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A BRIEF LOOK AT CFS EPIDEMIOLOGY

By Alan Cocchetto, NCF Medical Director, June 2022 – Copyright 2022

Epidemiology. I have had numerous chats through the years with patients and physicians regarding CFS epidemiology. Some of those I've talked to appear to have selective amnesia as they kind of remember what they want to remember regarding cluster outbreaks. Oh, they chat about it but don't come through regarding the interpretation or surrounding circumstances and the like.

What I've decided to do is to remind people about an interesting epidemiology paper by Dr. Seymour Grufferman. As such, I'm quoting the entire text from his paper and will let you, the reader, examine some of the more intriguing facts identified in this regard.

Below is the text from the paper titled, "Closeness of contacts between people in two clusters of Chronic Fatigue Syndrome: Evidence for an infectious etiology?" [1]

"This study assessed closeness of interpersonal contacts between individuals in clusters of chronic fatigue syndrome (CFS) as possible evidence of transmissibility or of common exposure to the source of a noninfectious etiologic agent. Two outbreaks of CFS in discrete occupational groups (members of a symphony orchestra and teachers at an elementary school) were studied to assess whether persons with CFS had closer contact with one another than they had with those members of each group who did not have CFS or whether they had more contact with each other than noninfected members had with other noninfected members of each group. Members of the two groups felt that they contracted CFS via workplace exposure to individuals with CFS. Thus, we defined the two occupational groups as the populations at risk.

Since both clusters occurred before the development of a consensus regarding the definition of CFS, a case of CFS was determined by a physician's diagnosis. Using current diagnostic criteria for CFS, five members of the orchestra met the research case definition of CFS. According to the latest Centers for Disease Control and Prevention (CDC) definition, three other members met Group 2 criteria. In the school cluster, three teachers met the current diagnostic criteria for CFS and four did not. Of the four not meeting the criteria, one was later found to have rheumatic fever and the other three met the criteria of Group 2 of the most recent CDC research case definition.

Members of the groups were asked about their personal contacts with the other members of their group before and during the early phase of each cluster. Contacts were assessed through hierarchical series of 11 questions that ranged from whether they knew the other person to whether they had had intimate contact with that person. Using these data, we developed methods to test the null hypothesis that there were no differences in the frequency or types of contacts between pairs of CFS patients and pairs chosen at random from the cohorts. Since the data consist of n(n - 1)/2 pairs of yes/no responses that are not independent, standard statistical methods used to compare two proportions do not apply here. Thus, for each exposure variable, we compared the observed proportions of case-to-case (C-C), case-to-noncase (C-NC), and noncase-to-noncase (NC-NC) pairs who had interpersonal contact, then computed a Knox-type test statistic and compared it with a corresponding test statistic from a simulated permutation distribution of subject pairs.

The first cluster affected eight individuals from the 67-member orchestra. Data were obtained for all eight members with CFS and 50 members without CFS. The second cluster affected seven teachers in an elementary school with a total of 38 teachers. Data were obtained for all seven teachers with CFS (one was found to have rheumatic fever) and 21 teachers without CFS. In the orchestra, members with and without CFS were very similar in mean age, race, and marital status. There were more women than men with CFS. In the school, teachers with CFS were slightly older than those without CFS, but the two groups were similar in sex, race, and marital status.

In the orchestra, there were significantly more C-C pairs than C-NC or NC-NC pairs who reported having shared an eating utensil (P = .037) or having shared a bedroom (P = <.0001). There were more C-C pairs for the variables "playing together in a chamber group" (P = .085) and "riding in a car together" (P = .056), but neither result was significant. The data on sharing a bed with a person and on intimate sexual contact were inevaluable because of the small numbers of such pairs (only one such pair in the C-C group). In the school investigation, there were also more contacts between C-C pairs than NC-NC pairs for the variables "riding in a car together" (P = .08), "riding on a bus together" (P = .10), and "eating a meal together" (P = .10). Although the differences observed in terms of proportions of C-C vs. NC-NC pairs with the specific shared exposure were similar in magnitude to those found for members of the orchestra, none of the differences were statistically significant, probably because of the smaller size of the school group.

These data suggest that in clusters of CFS, affected individuals appear to have had more frequent, and probably more intimate, contact with one another than with unaffected individuals, or than unaffected individuals had with each other. This result suggests interpersonal transmission or a common source of exposure to an etiologic agent."

Several concepts appear to jump off the page of which the first is the identification of the closeness of the contacts with perhaps the transmissibility or common exposure to the source of a noninfectious agent. These are key observations to be potentially answered by this paper since this article examines two cluster outbreaks; the first is associated with an orchestra while the second is with a school. What is significant here? More Case-Case pairs who either shared an eating utensil, a bedroom, played together in the orchestra or rode together in a car. I find these to be very interesting observations. So, the Case pairs were found to certainly "know" each other in more than the intimate sense since sharing a utensil is quite an intriguing observation for sure. Riding in a car and being in the orchestral group together certainly appears more casual. Likewise, for the school cluster, once again, the Case-Case pairs identified riding in a car or on a bus together or eating a meal together, all of which suggests casual transmission or common source of exposure to an agent.

In another paper looking at other CFS clusters, the authors state the following [2]: "Results from the study of this cluster suggest that comparisons between individuals with CFS and their close contacts is difficult because unaffected individuals may show similar patterns of laboratory abnormalities compatible with perturbations of immune function. This finding suggests transmission of an infectious agent or exposure to a common source of a noninfectious causal agent that might cause similar laboratory abnormalities in symptomatic and asymptomatic individuals."

In the Lyndonville cluster outbreak, which the NCF has commented on numerous times in the past, here are the epidemiological findings [3]: Statistical significance was identified for (A) Raw milk at any time and/or recently; (B) Raw eggs; (C) Exposure to dogs in the house; (D) Hot air home heating source; (E) Exposure to cats on property; (F) Appendicitis.

So here we are. I'm staring at a September 28, 2006 article in Science aptly titled, "Is Radiation Contagious? X-rayed fish may pass ill effects onto their unexposed companions" [4]. Here is the article quoted as follows:

"It's a fish story that sounds like science fiction: scientists studying the effects of radiation have discovered that trout exposed to x-rays can pass on the effects to nonirradiated fish. Although experts are skeptical, the researchers contend their study is one of the first to demonstrate the communicability of radiation responses between animals. In addition, the team says the findings underscore the need to investigate whether the phenomenon also can occur in humans.

Considerable previous research in cell cultures has demonstrated that low doses of ionizing radiation results in "bystander" effects, in which nearby, unexposed tissues suffer cell death, mutations, and tumor-inducing growth (ScienceNOW, 7 September 2005). However, few studies have been conducted on live animals. Fish are good candidates for study, because they communicate via chemicals in water. To see if radiated fish release signals to neighbors, a team led by radiation biologists Colin Seymour and Carmel Mothersill of McMaster University in Ontario, Canada, x-rayed pairs of rainbow trout in a water-filled tank for 5 minutes. The total radiation delivered, 0.5 gray (Gy), was high relative to environmental levels (from sources such as naturally occurring radon in rock), but significantly lower than equivalent human doses experienced in CAT-scans or cancer therapy.

The fish were then plunked in another tank with a pair of healthy, untreated trout for 2 hours. In addition, the team placed another pair of nonirradiated fish in the water tank in which the irradiated fish had been swimming. Each experiment was done four times. When the researchers later examined the fish, they found similar radiation effects in all three experimental groups. Cells in five different organs had died and other cells were expressing proteins associated with radiation responses. It's likely that the irradiated fish secreted chemicals--not yet identified--into the water, evoking radiation-like effects in the unexposed groups, the team reports online 27 September in Environmental Science & Technology. “The take-home message,” says Mothersill, “is that bystander effects occur in living organisms, and thus should be taken into account when determining radiation risks in humans and other animals.””

Since that time, numerous additional studies in mice and rats have confirmed the initial research results from the above-mentioned study. Perhaps given these findings, we need to embrace where research has taken us. More data is forthcoming but is the world truly ready for it? Time will tell. To patients, all I can say is that help is coming as we’re covering as much ground as we can as fast as we can.

References:

1. Closeness of Contacts Between People in Two Clusters of Chronic Fatigue Syndrome: Evidence for an Infectious Etiology? Seymour Grufferman, Roslyn A. Stone, Nancy L. Eby, Mary S. Huang, Susan B. Muldoon, Lili Penkower; Clinical Infectious Diseases, Volume 18, Issue Supplement_1, January 1994, Pages S54–S55, https://doi.org/10.1093/clinids/18.Supplement_1.S54-b; Published: 01 January 1994

2. Results of an Investigation of Three Clusters of Chronic Fatigue Syndrome; Seymour Grufferman, Paul H. Levine, Nancy L. Eby, Susan B. Muldoon, Mary S. Huang, Theresa L. Whiteside, Lili Penkower, Ronald B. Herberman; Clinical Infectious Diseases, Volume 18, Issue Supplement_1, January 1994, Pages S55–S56, https://doi.org/10.1093/clinids/18.Supplement_1.S55; Published: 01 January 1994

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4. https://www.science.org/content/article/radiation-contagious

PRESIDENT'S MESSAGE

By Gail Kansky – Copyright 2022

I got attacked by ME/CFS as a young child. My daughter was a colicky mess when she was a very young child but she got worse as she entered her teens. I brought her to every doctor possible until her pediatrician set her up with an appointment with the Director of Medicine from Harvard University. He saw her for ten minutes and then came out to see me in a waiting room He told me he knew what she had and it was "Myalgic Encephomyalitis." I said, "My what?" About 15 years later, I, too, was diagnosed.

ME/CFS was not in any book I could find in the local library. It didn't seem to be mentioned anywhere. And there didn't seem to be many physicians that knew about it. Certainly, there were a few that I met, such as the late Dr. Jay A. Goldstein, MD. It was recently mentioned in articles in my local newspaper when COVID-19 emerged, as both illnesses seemed to have similar, if not identical symptoms. It quickly found mentions in magazines as different as Time and Cosmopolitan. In June of this year, the National Academies wrote, "At the request of the U.S. Congress, the National Academies will form a committee of experts to help define the health and safety issues that need to be guided by an improved understanding of low dose and low dose rate radiation health effects and recommend a long-term strategic and prioritized research to address scientific research goals." We may also find out exactly how some politically famous people managed to recover after their ME diagnosis decades ago! The recent pandemic may turn out to be one of the best things to witness for the many millions who continue to suffer today. And the NCF may finally be able to cease existing!

Meanwhile, as summer settles in, I hope all ME/CFIDS patients will do themselves a favor and stay out of the sunshine as UVR (ultra violet radiation) is dangerous to us all.

NEWS IN 2022

By The National CFIDS Foundation, June 2022 – Copyright 2022

Although a fire destroyed the news we had in March, the following were able to be picked up and reported. On January 8, an article was printed in the International Journal of Molecular Sciences entitled “Commonalities in the Features of Cancer and Chronic Fatigue Syndrome (CFS): Evidence for Stress-Induced Phenotype Instability?” by Andrew Rusin, Colin Seymour, Alan Cocchetto, and Carmel Mothersill. Alan is our Medical Director and the other authors are from Canada's McMaster University. One stressor noted is ionizing radiation although, as the authors note, this must still be proven. The paper tells of many involvements and reports on what has been shown and what must still be proven.

