms including autonomic, immunologic, and cognitive dysfunction. Although neurological and cognitive aberrations have been consistently reported, relatively little is known regarding the regional cerebral blood flow (rCBF) in ME/CFS. In this study, we studied a cohort of 31 ME/CSF patients (average age: 42.8 ± 13.5 years) and 48 healthy controls (average age: 42.9 ± 12.0 years) using the pseudo-continuous arterial spin labeling (PCASL) technique on a whole-body clinical 3T MRI scanner. Besides routine clinical MRI, the protocol included a session of over 8 min-long rCBF measurement. The differences in the rCBF between the ME/CSF patients and healthy controls were statistically assessed with voxel-wise and AAL ROI-based two-sample t-tests. Linear regression analysis was also performed on the rCBF data by using the symptom severity score as the main regressor. In comparison with the healthy controls, the patient group showed significant hypoperfusion (uncorrected voxel wise $p \leq 0.001$, FWE $p \leq 0.01$) in several brain regions of the limbic system, including the anterior cingulate cortex, putamen, pallidum, and anterior ventral insular area. For the ME/CFS patients, the overall symptom severity score at rest was significantly associated with a reduced rCBF in the anterior cingulate cortex. The results of this study show that brain blood flow abnormalities in the limbic system may contribute to ME/CFS pathogenesis. Saliva fatigue biomarker index as a marker for severe myalgic encephalomyelitis/chronic fatigue syndrome in a community-based sample

Jason LA et. al; Fatigue: Biomedicine, Health & Behavior, DOI:10.1080/21641846.2021.1994222

Abstract: The prevalence of pediatric Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) has been estimated from an ethnically and sociodemographically diverse community-based random sample of 10,119 youth aged 5–17. We assessed whether a salivary biomarker of fatigue could identify youth with ME/CFS. Study design: We examined the ratio of the concentrations of 2 peptide fragments in saliva, referred to as the Fatigue Biomarker Index (FBI), in participants from our study diagnosed with ME/CFS ($n = 59$) and matched controls ($n = 39$).

Results: Significant overall differences were found in the FBI between those participants with severe ME/CFS and those with ME/CFS and the controls.

Conclusions: If confirmed in other populations, the FBI could serve as an objective test to aid in the diagnosis of severe ME/CFS.

Tryptophan Metabolites, Cytokines, and Fatty Acid Binding Protein 2 in Myalgic Encephalomyelitis / Chronic Fatigue Syndrome

Simonato M et. al; *Biomedicines* 2021, 9, 1724

Abstract: Patients with Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) differ for triggers, mode of start, associated symptoms, evolution, and biochemical traits. Therefore, serious attempts are underway to partition them into subgroups useful for a personalized medicine approach to the disease. Here, we investigated clinical and biochemical traits in 40 ME/CFS patients and 40 sex- and age-matched healthy controls. Particularly, we analyzed serum levels of some cytokines, Fatty Acid Binding Protein 2 (FABP-2), tryptophan, and some of its metabolites via serotonin and kynurenine. ME/CFS patients were heterogeneous for genetic background, trigger, start mode, symptoms, and evolution. ME/CFS patients had higher levels of IL-17A ($p = 0.018$), FABP-2 ($p = 0.002$), and 3-hydroxykynurenine ($p = 0.037$) and lower levels of kynurenine ($p = 0.012$) and serotonin ($p = 0.045$) than controls. Changes in kynurenine and 3-hydroxykynurenine were associated with increased kynurenic acid/kynurenine and 3-hydroxykynurenine/kynurenine ratios, indirect measures of kynurenine aminotransferases and kynurenine 3-monooxygenase enzymatic activities, respectively. No correlation was found among cytokines, FABP-2, and tryptophan metabolites, suggesting that inflammation, anomalies of the intestinal barrier, and changes of tryptophan metabolism may be independently associated with the pathogenesis of the disease. Interestingly, patients with the start of the disease after infection showed lower levels of kynurenine ($p = 0.034$) than those not starting after an infection. Changes in tryptophan metabolites and increased IL-17A levels in ME/CFS could both be compatible with anomalies in the sphere of energy metabolism. Overall, clinical traits together with serum biomarkers related to inflammation, intestine function, and tryptophan metabolism deserve to be further considered for the development of personalized medicine strategies for ME/CFS.