Published on March 4th in Frontiers in Immunology was, “Comparative analysis of extracellular vesicles in patients with severe and mild Myalgic Encephalomyelitis/Chronic Fatigue Syndrome” by many authors from California on one potential biomarker. On March 18, The Week chose as their Book of the Week a book titled, “Invisible Kingdom: Reimagining Chronic Illness” be Megan O'Rourke. She writes how for much of her adult life she suffered with many CFIDS symptoms, yet her doctor felt she wasn't sick, and multiple trips to the ER due to pain, which failed her as well. Less than a week later on March 24 an article appeared telling about a secret government training exercise that took place at a nuclear site and how these soldiers are still looking for answers today as their symptoms persist. On March 27, an article appeared in the Journal of Health Psychology done at universities in the UK as well as one in the US (Harvard). They hope that the treatment of Long Covid is never equivalent to many of the nonhelpful treatments some with CFIDS were subjected to. On the final day of March, The Journal of Clinical Investigation published an article on plasma metabolomics showed recovery from maximal exercise in CFIDS patients was disrupted by post-exertional malaise (PEM), a “hallmark symptom.”

It was also in March that Russian soldiers arrived in the Chernobyl nuclear site and some even dug trenches in the highly radioactive Red Forest. Many Russian soldiers got sick and they pulled out after just a month there. They have not commented on the high numbers of soldiers that got sick from radiation exposure.

Top scientific experts from around the world together published on April 1st in Frontiers in Medicine on how diagnosis for ME/CFS can be improved by extracellular vesicles in blood. They agree that further work in this area is warranted. A very long story on Long Covid and of ME/CFS was printed in the Montreal Gazette on April 2 where the patients, “have felt neglected by the system.” Some scientists in Canada are now looking into the links between the two illnesses. In the U.S., the nuclear power generation does not release any greenhouse gasses and our U.S.

Department of Energy categorizes it as “clean.” The U.S. spends billions of dollars on their nuclear plants according to NBC. They reported in April that there were 93 nuclear reactors in this country and licenses for an additional eight reactors are approved for construction. Another study was reported by Vascular Pharmacology in April entitled, “Decreased NO in endothelial cells exposed to plasma from ME/CFS patients.” The study was supported by ME Research UK and found nitric oxide is released by blood flow but people with ME/CFS had far less NO which may become a target for treatment in the future.

The end of April brought about a new template letter helped to be available via the U.K.'s ME Association and helps others understand why people with ME/CFS are more vulnerable when they contract COVID-19. The letter states, “People with a diagnosis of ME/CFS should be regarded as being clinically vulnerable in relation to COVID-19 infection. As a result, they may require help, support or modifications to all aspects of normal life...Research into the quality of life of people with ME/CFS has found that it can be just as disabling and can have a greater impact on function and wellbeing than many other chronic illnesses such as cancer and multiple sclerosis.” The letter is by Dr. Charles Sheppherd who is the medical advisor of the ME Association. Those with ME/CFS are at higher risk from COVID-19.

By May 1, an online article appeared ahead of the printed Respiratory of Molecular Cell Neuroscience entitled,” Elevated AGT13 in serum of patients with ME/CFS stimulates oxidative stress in microglial cells via activation of receptor for advanced glycation end products (RAGE).” They give results of their work showing ATG13 is upregulated in the blood of ME/CFS patients, what it does in the body, and how it interferes and initiates other problems among those with the illness. When all their results are taken together, they seem to show a pathological signal of our disease.

The May issue of the American Journal of Respiratory and Clinical Care Medicine had a printed paper entitled “Acute effect of pyridostigmine in exertional intolerance in Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS): A Randomized placebo-controlled clinical trial.” Because approximately one third of ME/CFS patients have SFN (small fiber neuropathy), they postulated that the neurovascular dysregulation that occurs during upright exercise be helped by pyridostigmine may help improve the patient's exercise tolerance and vascular regulation by helping to increase sympathetic outflow. After careful analysis and testing, they concluded, “Using pyridostigmine as an investigated tool, this study suggests that neurovascular dysregulation underlies acute exercise intolerance in ME/CFS. Additionally, we have new evidence that worsening vascular dysregulation results from prior exercise, which sheds insight into the post exertional malaise that is a hallmark of this syndrome.”

A lot of reports on Long Covid and ME/CFS compared them as similar because there were similar symptoms.

“THE WHY: THE HISTORIC ME/CFS CALL TO ARMS” BY HILLARY JOHNSON

By Kathy Collett (Twitter: @kathycollett7) – Copyright 2022

Patients admired Hillary Johnson's groundbreaking “Osler's Web” and now they welcome her new book in which the author provides a further insight into the scientific bias, misappropriation of ME federal research funds, the origins of the name, Chronic Fatigue Syndrome, and biological abnormalities leaving patients vulnerable and to their own devices.

The dealings with the CDC and NIH in the USA are well known to patients and have been detrimental in advancing ME; their control has held up progress. It has gone on for decades and, even with changes.

As a long-term ME patient, Hillary belongs to the era where there was an explosion of patients and doctors like Drs. Jay A. Goldstein and Paul Cheney worked tirelessly to assist patients, yet the problems still exist.

While patients have voiced their dissatisfaction particularly on Twitter, including the CDC and NIH in their tweets, they won't budge and the book was born from their experienced frustrations. Hillary has condensed the associated problems in her 98-page book and was able to prove the illness has an organic basis. Later, Professor Hokama also provided a valuable contribution.

While a lot of the NIH's and CDC's actions were behind closed doors, Twitter has been a good source to explain their appalling lack of concern too, and Hillary has kicked the door wide open.

Ed. Note: This article was also reprinted in ME International's June, 2022 newsletter.

JUST ASK!

By Alan Cocchetto, NCF Medical Director – Copyright 2022

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, help! My Social Security reviewer along with my insurance company is in need of additional information from me. Though I had previously provided them with a truck load of information, they just don't seem to understand the seriousness of this disease and how desperately ill I am. Could you address this in any capacity?

A: Here is the overview along with some additional information for Chronic Fatigue Syndrome:

Chronic Fatigue Syndrome (CFS) is a serious, long-term illness that affects many body systems. People with CFS are often not able to do their usual activities. At times, CFS may confine them to bed. People with CFS have severe fatigue and sleep problems. CFS may get worse after people with the illness try to do as much as they want or need to do. This symptom is called post-exertional malaise (PEM). Other symptoms can include problems with thinking and concentrating, pain, and dizziness.

According to an Institute of Medicine (IOM) report, an estimated 836,000 to 2.5 million Americans suffer from CFS. However, most of them have not been diagnosed.

Primary symptoms - Also called “core” symptoms, three primary symptoms are required for diagnosis:

1) Greatly lowered ability to do activities that were usual before the illness. This drop in activity level occurs along with fatigue and must last six months or longer. People with CFS have fatigue that is very different from just being tired. The fatigue of CFS:

Can be severe.

Is not a result of unusually difficult activity.

Is not relieved by sleep or rest.

Was not a problem before becoming ill (not life-long).

2) Worsening of CFS symptoms after physical or mental activity that would not have caused a problem before illness. This is known as post-exertional malaise (PEM). People with CFS often describe this experience as a “crash,” “relapse,” or “collapse.” During PEM, any CFS symptoms may get worse or first appear, including difficulty thinking, problems sleeping, sore throat, headaches, feeling dizzy, or severe tiredness. It may take days, weeks, or longer to recover from a crash. Sometimes patients may be house-bound or even completely bed-bound during crashes. People with CFS may not be able to predict what will cause a crash or how long it will last. As examples:

Attending a child’s school event may leave someone house-bound for a couple of days and not able to do needed tasks, like laundry.

Shopping at the grocery store may cause a physical crash that requires a nap in the car before driving home or a call for a ride home.

Taking a shower may leave someone with CFS bed-bound and unable to do anything for days.

Keeping up with work may lead to spending evenings and weekends recovering from the effort.

3) Sleep problems - People with CFS may not feel better or less tired, even after a full night of sleep. Some people with CFS may have problems falling asleep or staying asleep.

In addition to these core symptoms, one of the following two symptoms is required for diagnosis:

1) Problems with thinking and memory - Most people with CFS have trouble thinking quickly, remembering things, and paying attention to details. Patients often say they

have “brain fog” to describe this problem because they feel “stuck in a fog” and not able to think clearly.

2) Worsening of symptoms while standing or sitting upright. This is called orthostatic intolerance. People with CFS may be lightheaded, dizzy, weak, or faint while standing or sitting up. They may have vision changes like blurring or seeing spots.

Many but not all people with ME/CFS have other symptoms.

Pain is very common in people with CFS. The type of pain, where it occurs, and how bad it is varies a lot. The pain people with CFS feel is not caused by an injury. The most common types of pain in CFS are:

Muscle pain and aches

Joint pain without swelling or redness

Headaches, either new or worsening

Some people with CFS may also have:

Tender lymph nodes in the neck or armpits

A sore throat that happens often

Digestive issues, like irritable bowel syndrome

Chills and night sweats

Allergies and sensitivities to foods, odors, chemicals, light, or noise

Muscle weakness

Shortness of breath

Irregular heartbeat

According to a summary by the National Academies of Science Institute of Medicine, “Myalgic Encephalomyelitis (ME) and Chronic Fatigue Syndrome (CFS) are serious, debilitating conditions that affect millions of people in the United States and around the world. ME/CFS can cause significant impairment and disability. Despite substantial efforts by researchers to better understand ME/CFS, there is no known cause or effective treatment. Diagnosing the disease remains a challenge, and patients often struggle with their illness for years before an identification is made. Some health care providers have been skeptical about the serious physiological - rather than psychological - nature of the illness. Once diagnosed, patients often complain of receiving hostility from their health care provider as well as being subjected to treatment strategies that exacerbate their symptoms.”

In 2012, the National Cancer Institute's Division of Cancer Epidemiology concluded that CFS was associated with an increased risk of non-Hodgkin lymphoma (NHL). CFS was also associated with cancers of the pancreas, kidney, breast, oral cavity, and pharynx.

Several years ago, I was quoted in a CFS article as follows, "Every time you look closely at someone with this disease, you see immense suffering. There appears to be no limit as to the human toll that this disease is capable of exerting on patients."

Given the seriousness of this illness, I hope that this information provides you with some additional details that you or your physicians or others may not have known previously. Please feel free to contact us at the National CFIDS Foundation if we can be of further assistance to you.

ASK BERNIE THE ATTORNEY

By Bernard A. Kansky, Esq. – Copyright 2022

Q. I need to obtain Social Security Disability Benefits for the totally disabling Myalgic Encephalomyeliitis/CFIDS symptoms which I have been suffering for years. Despite all of the tests, examinations, and other reviews I have undergone, Social Security says they still do not have enough information. I believe they have enough information, but they do not know how to interpret the information which they have and have no understanding of Myalgic Encephalomyelitis/CFIDS to award me benefits to which I should be entitled. What tests or evidence can I provide them which will hopefully convince them that I am entitled to Social Security Disability Benefits?

A. The most favorable tests which I would recommend, which they should be able to understand and act upon favorably, would be the CPET Test (Cardiacpulmonary Exercise Test) and the Ten Minute Lean Test, where you go from a supine position to a standing position which results in a sudden increase of blood pressure and a sudden change in pulse.

The CPET Test should be performed on two (2) consecutive days, for the most accurate results and all tests and blood work should be carefully reported by your treating physician and should be accompanied by your disabling symptom check list.

If you have any questions for Bernie, please send them to: "Ask Bernie The Attorney," c/o The National CFIDS Foundation, Inc. 285 Beach Ave., Hull, MA 02045-1602, or email gailronda@aol.com. Keep fighting for what is right!

WHEN COMORBIDITIES BECOME CALAMITIES

By Kathy Collett (Twitter: @kathycollett7) – Copyright 2022

Long-Term Myalgic Encephalomyelitis patients have been concerned about the reframing of the disease which often feeds into the hands of those medical professionals who deny the existence of it.

Early research offered a lot and identified physical abnormalities and the researchers shared it at many ME conferences over the years. They forged connections with each other and the conferences were reported in various newsletters keeping patients and only those who know of the research from more recent times informed.

So, what happened? I believe as there has been a distinct lack of interest in ME by some GPs and specialists, it has resulted in various patients setting themselves up as authorities. On occasion they are completely unaware of the history and only know of research from more recent times. One person has been attempting to reframe ME by giving her slant on it and has added on unrelated comorbidities. She introduced a lot of different ones contrasting with the CDC's small number which are:

Fibromyalgia

Irritable Bowel Syndrome

Anxiety and Depression

Allergies and chemical sensitivities

The Canadian Consensus Criteria includes:

Myofascial Pain Syndrome (MPS)

Temporomandibular Joint Syndrome (TMJ)

Interstitial Cystitis

Raynaud's Phenomenon

Prolapsed Mitral Valve

Added to the above are the following from the International Consensus:

Hashimoto's Thyroiditis

Siccas

While Dr. Jay A. Goldstein included:

Dyspnea Sensory gating*

In Dr. David Bell's book, “The Disease of a Thousand Names,” he lists approximately 50 ME symptoms of which I have 40. I feel this clarifies whether or not a person has ME and is an ideal starting point.

Dr. Jay Goldstein's books revolved around neuroscience and brain dysfunction. He based this on his earlier research where he identified a decreased blood flow to the brains of patients using SPECT scans conducted with Dr. Mena in the late 1980s. This was followed by his groundbreaking books, “The Limbic Hypothesis,” “Betrayal By The Brain,” and “Tuning the Brain.” The scans provide proof of an organic disease and have been repeated many times over.

A former researcher who has ME started following me on Twitter and when she discovered my tweets regarding the above brain flow problems, she started tweeting it up to three times a week. At no point did she acknowledge Drs. Goldstein and Mena even when I pointed it out much later on. I think it is unethical when researchers don't acknowledge previous researchers’ work and reproduce it. This same person has added a lot of comorbidities and it is confusing, making it difficult to identify proof of connection. She also got excited when I mentioned Dr. Bell's book and she was clearly unaware of him, too. She then featured another of his books on Twitter. She developed the illness after the retirement of Drs. Goldstein and Bell and, although they documented their findings in the books, she didn't know about them.

It's been difficult for long-term ME patients to witness what has happened particularly when things were very progressive decades ago.

*Neural processes of filtering out redundant or irrelevant stimuli from all possible environmental stimuli reaching the brain. It prevents an overload of information in the higher cortical centers of the brain.

MEDICAL JOURNAL SUMMARIES

Clinical overlap between fibromyalgia and myalgic encephalomyelitis. A systematic review and meta-analysis

Ricardo Ramírez-Morales , Elyzabeth Bermúdez-Benítez, Laura-Aline Martínez-Martínez, Manuel Martínez-Lavín Autoimmun Rev 2022 Jun 8;103129. PMID: 35690247

Abstract: Myalgic encephalomyelitis is an illness characterized by profound malaise after mental or physical effort occurring in patients already suffering from constant fatigue. On the other hand, widespread pain and widespread allodynia are the core fibromyalgia clinical features. There is controversy on these two syndromes alikeness. Through the years, different diagnostic and/or classification criteria have been put forward to appraise both fibromyalgia and myalgic encephalomyelitis. The epidemiology of these two illnesses, and their overlap, may vary accordingly to the used definition. The most recent Wolfe et al. 2016 fibromyalgia diagnostic criteria incorporates three myalgic encephalomyelitis features including fatigue, waking unrefreshed and dyscognition. The objective of this meta-analysis was to define the clinical overlap between fibromyalgia and myalgic encephalomyelitis based on a systematic literature review.

Methods: PubMed, Embase, Lilacs, and Cochrane data bases were searched on January 25, 2021 linking the medical subject heading "Fibromyalgia" to the following terms "chronic fatigue syndrome", "myalgic encephalomyelitis" and "systemic exertion intolerance disease". Our review included all original articles in which the clinical overlap between fibromyalgia and

myalgic encephalomyelitis could be quantified based on recognized diagnostic or classification criteria. Articles scrutiny and selection followed the PRISMA guidelines. Each study quality was assessed according to GRADE recommendations. The global clinical overlap was calculated using a fixed effect model with inverse variance-weighted average method.

Results: Twenty one publications were included in the meta-analysis. Reviewed studies were highly dissimilar in their design, objectives, sample size, diagnostic criteria, and/or outcomes yielding a 98% heterogeneity index. Nevertheless, the clinical overlap between fibromyalgia and myalgic encephalomyelitis was a well defined outcome that could be reliably calculated despite the high heterogeneity value. All reviewed publications had moderate GRADE evidence level. Most evaluated articles used the old 1990 Wolfe et al. fibromyalgia diagnostic criteria. Myalgic encephalomyelitis and fibromyalgia diagnoses overlapped in 47.3% (95% CI: 45.97-48.63) of the reported cases.

Conclusion: This meta-analysis found prominent clinical overlap between fibromyalgia and myalgic encephalomyelitis. It seems likely that this concordance would be even higher when using the most recent Wolfe et al. 2016 fibromyalgia diagnostic criteria.

Comparing Operationalized Approaches for Substantial Reduction of Functioning in Chronic Fatigue Syndrome and Myalgic Encephalomyelitis

Elzbieta Wiedbusch, Leonard A Jason Arch Community Med . 2022;4(1):59-63. PMID: 35673386

Abstract: A core criterion for Chronic Fatigue Syndrome (CFS) and Myalgic Encephalomyelitis (ME) is a substantial reduction in functioning from pre-illness levels. Despite its ubiquity in diagnostic criteria, there is considerable debate regarding how to measure this domain. The current study assesses five distinct methods for measuring substantial reductions. The analysis used an international, aggregated dataset of patients (N = 2,368) and controls (N=359) to compare the effectiveness of each method. Four methods involved sophisticated analytic approaches using the Medical Outcomes Survey Short Form-36; the fifth method included a single self-report item on the DePaul Symptom Questionnaire (DSQ). Our main finding was that all methods produced comparable results, though the DSQ item was the most valid in differentiating patients from controls. Having a simple, reliable method to capture a substantial reduction in functioning has considerable advantages for patients and health care workers.

The Role of Kynurenine Pathway and NAD + Metabolism in Myalgic Encephalomyelitis/Chronic Fatigue Syndrome

Mona Dehhaghi, Hamed Kazemi Shariat Panahi, Bahar Kavyani, Benjamin Heng, Vanessa Tan, Nady Braidy, Gilles J Guillemin Aging Dis 2022 Jun 1;13(3):698-711. PMID: 35656104

Abstract: Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) is a serious, complex, and highly debilitating long-term illness. People with ME/CFS are typically unable to carry out their routine activities. Key hallmarks of the disease are neurological and gastrointestinal impairments accompanied by pervasive malaise that is exacerbated after physical and/or mental activity. Currently, there is no validated cure of biomarker signature for this illness. Impaired tryptophan (TRYP) metabolism is thought to play significant role in the pathobiology of ME/CFS. TRYP is an important precursor for serotonin and the essential pyridine nucleotide nicotinamide adenine dinucleotide (NAD+). TRYP has been associated with the development of some parts of the brain responsible for behavioural functions. The main catabolic route for TRYP is the kynurenine pathway (KP). The KP produces NAD+ and several neuroactive metabolites with neuroprotective (i.e., kynurenic acid (KYNA)) and neurotoxic (i.e., quinolinic acid (QUIN)) activities. Hyperactivation of the KP, whether compensatory or a driving mechanism of degeneration can limit the availability of NAD+ and exacerbate the symptoms of ME/CFS. This review discusses the potential association of altered KP metabolism in ME/CFS. The review also evaluates the role of the patient's gut microbiota on TRYP availability and KP activation. We propose that strategies aimed at raising the levels of NAD+ (e.g., using nicotinamide mononucleotide and nicotinamide riboside) may be a promising intervention to overcome symptoms of fatigue and to improve the quality of life in patients with ME/CFS. Future clinical trials should further assess the potential benefits of NAD+ supplements for reducing some of the clinical features of ME/CFS.

The Pathobiology of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: The Case for Neuroglial Failure

Herbert Renz-Polster, Marie-Eve Tremblay, Dorothee Bienzle, Joachim E Fischer Front Cell Neurosci 2022 May 9;16:888232. PMID: 35614970

Abstract: Although myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) has a specific and distinctive profile of clinical features, the disease remains an enigma because causal explanation of the pathobiological matrix is lacking. Several potential disease mechanisms have been identified, including immune abnormalities, inflammatory activation, mitochondrial alterations, endothelial and muscular disturbances, cardiovascular anomalies, and dysfunction of the peripheral and central nervous systems. Yet, it remains unclear whether and how these pathways may be related and orchestrated. Here we explore the hypothesis that a common

denominator of the pathobiological processes in ME/CFS may be central nervous system dysfunction due to impaired or pathologically reactive neuroglia (astrocytes, microglia and oligodendrocytes). We will test this hypothesis by reviewing, in reference to the current literature, the two most salient and widely accepted features of ME/CFS, and by investigating how these might be linked to dysfunctional neuroglia. From this review we conclude that the multifaceted pathobiology of ME/CFS may be attributable in a unifying manner to neuroglial dysfunction. Because the two key features - post exertional malaise and decreased cerebral blood flow - are also recognized in a subset of patients with post-acute sequelae COVID, we suggest that our findings may also be pertinent to this entity.