Pathomechanisms and possible interventions in myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS)

Fluge O et. al; *J Clin Invest.* 2021;131(14):e150377.

Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) is a disease with unknown etiology, no validated specific and sensitive biomarker, and no standard approved effective treatment. ME/CFS has a profound impact on the quality of life of both patients and caregivers and entails high costs for society. The severity varies among patients who are able to participate

to some extent in social life (mild), those who are mainly housebound (moderate) or bedridden (severe), and the very severely ill who are completely dependent on assistance for all daily living tasks, such as feeding or turning around in bed. Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) often starts in previously healthy individuals after an infection, the most common being infectious mononucleosis (EBV). It is more frequent in women and influenced by genetic predisposition. The main symptoms are postexertional malaise (PEM), fatigue, orthostatic intolerance, cognitive disturbances, sleep problems with inadequate restitution after rest, sensory hypersensitivity with pain, and symptoms related to autonomic and immune dysfunction. The prevalence is 0.1% to 0.8%, and ME/CFS must be distinguished from general fatigue, which is much more common in the population. Historically, there has been limited scientific interest in ME/CFS. However, research efforts have increased in the last decade. Although this has led to different hypotheses, a firmly established pathomechanism is lacking. Herein, we suggest a framework model for the initiation and maintenance of ME/CFS consisting of three principal steps: (a) an initial aberrant immune response; (b) an effector system for symptom generation and maintenance; and (c) compensatory adaptations.

Effect of Melatonin Plus Zinc Supplementation on Fatigue Perception in Myalgic Encephalomyelitis / Chronic Fatigue Syndrome: A Randomized, Double-Blind, Placebo-Controlled Trial

Castro-Marrero J et. al; *Antioxidants* (Basel). 2021 Jun 23;10(7):1010.

Abstract: Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) is a complex, multisystem, and profoundly debilitating condition, probably of multifactorial etiology. No effective approved drugs are currently available for its treatment. Several studies have proposed symptomatic treatment with melatonin and zinc supplementation in chronic illnesses; however, little is known about the synergistic effect of this treatment on fatigue-related symptoms in ME/CFS. The primary endpoint of the study was to assess the effect of oral melatonin plus zinc supplementation on fatigue in ME/CFS. Secondary measures included participants' sleep disturbances, anxiety/depression and health-related quality of life. A proof-of-concept, 16-week, randomized, placebo-controlled, double-blind trial was conducted in 50 ME/CFS patients assigned to receive either oral melatonin (1 mg) plus zinc (10 mg) supplementation (n = 24) or matching placebo (n = 26) once daily. Endpoint outcomes were evaluated at baseline, and then reassessed at 8 and 16 weeks of treatment and 4 weeks after treatment cessation, using self-reported outcome measures. The most relevant results were the significant reduction in the perception of physical fatigue in the Mel-Zinc group at the final treatment follow-up versus placebo ($p < 0.05$), and the significant improvement in the physical component summary at all follow-up visits in the experimental group. Urinary 6-sulfatoxymelatonin levels were significantly elevated though the treatment in experimental group vs. placebo ($p < 0.0001$); however, no significantly differences

were observed for zinc concentration among participants. Our findings suggest that oral melatonin plus zinc supplementation for 16 weeks is safe and potentially effective in reducing fatigue and improving the quality of life in ME/CFS. This clinical study was registered on ClinicalTrials.gov (NCT03000777).

Insights from myalgic encephalomyelitis/chronic fatigue syndrome may help unravel the pathogenesis of postacute COVID-19 syndrome

Komaroff AL et. al; Trends Mol Med. 2021 Sep;27(9):895-906.