Aberrations in the Cross-Talks Among Redox, Nuclear Factor-κB, and Wnt/ß-Catenin Pathway Signaling Underpin Myalgic Encephalomyelitis and Chronic Fatigue Syndrome

Michael Maes, Marta Kubera, Magdalena Kotańska Front Psychiatry 2022 May 6;13:822382. PMID: 35599774

Abstract: There is evidence that chronic fatigue spectrum disorders (CFAS-Ds), including myalgic encephalomyelitis (ME), chronic fatigue syndrome (CFS), and chronic fatigue with physiosomatic symptoms including when due to comorbid medical disease, are characterized by neuroimmune and neuro-oxidative biomarkers. This study was performed to delineate the protein-protein interaction (PPI) network of CFAS-D and to discover the pathways, molecular patterns, and domains enriched in their PPI network. We performed network, enrichment, and annotation analyses using differentially expressed proteins and metabolics, which were established in patients with CFAS-D. The PPI network analysis revealed that the backbone of the highly connective CFAS-D network comprises NFKB1, CTNNB1, ALB, peroxides, NOS2, tumor necrosis factor (TNF), and interleukin-6 (IL-6) and that the network comprises interconnected immune-oxidative-nitrosative and Wnt/ß-catenin subnetworks. Multiomics enrichment analysis shows that the CFAS-D network is highly significantly associated with cellular (antioxidant) detoxification, hydrogen peroxide metabolic process, peroxidase and oxidoreductase activity, interleukin-10 (IL-10) anti-inflammatory signaling and neurodegenerative canonical Wnt, the ß-catenin complex, cadherin domains, cell-cell junctions and TLR2/4 pathways, and the transcription factors nuclear factor kappa B (NF-κB) and RELA. The top 10 DOID annotations of the CFAS-D network include four intestinal, three immune system disorders, cancer, and infectious disease. The custom Gene Ontology (GO) term annotation analysis revealed that the CFAS-D network is associated with a response to a toxic substance, lipopolysaccharides, bacterium, or virus. In conclusion, CFAS-D may be triggered by a variety of stimuli and their effects are mediated by aberrations in the cross-talks between redox, NF-κB,

and Wnt/ß-catenin signaling pathways leading to dysfunctions in multicellular organismal homeostatic processes.

Cytokine network analysis in a community-based pediatric sample of patients with myalgic encephalomyelitis/chronic fatigue syndrome

Leonard A Jason, Caroline L Gaglio, Jacob Furst, Mohammed Islam, Matthew Sorenson, Karl E Conroy, Ben Z Katz

Objectives: Studies have demonstrated immune dysfunction in adolescents with Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS); however, evidence is varied. The current study used network analysis to examine relationships between cytokines among a sample of pediatric participants with ME/CFS.

Methods: 10,119 youth aged 5-17 in the Chicagoland area were screened for ME/CFS; 111 subjects and controls were brought in for a physician examination and completed a blood draw. Youth were classified as controls (Cs, N = 43), ME/CFS (N = 23) or severe (S-ME/CFS, N = 45). Patterns of plasma cytokine networks were analyzed.

Results: All participant groups displayed a primary network of interconnected cytokines. In the ME/CFS group, inflammatory cytokines IL-12p70, IL-17A, and IFN-γ were connected and included in the primary membership, suggesting activation of inflammatory mechanisms. The S-ME/CFS group demonstrated a strong relationship between IL-17A and IL-23, a connection associated with chronic inflammation. The relationships of IL-6 and IL-8 in ME/CFS and S-ME/CFS participants also differed from Cs. Together, these results indicate pro-inflammatory responses in our illness populations. Discussion: Our data imply biological differences between our three participant groups, with ME/CFS and S-ME/CFS participants demonstrating an inflammatory profile. Examining co-expression of cytokines may aid in the identification of a biomarker for pediatric ME/CFS.

Alteration of Cortical Volume and Thickness in Myalgic Encephalomyelitis/Chronic Fatigue Syndrome

Kiran Thapaliya, Sonya Marshall-Gradisnik, Donald Staines, Jiasheng Su, Leighton Barnden Front Neurosci 2022 Apr 22;16:848730. PMID: 35527811

Abstract: Myalgic Encephalomyelitis/Chronic fatigue syndrome (ME/CFS) patients suffer from neurocognitive impairment. In this study, we investigated cortical volumetric and thickness changes in ME/CFS patients and healthy controls (HC). We estimated mean surface-based cortical volume and thickness from 18 ME/CFS patients who met International Consensus

Criteria (ICC) and 26 HC using FreeSurfer. Vertex-wise analysis showed significant reductions in the caudal middle frontal gyrus ($p = 0.0016$) and precuneus ($p = 0.013$) thickness in ME/CFS patients compared with HC. Region based analysis of sub-cortical volumes found that amygdala volume ($p = 0.002$) was significantly higher in ME/CFS patients compared with HC. We also performed interaction-with-group regressions with clinical measures to test for cortical volume and thickness correlations in ME/CFS with opposite slopes to HC (abnormal). ME/CFS cortical volume and thickness regressions with fatigue, heart-rate variability, heart rate, sleep disturbance score, respiratory rate, and cognitive performance were abnormal. Our study demonstrated different cortical volume and thickness in ME/CFS patients and showed abnormal cortical volume and thickness regressions with key symptoms of ME/CFS patients.

Neurovascular Dysregulation and Acute Exercise Intolerance in ME/CFS: A Randomized, PlaceboControlled Trial of Pyridostigmine

Phillip Joseph, Rosa Pari, Sarah Miller, Arabella Warren, Mary Catherine Stovall, Johanna Squires, Chia-Jung Chang, Wenzhong Xiao, Aaron B Waxman, David M Systrom Chest 2022 May 5;S0012-3692(22)00890-X. PMID: 35526605

Abstract: Background: Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) is characterized by intractable fatigue, post-exertional malaise, and orthostatic intolerance, but its pathophysiology is poorly understood. Pharmacologic cholinergic stimulation was used to test the hypothesis that neurovascular dysregulation underlies exercise intolerance in ME/CFS. Research question: Does neurovascular dysregulation contribute to exercise intolerance in ME/CFS and can its treatment improve exercise capacity?

Methods: Forty-five subjects with ME/CFS were enrolled in a single-center, randomized, double-blind, placebo-controlled trial. Subjects were assigned in a 1:1 ratio to receive a 60 mg dose of oral pyridostigmine or placebo after an invasive cardiopulmonary exercise test (iCPET). A second iCPET was performed 50 minutes later. The primary end point was the difference in peak exercise oxygen uptake (VO2). Secondary end points included exercise pulmonary and systemic hemodynamics and gas exchange.

Results: Twenty-three subjects were assigned to pyridostigmine and 22 to placebo. The peak VO2 increased after pyridostigmine but decreased after placebo (13.3 ± 13.4 mL/min vs. -40.2 ± 21.3 mL/min, $P<0.05$). The treatment effect of pyridostigmine was 53.6 mL/min (95% CI, -105.2 to -2.0). Peak versus rest VO2 (25.9 ± 15.3 mL/min vs. -60.8 ± 25.6 mL/min, $P<0.01$), cardiac output (-0.2 ± 0.6 L/min vs. -1.9 ± 0.6 L/min, $P<0.05$), and RAP (1.0 ± 0.5 mm Hg vs. -0.6 ± 0.5 mm Hg, $P<0.05$) were greater in the pyridostigmine group compared to placebo.

Interpretation: Pyridostigmine improves peak VO2 in ME/CFS by increasing cardiac output and right ventricular filling pressures. Worsening peak exercise VO2, Qc, and RAP after placebo may signal the onset of post-exertional malaise. We suggest treatable neurovascular dysregulation underlies acute exercise intolerance in ME/CFS.

Impact of myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) on the quality of life of people with ME/CFS and their partners and family members: an online cross-sectional survey

Jui Vyas, Nina Muirhead, Ravinder Singh , Rachel Ephgrave, Andrew Y Finlay BMJ Open 2022 May 2;12(5):e058128. PMID: 35501074

Objectives: The aim of this study was to assess the impact of myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) on the quality of life (QoL) of people with ME/CFS and their relative or partner (family member).

Design: A patient-partner, multinational, subject-initiated, cross-sectional online survey.

Setting: International survey using ME/CFS charities, support groups and social media.

Participants: Participants were self-selected with recruitment via social media. Inclusion criteria were aged 18 years or over and reported diagnosis of ME/CFS by health professional. 1418 people with ME/CFS and their 1418 family members from 30 countries participated in the survey. Participants with ME/CFS had a mean age of 45.8 years (range 18-81) and were predominantly women (1214 (85.6%) of 1418). Family members had a mean age of 51.9 years (range 18-87) and were predominantly men (women: 504 (35.5%) of 1418). 991 (70%) family members were partners of the people with ME/CFS.

Interventions: EuroQoL-5 Dimension (EQ-5D-3L), completed by people with ME/CFS, and Family Reported Outcome Measure (FROM-16) questionnaire, completed by family members.

Results: The mean overall health status on a Visual Analogue Scale for people with ME/CFS was 33.8 (0=worst, 100=best). People with ME/CFS were most affected by ability to perform usual activities, pain, mobility, self-care and least impacted by anxiety. For family members, the overall mean FROM16 score was 17.9 (0=no impact, 32=worst impact), demonstrating a major impact on QoL. Impact on QoL was significantly correlated between the person with ME/CFS and their family member ($p<0.0001$). Family members were most impacted emotionally by worry, frustration and sadness and personally by family activities, holidays, sex life and finances.

Conclusions: To the best of our knowledge, this is the largest study on the impact of the QoL of persons with ME/CFS and their family members. While open participation surveys are limited by selection bias, this research has revealed a significant worldwide burden of ME/CFS on the QoL of people with ME/CFS and their family members.

Molecular Hydrogen as a Medical Gas for the Treatment of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: Possible Efficacy Based on a Literature Review

Shin-Ichi Hirano, Yusuke Ichikawa, Bunpei Sato, Yoshiyasu Takefuji, Fumitake Satoh Front Neurol 2022 Apr 11;13:841310. PMID: 35493814

Abstract: Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) is a disorder that is characterized by fatigue that persists for more than 6 months, weakness, sleep disturbances, and cognitive dysfunction. There are multiple possible etiologies for ME/CFS, among which mitochondrial dysfunction plays a major role in abnormal energy metabolism. The potential of many substances for the treatment of ME/CFS has been examined; however, satisfactory outcomes have not yet been achieved. The development of new substances for curative, not symptomatic, treatments is desired. Molecular hydrogen (H2) ameliorates mitochondrial dysfunction by scavenging hydroxyl radicals, the most potent oxidant among reactive oxygen species. Animal experiments and clinical trials reported that H2 exerted ameliorative effects on acute and chronic fatigue. Therefore, we conducted a literature review on the mechanism by which H2 improves acute and chronic fatigue in animals and healthy people and showed that the attenuation of mitochondrial dysfunction by H2 may be involved in the ameliorative effects. Although further clinical trials are needed to determine the efficacy and mechanism of H2 gas in ME/CFS, our literature review suggested that H2 gas may be an effective medical gas for the treatment of ME/CFS.

EBV/HHV-6A dUTPases contribute to myalgic encephalomyelitis/chronic fatigue syndrome pathophysiology by enhancing TFH cell differentiation and extrafollicular activities

Brandon S Cox, Khaled Alharshawi, Irene Mena-Palomo, William P Lafuse, Maria Eugenia Ariza JCI Insight 2022 Jun 8;7(11):e158193. PMID: 35482424

Abstract: Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) is a chronic, debilitating, multisystem illness of unknown etiology for which no cure and no diagnostic tests are available. Despite increasing evidence implicating EBV and human herpesvirus 6A (HHV-6A) as potential causative infectious agents in a subset of patients with ME/CFS, few mechanistic studies address a causal relationship. In this study we examined a large ME/CFS cohort and controls and demonstrated a significant increase in activin A and IL-21 serum levels, which

correlated with seropositivity for antibodies against the EBV and HHV-6 protein deoxyuridine triphosphate nucleotidohydrolase (dUTPases) but no increase in CXCL13. These cytokines are critical for T follicular helper (TFH) cell differentiation and for the generation of high-affinity antibodies and long-lived plasma cells. Notably, ME/CFS serum was sufficient to drive TFH cell differentiation via an activin A-dependent mechanism. The lack of simultaneous CXCL13 increase with IL-21 indicates impaired TFH function in ME/CFS. In vitro studies revealed that virus dUTPases strongly induced activin A secretion while in vivo, EBV dUTPase induced the formation of splenic marginal zone B and invariant NKTFH cells. Together, our data indicate abnormal germinal center (GC) activity in participants with ME/CFS and highlight a mechanism by which EBV and HHV6 dUTPases may alter GC and extrafollicular antibody responses.

Bodies in lockdown: Young women's narratives of falling severely ill with ME/CFS during childhood and adolescence

Silje Helen Krabbe, Anne Marit Mengshoel, Wenche Schrøder Bjorbækmo, Unni Sveen, Karen Synne Groven Health Care Women Int 2022 Apr 11;1-23. PMID: 35404768

Abstract: Thirteen women (16-30 years) storied their experiences about the process of falling severely ill with Myalgic Encephalomyelitis/Chronic Fatigue Syndrome during childhood and adolescence. We performed a narrative analysis informed by phenomenology which yielded three central themes: The active and meaningful life I used to live; gradually developing unhomeliness and feeling pushed toward the edge; and left abandoned on the sidelines. Out of the incomprehensible and unpredictable emerges an understanding of the scale of their ordeal, along with advice that may have made it worse. This portrays a gradual developing uncertain, unhomely life situation with no outlooks for future recovery.

Plasma metabolomics reveals disrupted response and recovery following maximal exercise in myalgic encephalomyelitis/chronic fatigue syndrome

Arnaud Germain, Ludovic Giloteaux, Geoffrey E Moore, Susan M Levine, John K Chia, Betsy A Keller, Jared Stevens, Carl J Franconi, Xiangling Mao, Dikoma C Shungu, Andrew Grimson, Maureen R Hanson JCI Insight 2022 May 9;7(9):e157621. PMID: 35358096

Abstract: Post-exertional malaise (PEM) is a hallmark symptom of myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS). We monitored the evolution of 1157 plasma metabolites in 60 ME/CFS (45 female, 15 male) and 45 matched healthy control participants (30 female, 15 male) before and after 2 maximal cardiopulmonary exercise test (CPET) challenges separated by 24 hours, with the intent of provoking PEM in patients. Four time points allowed exploration of the metabolic response to maximal energy-producing capacity

and the recovery pattern of participants with ME/CFS compared with the healthy control group. Baseline comparison identified several significantly different metabolites, along with an enriched percentage of yet-to-be identified compounds. Additionally, temporal measures demonstrated an increased metabolic disparity between cohorts, including unknown metabolites. The effects of exertion in the ME/CFS cohort predominantly highlighted lipid-related as well as energy-related pathways and chemical structure clusters, which were disparately affected by the first and second exercise sessions. The 24-hour recovery period was distinct in the ME/CFS cohort, with over a quarter of the identified pathways statistically different from the controls. The pathways that are uniquely different 24 hours after an exercise challenge provide clues to metabolic disruptions that lead to PEM. Numerous altered pathways were observed to depend on glutamate metabolism, a crucial component of the homeostasis of many organs in the body, including the brain.

Volumetric differences in hippocampal subfields and associations with clinical measures in myalgic encephalomyelitis/chronic fatigue syndrome

Kiran Thapaliya, Donald Staines, Sonya Marshall-Gradisnik, Jiasheng Su, Leighton Barnden J Neurosci Res 2022 Jul;100(7):1476-1486. PMID: 35355311

Abstract: Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) patients suffer from a cognitive and memory dysfunction. Because the hippocampus plays a key role in both cognition and memory, we tested for volumetric differences in the subfields of the hippocampus in ME/CFS. We estimated hippocampal subfield volumes for 25 ME/CFS patients who met Fukuda criteria only (ME/CFSFukuda), 18 ME/CFS patients who met the stricter ICC criteria (ME/CFSICC), and 25 healthy controls (HC). Group comparisons with HC detected extensive differences in subfield volumes in ME/CFSICC but not in ME/CFSFukuda . ME/CFSICC patients had significantly larger volume in the left subiculum head ($p < 0.001$), left presubiculum head ($p = 0.0020$), and left fimbria ($p = 0.004$). Correlations of hippocampus subfield volumes with clinical measures were stronger in ME/CFSICC than in ME/CFSFukuda patients. In ME/CFSFukuda patients, we detected positive correlations between fatigue and hippocampus subfield volumes and a negative correlation between sleep disturbance score and the right CA1 body volume. In ME/CFSICC patients, we detected a strong negative relationship between fatigue and left hippocampus tail volume. Strong negative relationships were also detected between pain and SF36 physical scores and two hippocampal subfield volumes (left: GC-ML-DG head and CA4 head). Our study demonstrated that volumetric differences in hippocampal subfields have strong statistical inference for patients meeting the ME/CFSICC case definition and confirms hippocampal involvement in the cognitive and memory problems of ME/CFSICC patients.

Predictors for Developing Severe Myalgic Encephalomyelitis/Chronic Fatigue Syndrome Following Infectious Mononucleosis

Leonard A Jason, Joseph Cotler, Mohammed F Islam, Jacob Furst, Ben Z Katz J Rehabil Ther 2022;4(1):1-5. PMID: 35350440

Background: About 10% of individuals who contract infectious mononucleosis (IM) have symptoms 6 months later that meet criteria for myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS). Our study for the first time examined whether it is possible to predict who will develop ME/CFS following IM.

Methods: We have reported on a prospectively recruited cohort of 4,501 college students, of which 238 (5.3%) developed IM. Those who developed IM were followed-up at six months to determine whether they recovered or met criteria for ME/CFS. The present study focuses on 48 students who after six months had a diagnosis of ME/CFS, and a matched control group of 58 students who had no further symptoms after their IM. All of these 106 students had data at baseline (at least 6 weeks prior to the development of IM), when experiencing IM, and 6 months following IM. Of those who did not recover from IM, there were two groups: 30 were classified as ME/CFS and 18 were classified as severe ME/CFS. We measured the results of 7 questionnaires, physical examination findings, the severity of mononucleosis and cytokine analyses at baseline (pre-illness) and at the time of IM. We examined predictors (e.g., pre-illness variables as well as variables at onset of IM) of those who developed ME/CFS and severe ME/CFS following IM.

Perspective: Drawing on Findings From Critical Illness to Explain Myalgic Encephalomyelitis/Chronic Fatigue Syndrome

Dominic Stanculescu, Jonas Bergquist Front Med (Lausanne) 2022 Mar 8;9:818728. PMID: 35345768

Abstract: We propose an initial explanation for how myalgic encephalomyelitis / chronic fatigue syndrome (ME/CFS) could originate and perpetuate by drawing on findings from critical illness research. Specifically, we combine emerging findings regarding (a) hypoperfusion and endotheliopathy, and (b) intestinal injury in these illnesses with our previously published hypothesis about the role of (c) pituitary suppression, and (d) low thyroid hormone function associated with redox imbalance in ME/CFS. Moreover, we describe interlinkages between these pathophysiological mechanisms as well as "vicious cycles" involving cytokines and inflammation that may contribute to explain the chronic nature of these illnesses. This paper summarizes and expands on our previous publications about the relevance of findings from critical illness for ME/CFS. New knowledge on diagnostics, prognostics and treatment strategies could be gained

through active collaboration between critical illness and ME/CFS researchers, which could lead to improved outcomes for both conditions.

Long Covid at the crossroads: Comparisons and lessons from the treatment of patients with myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS)

Joanne Hunt, Charlotte Blease, Keith J Geraghty J Health Psychol 2022 Mar 27;13591053221084494. PMID: 35341334

Abstract: Whilst parallels have been drawn between Long Covid and myalgic encephalomyelitis/ chronic fatigue syndrome (ME/CFS), there is a well-documented history of negative stereotyping and marginalisation of patients with ME/CFS. A socio-politically oriented comparison of scientific, clinical and societal responses to Long Covid and ME/CFS is thus important to prevent similar harms arising among Long Covid patients. We identify four reasons for injustices in the treatment of ME/CFS patients, and discuss the risk of Long Covid following a similar trajectory. We conclude with policy and practice recommendations to help prevent such injustices arising again, including consideration of critical reflexivity in medical education.

Genetic association study in myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) identifies several potential risk loci

Riad Hajdarevic 1 , Asgeir Lande 2 , Jesper Mehlsen 3 , Anne Rydland 4 , Daisy D Sosa 5 , Elin B Strand 6 , Olav Mella 7 , Flemming Pociot 8 , Øystein Fluge 7 , Benedicte A Lie 9 , Marte K Viken 10 Affiliations PMID: 35318112 DOI: 10.1016/j.bbi.2022.03.010

Abstract: Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) is a disease of unknown etiology and pathogenesis, which manifests in a variety of symptoms like post-exertional malaise, brain fog, fatigue and pain. Hereditability is suggested by an increased disease risk in relatives, however, genome-wide association studies in ME/CFS have been limited by small sample sizes and broad diagnostic criteria, therefore no established risk loci exist to date. In this study, we have analyzed three ME/CFS cohorts: a Norwegian discovery cohort (N = 427), a Danish replication cohort (N = 460) and a replication dataset from the UK biobank (N = 2105). To the best of our knowledge, this is the first ME/CFS genome-wide association study of this magnitude incorporating 2532 patients for the genome-wide analyses and 460 patients for a targeted analysis. Even so, we did not find any ME/CFS risk loci displaying genome-wide significance. In the Norwegian discovery cohort, the TPPP gene region showed the most significant association (rs115523291, P = 8.5 × 10-7), but we could not replicate the top SNP. However, several other SNPs in the TPPP gene identified in the Norwegian discovery cohort showed modest association signals in the self-reported UK biobank CFS cohort, which was also

present in the combined analysis of the Norwegian and UK biobank cohorts, TPPP (rs139264145; P = 0.00004). Interestingly, TPPP is expressed in brain tissues, hence it will be interesting to see whether this association, with time, will be verified in even larger cohorts. Taken together our study, despite being the largest to date, could not establish any ME/CFS risk loci, but comprises data for future studies to accumulate the power needed to reach genome-wide significance.