Abstract: Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) can cause chronic and acute disease. Postacute sequelae of SARS-CoV-2 infection (PASC) include injury to the lungs, heart, kidneys, and brain that may produce a variety of symptoms. PASC also includes a post-coronavirus disease 2019 (COVID-19) syndrome ('long COVID') with features that can follow other acute infectious diseases and myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS). Here we summarize what is known about the pathogenesis of ME/CFS and of 'acute' COVID-19, and we speculate that the pathogenesis of post-COVID-19 syndrome in some people may be similar to that of ME/CFS. We propose molecular mechanisms that might explain the fatigue and related symptoms in both illnesses, and we suggest a research agenda for both ME/CFS and post-COVID-19 syndrome.

Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: When Suffering Is Multiplied

Komaroff AL; Healthcare (Basel). 2021 Jul 20;9(7):919.

Abstract: Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) is an illness defined predominantly by symptoms. Routine laboratory test results often are normal, raising the question of whether there are any underlying objective abnormalities. In the past 20 years, however, new research technologies have uncovered a series of biological abnormalities in people with ME/CFS. Unfortunately, many physicians remain unaware of this, and some tell patients that "there is nothing wrong" with them. This skepticism delegitimizes, and thereby multiplies, the patients' suffering.

Effect of Dietary Coenzyme Q10 Plus NADH Supplementation on Fatigue Perception and Health-Related Quality of Life in Individuals with Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: A Prospective, Randomized, Double-Blind, Placebo-Controlled Trial

Castro-Marrero J et. al; Nutrients. 2021 Jul 30;13(8):2658.

Abstract: Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) is a complex, multisystem, and profoundly debilitating neuroimmune disease, probably of post-viral multifactorial etiology. Unfortunately, no accurate diagnostic or laboratory tests have been established, nor are any universally effective approved drugs currently available for its treatment. This study aimed to examine whether oral coenzyme Q10 and NADH (reduced form of nicotinamide adenine dinucleotide) cosupplementation could improve perceived fatigue, unrefreshing sleep, and health-related quality of life in ME/CFS patients. A 12-week prospective, randomized, double-blind, placebo-controlled trial was conducted in 207 patients with ME/CFS, who were randomly allocated to one of two groups to receive either 200 mg of CoQ10 and 20 mg of NADH (n = 104) or matching placebo (n = 103) once daily. Endpoints were simultaneously evaluated at baseline, and then reassessed at 4- and 8-week treatment visits and four weeks after treatment cessation, using validated patient-reported outcome measures. A significant reduction in cognitive fatigue perception and overall FIS-40 score ($p < 0.001$ and $p = 0.022$, respectively) and an improvement in HRQoL (health-related quality of life (SF-36)) ($p < 0.05$) from baseline were observed within the experimental group over time. Statistically significant differences were also shown for sleep duration at 4 weeks and habitual sleep efficiency at 8 weeks in follow-up visits from baseline within the experimental group ($p = 0.018$ and $p = 0.038$, respectively). Overall, these findings support the use of CoQ10 plus NADH supplementation as a potentially safe therapeutic option for reducing perceived cognitive fatigue and improving the health-related quality of life in ME/CFS patients. Future interventions are needed to corroborate these clinical benefits and also explore the underlying pathomechanisms of CoQ10 and NADH administration in ME/CFS.

Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: Essentials of Diagnosis and Management
Bateman L et. al; Mayo Clin Proc. 2021 Nov;96(11):2861-2878.