Genetic association study in myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) identifies several potential risk loci

Riad Hajdarevic, Asgeir Lande, Jesper Mehlsen, Anne Rydland, Daisy D Sosa, Elin B Strand, Olav Mella, Flemming Pociot, Øystein Fluge, Benedicte A Lie, Marte K Viken Brain Behav Immun 2022 May;102:362-369. PMID: 35318112

Abstract: Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) is a disease of unknown etiology and pathogenesis, which manifests in a variety of symptoms like post-exertional malaise, brain fog, fatigue and pain. Hereditability is suggested by an increased disease risk in relatives, however, genome-wide association studies in ME/CFS have been limited by small sample sizes and broad diagnostic criteria, therefore no established risk loci exist to date. In this study, we have analyzed three ME/CFS cohorts: a Norwegian discovery cohort (N = 427), a Danish replication cohort (N = 460) and a replication dataset from the UK biobank (N = 2105). To the best of our knowledge, this is the first ME/CFS genome-wide association study of this magnitude incorporating 2532 patients for the genomewide analyses and 460 patients for a targeted analysis. Even so, we did not find any ME/CFS risk loci displaying genome-wide significance. In the Norwegian discovery cohort, the TPPP gene region showed the most significant association (rs115523291, P = 8.5 × 10-7), but we could not replicate the top SNP. However, several other SNPs in the TPPP gene identified in the Norwegian discovery cohort showed modest association signals in the self-reported UK biobank CFS cohort, which was also present in the combined analysis of the Norwegian and UK biobank cohorts, TPPP (rs139264145; P = 0.00004). Interestingly, TPPP is expressed in brain tissues, hence it will be interesting to see whether this association, with time, will be verified in even larger cohorts. Taken together our study, despite being the largest to date, could not establish any ME/CFS risk loci, but comprises data for future studies to accumulate the power needed to reach genome-wide significance.

NCF COMMENT: Tubulin polymerization-promoting protein is a protein that in humans is encoded by the TPPP gene. This protein has been linked to multiple sclerosis myelin lesions and CSF abnormalities in multiple sclerosis patients. This has also been linked to Parkinson's and Alzheimer's Disease.

Endothelial dysfunction and altered endothelial biomarkers in patients with post-COVID-19 syndrome and chronic fatigue syndrome (ME/CFS)

Milan Haffke, Helma Freitag, Gordon Rudolf, Martina Seifert, Wolfram Doehner, Nadja Scherbakov, Leif Hanitsch, Kirsten Wittke, Sandra Bauer, Frank Konietschke, Friedemann Paul, Judith BellmannStrobl, Claudia Kedor, Carmen Scheibenbogen, Franziska Sotzny J Transl Med 2022 Mar 22;20(1):138. PMID: 35317812

Background: Fatigue, exertion intolerance and post-exertional malaise are among the most frequent symptoms of Post-COVID Syndrome (PCS), with a subset of patients fulfilling criteria for Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS). As SARS-CoV-2 infects endothelial cells, causing endotheliitis and damaging the endothelium, we investigated endothelial dysfunction (ED) and endothelial biomarkers in patients with PCS.

Methods: We studied the endothelial function in 30 PCS patients with persistent fatigue and exertion intolerance as well as in 15 age- and sex matched seronegative healthy controls (HCs). 14 patients fulfilled the diagnostic criteria for ME/CFS. The other patients were considered to have PCS. Peripheral endothelial function was assessed by the reactive hyperaemia index (RHI) using peripheral arterial tonometry (PAT) in patients and HCs. In a larger cohort of patients and HCs, including postCOVID reconvalescents (PCHCs), Endothelin-1 (ET-1), Angiopoietin-2 (Ang-2), Endocan (ESM-1), IL-8, Angiotensin-Converting Enzyme (ACE) and ACE2 were analysed as endothelial biomarkers.

Results: Five of the 14 post-COVID ME/CFS patients and five of the 16 PCS patients showed ED defined by a diminished RHI (< 1.67), but none of HCs exhibited this finding. A paradoxical positive correlation of RHI with age, blood pressure and BMI was found in PCS but not ME/CFS patients. The ET-1 concentration was significantly elevated in both ME/CFS and PCS patients compared to HCs and PCHCs. The serum Ang-2 concentration was lower in both PCS patients and PCHCs compared to HCs.

Conclusion: A subset of PCS patients display evidence for ED shown by a diminished RHI and altered endothelial biomarkers. Different associations of the RHI with clinical parameters as well as varying biomarker profiles may suggest distinct pathomechanisms among patient subgroups.

Comparative Analysis of Extracellular Vesicles in Patients with Severe and Mild Myalgic Encephalomyelitis/Chronic Fatigue Syndrome

Hector Bonilla, Dylan Hampton, Erika G Marques de Menezes, Xutao Deng, José G Montoya, Jill Anderson, Philip J Norris Front Immunol 2022 Mar 4;13:841910. PMID: 35309313

Abstract: Myalgic encephalomyelitis, or chronic fatigue syndrome (ME/CFS) is a serious disease whose cause has yet to be identified. Objective markers of the disease are also not well understood and would serve as important tools in diagnosis and management. One potential biomarker or transmitter of immune signals in ME/CFS is the extracellular vesicle (EV) compartment. These small, membrane bound particles have been shown to play a key role in intercellular signaling. Our laboratory has focused on methods of detection of EVS in clinical samples. In this study we explored whether the prevalence of EVs in the plasma of participants with mild or severe ME/CFS differed from the plasma of healthy control participants. By staining for multiple cell surface molecules, plasma EVs could be fingerprinted as to their cell of origin. Our study revealed a significant correlation between severe ME/CSF and levels of EVs bearing the B cell marker CD19 and the platelet marker CD41a, though these changes were not significant after correction for multiple comparisons. These findings point to potential dysregulation of B cell and platelet activation or homeostasis in ME/CFS, which warrants validation in a replication cohort and further exploration of potential mechanisms underlying the association.

Cardiopulmonary, metabolic, and perceptual responses during exercise in Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS): A Multi-site Clinical Assessment of ME/CFS (MCAM) sub-study

Dane B Cook, Stephanie VanRiper, Ryan J Dougherty, Jacob B Lindheimer, Michael J Falvo, Yang Chen, Jin-Mann S Lin, Elizabeth R Unger, MCAM Study Group PLoS One 2022 Mar 15;17(3):e0265315. PMID: 35290404

Background: Cardiopulmonary exercise testing has demonstrated clinical utility in myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS). However, to what extent exercise responses are independent of, or confounded by, aerobic fitness remains unclear.

Purpose: To characterize and compare exercise responses in ME/CFS and controls with and without matching for aerobic fitness.

Methods: As part of the Multi-site Clinical Assessment of ME/CFS (MCAM) study, 403 participants (n = 214 ME/CFS; n = 189 controls), across six ME/CFS clinics, completed ramped cycle ergometry to volitional exhaustion. Metabolic, heart rate (HR), and ratings of perceived exertion (RPE) were measured. Ventilatory equivalent ([Formula: see text], [Formula: see text]), metrics of ventilatory efficiency, and chronotropic incompetence (CI) were calculated. Exercise variables were compared using Hedges' g effect size with 95% confidence intervals. Differences in cardiopulmonary and perceptual features during exercise were analyzed using linear mixed effects models with repeated measures for relative exercise intensity (20-100% peak [Formula:

see text]). Subgroup analyses were conducted for 198 participants (99 ME/CFS; 99 controls) matched for age (±5 years) and peak [Formula: see text] (~1 ml/kg/min-1).

Results: Ninety percent of tests (n = 194 ME/CFS, n = 169 controls) met standard criteria for peak effort. ME/CFS responses during exercise (20-100% peak [Formula: see text]) were significantly lower for ventilation, breathing frequency, HR, measures of efficiency, and CI and significantly higher for [Formula: see text], [Formula: see text] and RPE ($p<0.05$adjusted), and higher tidal volumes were identified for ME/CFS ($p<0.05$adjusted). Exercise responses at the gas exchange threshold, peak, and for measures of ventilatory efficiency (e.g., [Formula: see text]) were generally reflective of those seen throughout exercise (i.e., 20-100%).

Conclusion: Compared to fitness-matched controls, cardiopulmonary responses to exercise in ME/CFS are characterized by inefficient exercise ventilation and augmented perception of effort. These data highlight the importance of distinguishing confounding fitness effects to identify responses that may be more specifically associated with ME/CFS.

Review of the Midbrain Ascending Arousal Network Nuclei and Implications for Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS), Gulf War Illness (GWI) and Postexertional Malaise (PEM)

James N Baraniuk Brain Sci 2022 Jan 19;12(2):132. PMID: 35203896

Abstract: Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS and Gulf War Illness (GWI) share features of post-exertional malaise (PEM), exertional exhaustion, or postexertional symptom exacerbation. In a two-day model of PEM, submaximal exercise induced significant changes in activation of the dorsal midbrain during a high cognitive load working memory task (Washington 2020) (Baraniuk this issue). Controls had no net change. However, ME/CFS had increased activity after exercise, while GWI had significantly reduced activity indicating differential responses to exercise and pathological mechanisms. These data plus findings of the midbrain and brainstem atrophy in GWI inspired a review of the anatomy and physiology of the dorsal midbrain and isthmus nuclei in order to infer dysfunctional mechanisms that may contribute to disease pathogenesis and postexertional malaise. The nuclei of the ascending arousal network were addressed. Midbrain and isthmus nuclei participate in threat assessment, awareness, attention, mood, cognition, pain, tenderness, sleep, thermoregulation, light and sound sensitivity, orthostatic symptoms, and autonomic dysfunction and are likely to contribute to the symptoms of postexertional malaise in ME/CFS and GWI.

Saliva Fatigue Biomarker Index As a Marker for Severe Myalgic Encephalomyelitis/Chronic Fatigue Syndrome in a Community Based Sample

Leonard A Jason, John Kalns, Alicia Richarte, Ben Z Katz, Chelsea Torres Fatigue 2021;9(4):189-195. PMID: 35186443

Objective: 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. A team of physicians made a final diagnosis of ME/CFS if the participants met criteria for up to three selected case definitions following medical and psychiatric evaluations. 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.

Physiological assessment of orthostatic intolerance in chronic fatigue syndrome

Benjamin H Natelson, Jin-Mann S Lin, Michelle Blate, Sarah Khan, Yang Chen, Elizabeth R Unger J Transl Med 2022 Feb 16;20(1):95. PMID: 35172863

Background: Orthostatic intolerance-OI is common in Myalgic Encephalomyelitis/Chronic Fatigue Syndrome-ME/CFS. We used a 10-min passive vertical lean test as orthostatic challenge-OC and measured changes in vitals and end tidal CO2 (eTCO2). An abnormal physiologic response to OC was identified in 60% of the 63 patients evaluated from one to three times over several years. Hypocapnia, either resting or induced by OC, was the most frequent abnormality, followed by postural orthostatic tachycardia.

Objective: Evaluate the physiologic response of patients with ME/CFS to a standardized OC.

Design: Respiratory and heart rate, blood pressure and eTCO2 were recorded twice at the end of 10- min supine rest and then every minute during the 10-min lean. Hypocapnia was eTCO2 ≤ 32 mmHg. Orthostatic tachycardia was heart rate increase ≥ 30 beats per minute compared with resting or ≥ 120 BPM. Orthostatic hypotension was decreased systolic pressure ≥ 20 mmHg from baseline. Tachypnea was respiratory rate of ≥ 20 breaths per minute-either supine or

leaning. Questionnaire data on symptom severity, quality of life and mood were collected at visit #2.

Patients: 63 consecutive patients fulfilling the 1994 case definition for CFS underwent lean testing at first visit and then annually at visit 2 (n = 48) and 3 (n = 29).

Measures: Supine hypocapnia; orthostatic tachycardia, hypocapnia or hypotension.

Results: The majority of ME/CFS patients (60.3%, 38/63) had an abnormality detected during a lean test at any visit (51%, 50% and 45% at visits 1, 2 and 3, respectively). Hypocapnia at rest or induced by OC was more common and more likely to persist than postural orthostatic tachycardia. Anxiety scores did not differ between those with and without hypocapnia.

Conclusions: The 10-min lean test is useful in evaluation of OI in patients with ME/CFS. The most frequent abnormality, hypocapnia, would be missed without capnography.

Impaired TRPM3-dependent calcium influx and restoration using Naltrexone in natural killer cells of myalgic encephalomyelitis/chronic fatigue syndrome patients

Natalie Eaton-Fitch, Stanley Du Preez, Hélène Cabanas, Katsuhiko Muraki, Donald Staines, Sonya Marshall-Gradisnik J Transl Med 2022 Feb 16;20(1):94. PMID: 35172836

Background: Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) is a serious disorder of unknown aetiology. While the pathomechanism of ME/CFS remains elusive, reduced natural killer (NK) cell cytotoxic function is a consistent immunological feature. NK cell effector functions rely on long-term sustained calcium (Ca^{2+}) influx. In recent years evidence of transient receptor potential melastatin 3 (TRPM3) dysfunction supports the hypothesis that ME/CFS is potentially an ion channel disorder. Specifically, reports of single nucleotide polymorphisms, low surface expression and impaired function of TRPM3 have been reported in NK cells of ME/CFS patients. It has been reported that mu (μ)-opioid receptor (μOR) agonists, known collectively as opioids, inhibit TRPM3. Naltrexone hydrochloride (NTX), a μOR antagonist, negates the inhibitory action of μOR on TRPM3 function. Importantly, it has recently been reported that NTX restores impaired TRPM3 function in NK cells of ME/CFS patients.

Methods: Live cell immunofluorescent imaging was used to measure TRPM3-dependent Ca^{2+} influx in NK cells isolated from n = 10 ME/CFS patients and n = 10 age- and sex-matched healthy controls (HC) following modulation with TRPM3-agonist, pregnenolone sulfate (PregS) and TRPM3- antaognist, ononetin. The effect of overnight (24 h) NTX in vitro treatment on TRPM3-dependent Ca^{2+} influx was determined.

Results: The amplitude ($p < 0.0001$) and half-time of Ca^{2+} response ($p < 0.0001$) was significantly reduced at baseline in NK cells of ME/CFS patients compared with HC. Overnight

treatment of NK cells with NTX significantly improved TRPM3-dependent Ca2+ influx in ME/CFS patients. Specifically, there was no significance between HC and ME/CFS patients for half-time response, and the amplitude of Ca2+ influx was significantly increased in ME/CFS patients ($p < 0.0001$).

Conclusion: TRPM3-dependent Ca2+ influx was restored in ME/CFS patients following overnight treatment of isolated NK cells with NTX in vitro. Collectively, these findings validate that TRPM3 loss of function results in altered Ca2+ influx supporting the growing evidence that ME/CFS is a TRP ion channel disorder and that NTX provides a potential therapeutic intervention for ME/CFS.

Systematic review and meta-analysis of cognitive impairment in myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS)

Mehdi Aoun Sebaiti, Mathieu Hainselin, Yannick Gounden, Carmen Adella Sirbu, Slobodan Sekulic, Lorenzo Lorusso, Luis Nacul, François Jérôme Authier Sci Rep 2022 Feb 9;12(1):2157. PMID: 35140252

Abstract: Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) is commonly associated with cognitive complaints. To bring out the neuropsychological symptomatology inherent to ME/CFS, we conducted a systematic review according to PRISMA and MOOSE guidelines of the literature through the analysis of 764 studies published between 1988 and 2019 by using PubMed Central website and Clarivate analytics platform. We performed a meta-analysis to delineate an idea of the neuropsychological profile inherent in ME/CFS. The clinical picture typically affects visuo-spatial immediate memory ($g = - 0.55$, $p = 0.007$), reading speed ($g = - 0.82$, $p = 0.0001$) and graphics gesture ($g = - 0.59$, $p = 0.0001$). Analysis also revealed difficulties in several processes inherent in episodic verbal memory (storage, retrieval, recognition) and visual memory (recovery) and a low efficiency in attentional abilities. Executive functions seemed to be little or not affected and instrumental functions appeared constantly preserved. With regard to the complexity and heterogeneity of the cognitive phenotype, it turns out that determining a sound clinical picture of ME/CFS cognitive profile must go through a neuropsychological examination allowing a complete evaluation integrating the notion of agreement between the choice and the number of tests and the complexity intrinsic to the pathology.

Decreased NO production in endothelial cells exposed to plasma from ME/CFS patients

Romina Bertinat, Roberto Villalobos-Labra, Lidija Hofmann, Jennifer Blauensteiner, Nuno Sepúlveda, Francisco Westermeier Vascul Pharmacol 2022 Apr;143:106953. PMID: 35074481

Abstract: Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) is a debilitating disease characterized by severe and persistent fatigue. Along with clinical studies showing endothelial dysfunction (ED) in a subset of ME/CFS patients, we have recently reported altered ED-related microRNAs in plasma from affected individuals. Inadequate nitric oxide (NO), mainly produced by the endothelial isoform of nitric oxide synthase (eNOS) in endothelial cells (ECs), is a major cause of ED. In this study, we hypothesized that plasma from that cohort of ME/CFS patients induces eNOS-related ED in vitro. To test this, we cultured human umbilical vein endothelial cells (HUVECs) in the presence of plasma from either ME/CFS patients (ME/CFS-plasma, n = 11) or healthy controls (HC-plasma, n = 12). Then, we measured the NO production in the absence and presence of tyrosine kinase and G protein-coupled receptors agonists (TKRs and GPCRs, respectively), well-known to activate eNOS in ECs. Our data showed that HUVECs incubated with ME/CFS-plasma produced less NO either in the absence or presence of eNOS activators compared to ones in presence of HC-plasma. Also, the NO production elicited by bradykinin, histamine, and acetylcholine (GPCRs agonists) was more affected than the one triggered by insulin (TKR agonist). Finally, inhibitory eNOS phosphorylation at Thr495 was higher in HUVECs treated with ME/CFS-plasma compared to the same treatment with HC-plasma. In conclusion, this study in vitro shows a decreased NO production in HUVECs exposed to plasma from ME/CFS patients, suggesting an unreported role of eNOS in the pathophysiology of this disease.

Commonalities in the Features of Cancer and Chronic Fatigue Syndrome (CFS): Evidence for StressInduced Phenotype Instability?

Andrej Rusin, Colin Seymour, Alan Cocchetto, Carmel Mothersill Int J Mol Sci 2022 Jan 8;23(2):691. PMID: 35054876

Abstract: Chronic Fatigue Syndrome/Myalgic Encephalomyelitis (CFS/ME) and Cancer-Related Fatigue (CRF) are syndromes with considerable overlap with respect to symptoms. There have been many studies that have compared the two conditions, and some of this research suggests that the etiologies of the conditions are linked in some cases. In this narrative review, CFS/ME and cancer are introduced, along with their known and putative mechanistic connections to multiple stressors including ionizing radiation. Next, we summarize findings from the literature that suggest the involvement of HPA-axis dysfunction, the serotonergic system, cytokines and inflammation, metabolic insufficiency and mitochondrial dysfunction, and genetic changes in CRF and CFS/ME. We further suspect that the manifestation of fatigue in both diseases and its causes could indicate that CRF and CFS/ME lie on a continuum of potential biological effects which occur in response to stress. The response to this stress likely varies depending on predisposing factors such as genetic background. Finally, future research ideas are suggested with a focus on determining if common biomarkers exist in CFS/ME patients and those

afflicted with CRF. Both CFS/ME and CRF are relatively heterogenous syndromes, however, it is our hope that this review assists in future research attempting to elucidate the commonalities between CRF and CFS/ME.

Differential Effects of Exercise on fMRI of the Midbrain Ascending Arousal Network Nuclei in Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) and Gulf War Illness (GWI) in a Model of Postexertional Malaise (PEM)

James N Baraniuk, Alison Amar, Haris Pepermitwala, Stuart D Washington Brain Sci 2022 Jan 5;12(1):78. PMID: 35053821

Background: Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS), Gulf War Illness (GWI) and control subjects underwent fMRI during difficult cognitive tests performed before and after submaximal exercise provocation (Washington 2020). Exercise caused increased activation in ME/CFS but decreased activation for GWI in the dorsal midbrain, left Rolandic operculum and right middle insula. Midbrain and isthmus nuclei participate in threat assessment, attention, cognition, mood, pain, sleep, and autonomic dysfunction.

Methods: Activated midbrain nuclei were inferred by a re-analysis of data from 31 control, 36 ME/CFS and 78 GWI subjects using a seed region approach and the Harvard Ascending Arousal Network.

Results: Before exercise, control and GWI subjects showed greater activation during cognition than ME/CFS in the left pedunculotegmental nucleus. Post exercise, ME/CFS subjects showed greater activation than GWI ones for midline periaqueductal gray, dorsal and median raphe, and right midbrain reticular formation, parabrachial complex and locus coeruleus. The change between days (delta) was positive for ME/CFS but negative for GWI, indicating reciprocal patterns of activation. The controls had no changes.

Conclusions: Exercise caused the opposite effects with increased activation in ME/CFS but decreased activation in GWI, indicating different pathophysiological responses to exertion and mechanisms of disease. Midbrain and isthmus nuclei contribute to postexertional malaise in ME/CFS and GWI.

The Gut Microbiome in Myalgic Encephalomyelitis (ME)/Chronic Fatigue Syndrome (CFS)

Rahel S König, Werner C Albrich, Christian R Kahlert, Lina Samira Bahr, Ulrike Löber, Pietro Vernazza, Carmen Scheibenbogen, Sofia K Forslund Front Immunol 2022 Jan 3;12:628741.