Abstract: Despite myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) affecting millions of people worldwide, many clinicians lack the knowledge to appropriately diagnose or manage ME/CFS. Unfortunately, clinical guidance has been scarce, obsolete, or potentially harmful. Consequently, up to 91% of patients in the United States remain undiagnosed, and those diagnosed often receive inappropriate treatment. These problems are of increasing importance because after acute COVID-19, a significant percentage of people remain ill for many months with an illness similar to ME/CFS. In 2015, the US National Academy of Medicine published new evidence-based clinical diagnostic criteria that have been adopted by the US Centers for Disease Control and Prevention. Furthermore, the United States and other governments as well as major health care organizations have recently withdrawn graded exercise and cognitive-behavioral therapy as the treatment of choice for patients with ME/CFS. Recently, 21 clinicians specializing in ME/CFS convened to discuss best clinical practices for adults affected

by ME/CFS. This article summarizes their top recommendations for generalist and specialist health care providers based on recent scientific progress and decades of clinical experience. There are many steps that clinicians can take to improve the health, function, and quality of life of those with ME/CFS, including those in whom ME/CFS develops after COVID-19. Patients with a lingering illness that follows acute COVID-19 who do not fully meet criteria for ME/CFS may also benefit from these approaches.

An Audit of UK Hospital Doctors' Knowledge and Experience of Myalgic Encephalomyelitis

Hng KN et. al; *Medicina (Kaunas)*. 2021 Aug 27;57(9):885.

Abstract: Background and Objectives: There is some evidence that knowledge and understanding of ME among doctors is limited. Consequently, an audit study was carried out on a group of hospital doctors attending a training event to establish how much they knew about ME and their attitudes towards it. **Materials and Methods:** Participants at the training event were asked to complete a questionnaire, enquiring about prior knowledge and experience of ME and their approaches to diagnosis and treatment. A total of 44 completed questionnaires were returned. Responses were tabulated, proportions selecting available options determined, 95% confidence limits calculated, and the significance of associations determined by Fisher's exact test. **Results:** Few respondents had any formal teaching on ME, though most had some experience of it. Few knew how to diagnose it and most lacked confidence in managing it. None of the respondents who had had teaching or prior experience of ME considered it a purely physical illness. Overall, 91% of participants believed ME was at least in part psychological. Most participants responded correctly to a series of propositions about the general epidemiology and chronicity of ME. There was little knowledge of definitions of ME, diagnosis, or of clinical manifestations. Understanding about appropriate management was very deficient. Similarly, there was little appreciation of the impact of the disease on daily living or quality of life. Where some doctors expressed confidence diagnosing or managing ME, this was misplaced as they were incorrect on the nature of ME, its diagnostic criteria and its treatment. **Conclusion:** This audit demonstrates that most doctors lack training and clinical expertise in ME. Nevertheless, participants recognised a need for further training and indicated a wish to participate in this. It is strongly recommended that factually correct and up-to-date medical education on ME be made a priority at undergraduate and postgraduate levels. It is also recommended that this audit be repeated following a period of medical education.

Limbic Perfusion Is Reduced in Patients with Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS)

Li X et. al; Tomography 2021 Nov 1;7(4):675-687.

Abstract: Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) is an illness characterized by a diverse range of debilitating symptoms including autonomic, immunologic, and cognitive dysfunction. Although neurological and cognitive aberrations have been consistently reported, relatively little is known regarding the regional cerebral blood flow (rCBF) in ME/CFS. In this study, we studied a cohort of 31 ME/CSF patients (average age: 42.8 ± 13.5 years) and 48 healthy controls (average age: 42.9 ± 12.0 years) using the pseudo-continuous arterial spin labeling (PCASL) technique on a whole-body clinical 3T MRI scanner. Besides routine clinical MRI, the protocol included a session of over 8 min-long rCBF measurement. The differences in the rCBF between the ME/CSF patients and healthy controls were statistically assessed with voxel-wise and AAL ROI-based two-sample t-tests. Linear regression analysis was also performed on the rCBF data by using the symptom severity score as the main regressor. In comparison with the healthy controls, the patient group showed significant hypoperfusion (uncorrected voxel wise $p \leq 0.001$, FWE $p \leq 0.01$) in several brain regions of the limbic system, including the anterior cingulate cortex, putamen, pallidum, and anterior ventral insular area. For the ME/CFS patients, the overall symptom severity score at rest was significantly associated with a reduced rCBF in the anterior cingulate cortex. The results of this study show that brain blood flow abnormalities in the limbic system may contribute to ME/CFS pathogenesis.

Deficient butyrate-producing capacity in the gut microbiome of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome patients is associated with fatigue symptoms

Guo C et. al; Preprint at <https://www.medrxiv.org/content/10.1101/2021.10.27.21265575v1> 10/28/21

Abstract: Background Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) is a complex, debilitating disease of unknown cause for which there is no specific therapy. Patients suffering from ME/CFS commonly experience persistent fatigue, post-exertional malaise, cognitive dysfunction, sleep disturbances, orthostatic intolerance, fever and irritable bowel syndrome (IBS). Recent evidence implicates gut microbiome dysbiosis in ME/CFS. However, most prior studies are limited by small sample size, differences in clinical criteria used to define cases, limited geographic sampling, reliance on bacterial culture or 16S rRNA gene sequencing, or insufficient consideration of confounding factors that may influence microbiome composition. In the present study, we evaluated the fecal microbiome in the largest prospective, case-control study to date ($n=106$ cases, $n=91$ healthy controls), involving subjects from geographically diverse communities across the United States.

Results: Using shotgun metagenomics and qPCR and rigorous statistical analyses that controlled for important covariates, we identified decreased relative abundance and quantity of Faecalibacterium, Roseburia, and Eubacterium species and increased bacterial load in feces of subjects with ME/CFS. These bacterial taxa play an important role in the production of butyrate, a multifunctional bacterial metabolite that promotes human health by regulating energy metabolism, inflammation, and intestinal barrier function. Functional metagenomic and qPCR analyses were consistent with a deficient microbial capacity to produce butyrate along the acetyl-CoA pathway in ME/CFS. Metabolomic analyses of short-chain fatty acids (SCFAs) confirmed that fecal butyrate concentration was significantly reduced in ME/CFS. Further, we found that the degree of deficiency in butyrate-producing bacteria correlated with fatigue symptom severity among ME/CFS subjects. Finally, we provide evidence that IBS comorbidity is an important covariate to consider in studies investigating the microbiome of ME/CFS subjects, as differences in microbiota alpha diversity, some bacterial taxa, and propionate were uniquely associated with self-reported IBS diagnosis.

Conclusions: Our findings indicate that there is a core deficit in the butyrate-producing capacity of the gut microbiome in ME/CFS subjects compared to healthy controls. The relationships we observed among symptom severity and these gut microbiome disturbances may be suggestive of a pathomechanistic linkage, however, additional research is warranted to establish any causal relationship. These findings provide support for clinical trials that explore the utility of dietary, probiotic and prebiotic interventions to boost colonic butyrate production in ME/CFS.

IN MEMORIUM

The following names have been added to our Memorial List available on our website. Our sincere condolences to the friends and families of all those on our Memorial List. This list shows why a better education is needed by the medical staffs worldwide along with better research that will help all patients.



Julie Bond died July 19, 2018. She was first diagnosed with mononucleosis when she was a college student. She continued with college despite the illness affecting her dramatically and graduated Magna Cum Laude many years later. She was hired and was working but her illness made her miss many days of work until she was fired. She applied for disability and fought for it for 4 years. (Source: Paggy Nagle)

Marisa D’Ercole, 19, took her life at age 19 after barely being able to leave her bed. She created her own support group via Instagram and had more than 2,000 followers. “Daisy” was housebound and struggled through each day yet was “never being able to fall asleep at night,” had “constant pain,” and found herself “constantly vomiting.” She had dreamed of traveling the world but her home in Australia was locked down during the Covid pandemic. She died on August 5, 2021 leaving her parents, a sister, and many others who could not change her agony of CFIDS/ME.

Kristina Hines died October 23, 2021.

Michaela Lex was a patient from Germany who had a very severe case of ME. She was determined, when she became sick, to make ME less invisible. (More information welcomed on this patient.)

Rene Mebus, 26, died on June 30, 2020 after suffering from an extremely severe case of CFIDS/ME just three years earlier. He had graduated college as a mechanical engineer and was working toward a master’s degree and helping the voluntary fire brigade as well as designing a website for his district fire brigade and helping them in other ways when illness ended his help. He became bedridden and could not tolerate light or any noise and continued to worsen until he became paralyzed and had seizures. A stay at a hospital only worsened him and even morphine could not alleviate his pain. He is missed by many friends and relatives including his parents and a brother. His brother also has CFIDS/ME.

Maeve Boothby-O’Neill, 27, died October 3, 2021 in the UK. Her father, a journalist who often wrote about ME, let others know, “Bit by bit, this awful illness stole the youth, promise, independence and eventually the life of an intelligent, creative, wonderful young woman,” She needed a feeding tube this past March and went to the Wonford Hospital where they did not believe ME existed and treated her terribly. A psychiatrist had begun the hospital’s evil dismissal of ME years ago and when an expert went there to explain ME, they remained dismissive and did not respond to calls about her deteriorating condition. She is survived by her parents, Sean and Sarah, her siblings and many others who remain horrified at the way the hospital was so dismissive.

David A. Petrosky, 68, died in his sleep on May 12, 2021, after having ME since he was much younger. Dave was political savvy and exceptional with baseball statistics. He was an entertainment director at a housing complex but they evicted him for no good reason. He experienced a stroke and a heart attack and was wheelchair-bound but tried not to let that ruin his life. Dave grew up in Massachusetts and was helpful to many before ME attacked him. He was misdiagnosed for many years. He had two brothers and Arnie, who remained in Massachusetts close to Dave, did what he could to get care for him. He is missed by him and many relatives and friends. (Source: Gail Kansky)

Claudia Wendlandt died in mid-October of 2021 in Georgia and will be missed by many CFIDS/ME patients there as well as many others as she created and led a support group for decades. Her own ME story was published in 1996 by the Atlanta-Journal Constitution. She established a statewide support group for “CFS/FM” after securing a state proclamation to observe her disease for the May awareness day. Despite her own health that continued to grow more severe, Claudia remained determined to advocate for the illness to make others aware of her chronic disease. (Source: a friend of Claudia on twitter)

Lotta Winstrom, took her own life on January of 2020. Lotta was from Sweden where she worked in a retirement facility as well as a kindergarten. Lotta fell ill with CFIDS/ME and, three years later, was finally diagnosed correctly. By that time, she had married and, after a few years, became a single mother for her son. She is missed by many who knew her as well as her son and her husband. She was 53 when she ended her life after not being able to be touched and was kept in a dark room with no noise as she had become so severe that her life was intolerable.

Danya Zucker, 66, took her own life after battling ME for many years. Danya was a teacher in the northeast when she first became sick. After several doctors misdiagnosed her, she was finally diagnosed correctly but her ME worsened until she had to move back home with her parents, Eitan and Lee, in Eugene, Oregon. Danya was one of three sisters. She remained in touch with the NCF until she could no longer bear the misery of such severe ME. She spent the last two weeks of her life organizing everything she could of her affairs and died on July 24, 2021. Her friends and family miss her immensely yet understand why she chose to end her life. She was a member of the NCF and stayed in touch with many for as long as it was possible for her to do so. (Source: Sister and several friends)

Anil van der Zee, 35, died on July 26, 2020, from Covid after dealing with CFIDS/ME for many years. He was known as a researcher and a historian. One admirer who knew him said he died from neglect until his condition became too severe and found it difficult to breath. (Source: A fellow sufferer of CFIDS/ME announced his death on twitter)

DONATIONS

The National CFIDS Foundation is immensely grateful to each person listed below. Every penny of their donation has gone to fund research that will eventually help us all live our lives better than ME/CFIDS has allowed thus far. Each donation to the NCF is tax deductible to the full extent allowed by US federal law as our charity is a federally approved 501(c)(3).



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Tony and Jean Camuti

SUPPORTER

Greg Hartz

Linus Matheme

Betty Pippins

Sparks of Joy

Gail & Bernie Kansky