Abstract: Myalgic encephalomyelitis (ME) or Chronic Fatigue Syndrome (CFS) is a neglected, debilitating multi-systemic disease without diagnostic marker or therapy. Despite

evidence for neurological, immunological, infectious, muscular and endocrine pathophysiological abnormalities, the etiology and a clear pathophysiology remains unclear. The gut microbiome gained much attention in the last decade with manifold implications in health and disease. Here we review the current state of knowledge on the interplay between ME/CFS and the microbiome, to identify potential diagnostic or interventional approaches, and propose areas where further research is needed. We iteratively selected and elaborated on key theories about a correlation between microbiome state and ME/CFS pathology, developing further hypotheses. Based on the literature we hypothesize that antibiotic use throughout life favours an intestinal microbiota composition which might be a risk factor for ME/CFS. Main proposed pathomechanisms include gut dysbiosis, altered gut-brain axis activity, increased gut permeability with concomitant bacterial translocation and reduced levels of short-chain-fatty acids, Dlactic acidosis, an abnormal tryptophan metabolism and low activity of the kynurenine pathway. We review options for microbiome manipulation in ME/CFS patients including probiotic and dietary interventions as well as fecal microbiota transplantations. Beyond increasing gut permeability and bacterial translocation, specific dysbiosis may modify fermentation products, affecting peripheral mitochondria. Considering the gut-brain axis we strongly suspect that the microbiome may contribute to neurocognitive impairments of ME/CFS patients. Further larger studies are needed, above all to clarify whether D-lactic acidosis and early-life antibiotic use may be part of ME/CFS etiology and what role changes in the tryptophan metabolism might play. An association between the gut microbiome and the disease ME/CFS is plausible. As causality remains unclear, we recommend longitudinal studies. Activity levels, bedridden hours and disease progression should be compared to antibiotic exposure, drug intakes and alterations in the composition of the microbiota. The therapeutic potential of fecal microbiota transfer and of targeted dietary interventions should be systematically evaluated.

Evidence for Peroxisomal Dysfunction and Dysregulation of the CDP-Choline Pathway in Myalgic Encephalomyelitis/Chronic Fatigue Syndrome

Xiaoyu Che, Christopher R Brydges, Yuanzhi Yu, Adam Price, Shreyas Joshi, Ayan Roy, Bohyun Lee, Dinesh K Barupal, Aaron Cheng, Dana March Palmer, Susan Levine, Daniel L Peterson, Suzanne D Vernon, Lucinda Bateman, Mady Hornig, Jose G Montoya, Anthony L Komaroff, Oliver Fiehn, W Ian Lipkin medRxiv 2022 Jan 11;2021.06.14.21258895. PMID: 35043127

Background: Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) is a chronic and debilitating disease that is characterized by unexplained physical fatigue unrelieved by rest. Symptoms also include cognitive and sensory dysfunction, sleeping disturbances, orthostatic intolerance, and gastrointestinal problems. A syndrome clinically similar to ME/CFS has been reported following welldocumented infections with the coronaviruses SARS-CoV and MERS-CoV. At least 10% of COVID-19 survivors develop post acute sequelae of SARS-CoV-2 infection (PASC).

Although many individuals with PASC have evidence of structural organ damage, a subset have symptoms consistent with ME/CFS including fatigue, post exertional malaise, cognitive dysfunction, gastrointestinal disturbances, and postural orthostatic intolerance. These common features in ME/CFS and PASC suggest that insights into the pathogenesis of either may enrich our understanding of both syndromes, and could expedite the development of strategies for identifying those at risk and interventions that prevent or mitigate disease.

Methods: Using regression, Bayesian and enrichment analyses, we conducted targeted and untargeted metabolomic analysis of 888 metabolic analytes in plasma samples of 106 ME/CFS cases and 91 frequency-matched healthy controls.

Results: In ME/CFS cases, regression, Bayesian and enrichment analyses revealed evidence of peroxisomal dysfunction with decreased levels of plasmalogens. Other findings included decreased levels of several membrane lipids, including phosphatidylcholines and sphingomyelins, that may indicate dysregulation of the cytidine-5â€™-diphosphocholine pathway. Enrichment analyses revealed decreased levels of choline, ceramides and carnitines, and increased levels of long chain triglycerides (TG) and hydroxy-eicosapentaenoic acid. Elevated levels of dicarboxylic acids were consistent with abnormalities in the tricarboxylic acid cycle. Using machine learning algorithms with selected metabolites as predictors, we were able to differentiate female ME/CFS cases from female controls (highest AUC=0.794) and ME/CFS cases without self-reported irritable bowel syndrome (sr-IBS) from controls without sr-IBS (highest AUC=0.873).

Conclusion: Our findings are consistent with earlier ME/CFS work indicating compromised energy metabolism and redox imbalance, and highlight new abnormalities that may provide insights into the pathogenesis of ME/CFS.

Stigma perceived by patients with functional somatic syndromes and its effect on health outcomes - A systematic review

Charlotte Ko, Peter Lucassen, Britt van der Linden, Aranka Ballering, Tim Olde Hartman J Psychosom Res 2022 Mar;154:110715. PMID: 35016138

Background: Patients with functional somatic syndromes (FSS) experience stigma which arguably affects their health.

Aim: To determine the presence of perceived stigma and its effects on physical and mental health in patients with FSS compared to patients with comparable explained conditions.

Methods: A comprehensive search of PubMed, Embase, PsycINFO, CINAHL and Cochrane Library was performed to select studies focusing on stigma perceived by patients with

irritable bowel syndrome (IBS), fibromyalgia (FM) or chronic fatigue syndrome (CFS), comparing these patients to patients with comparable but explained conditions.

Results: We identified 1931 studies after duplicate removal. After screening we included eight studies: one study about all three FSS, one about IBS, five about FM and one about CFS. We found that patients with IBS did not consistently experience higher levels of stigma than those with a comparable explained condition. Patients with CFS and FM experienced higher levels of stigma compared to patients with comparable explained conditions. All studies showed a correlation between stigma and negative health outcomes.

Discussion: Patients with FSS experience stigma and negative health outcomes. However, experiencing stigma is not restricted to patients with FSS, as many patients with explained health conditions also experience stigma. Whether stigma has more negative health consequences in patients with FSS compared to patients with explained health conditions remains unclear and should be assessed in future research.

Brainstem Abnormalities in Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: A Scoping Review and Evaluation of Magnetic Resonance Imaging Findings

Todd Nelson, Lan-Xin Zhang, Hui Guo, Luis Nacul, Xiaowei Song Front Neurol 2021 Dec 17;12:769511. PMID: 34975729

Background: Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) is a multisystem medical condition with heterogeneous symptom expression. Currently, there is no effective cure or treatment for the standard care of patients. A variety of ME/CFS symptoms can be linked to the vital life functions of the brainstem, the lower extension of the brain best known as the hub relaying information back and forth between the cerebral cortex and various parts of the body.

Objective/Methods: Over the past decade, Magnetic Resonance Imaging (MRI) studies have emerged to understand ME/CFS with interesting findings, but there has lacked a synthesized evaluation of what has been found thus far regarding the involvement of the brainstem. We conducted this study to review and evaluate the recent MRI findings via a literature search of the MEDLINE database, from which 11 studies met the eligibility criteria.

Findings: Data showed that MRI studies frequently reported structural changes in the white and gray matter. Abnormalities of the functional connectivity within the brainstem and with other brain regions have also been found. The studies have suggested possible mechanisms including astrocyte dysfunction, cerebral perfusion impairment, impaired nerve conduction, and neuroinflammation involving the brainstem, which may at least partially explain a substantial portion of the ME/CFS symptoms and their heterogeneous presentations in individual patients.

Conclusions: This review draws research attention to the role of the brainstem in ME/CFS, helping enlighten future work to uncover the pathologies and mechanisms of this complex medical condition, for improved management and patient care.

Submaximal Exercise Provokes Increased Activation of the Anterior Default Mode Network During the Resting State as a Biomarker of Postexertional Malaise in Myalgic Encephalomyelitis/Chronic Fatigue Syndrome

Rakib U Rayhan, James N Baraniuk Front Neurosci 2021 Dec 15;15:748426. PMID: 34975370

Background: Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) is characterized by disabling fatigue and postexertional malaise. We developed a provocation paradigm with two submaximal bicycle exercise stress tests on consecutive days bracketed by magnetic resonance imaging, orthostatic intolerance, and symptom assessments before and after exercise in order to induce objective changes of exercise induced symptom exacerbation and cognitive dysfunction. Method: Blood oxygenation level dependent (BOLD) scans were performed while at rest on the preexercise and postexercise days in 34 ME/CFS and 24 control subjects. Seed regions from the FSL data library with significant BOLD signals were nodes that clustered into networks using independent component analysis. Differences in signal amplitudes between groups on pre- and post-exercise days were determined by general linear model and ANOVA. Results: The most striking exercise-induced effect in ME/CFS was the increased spontaneous activity in the medial prefrontal cortex that is the anterior node of the Default Mode Network (DMN). In contrast, this region had decreased activation for controls. Overall, controls had higher BOLD signals suggesting reduced global cerebral blood flow in ME/CFS. Conclusion: The dynamic increase in activation of the anterior DMN node after exercise may be a biomarker of postexertional malaise and symptom exacerbation in CFS. The specificity of this postexertional finding in ME/CFS can now be assessed by comparison to post-COVID fatigue, Gulf War Illness, fibromyalgia, chronic idiopathic fatigue, and fatigue in systemic medical and psychiatric diseases.

Markers of Cardiac Autonomic Function During Consecutive Day Peak Exercise Tests in People With Myalgic Encephalomyelitis/Chronic Fatigue Syndrome

Maximillian J Nelson, Jonathan D Buckley, Rebecca L Thomson, Clint R Bellenger, Kade Davison Front Physiol 2021 Dec 14;12:771899. PMID: 34970156

Abstract: Patients with Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) have been shown to exhibit altered ventilatory characteristics on the second of two progressive maximal cardiopulmonary exercise tests (CPET) performed on consecutive days. However, maximal exercise can exacerbate symptoms for ME/CFS patients and cause significant post-

exertional malaise. Assessment of heart rate (HR) parameters known to track post-exertional fatigue may represent more effective physiological markers of the condition and could potentially negate the need for maximal exercise testing. Sixteen ME/CFS patients and 10 healthy controls underwent a sub-maximal warm-up followed by CPET on two consecutive days. Ventilation, ratings of perceived exertion, work rate (WR) and HR parameters were assessed throughout on both days. During sub-maximal warm-up, a time effect was identified for the ratio of low frequency to high frequency power of HR variability ($p=0.02$) during sub-maximal warm-up, and for HR at ventilatory threshold ($p=0.03$), with both being higher on Day Two of testing. A significant group ($p<0.01$) effect was identified for a lower post-exercise HR recovery (HRR) in ME/CFS patients. Receiver operator characteristic curve analysis of HRR revealed an area under the curve of 74.8% ($p=0.02$) on Day One of testing, with a HRR of 34.5bpm maximizing sensitivity (63%) and specificity (40%) suggesting while HRR values are altered in ME/CFS patients, low sensitivity and specificity limit its potential usefulness as a biomarker of the condition.

Lessons From Heat Stroke for Understanding Myalgic Encephalomyelitis/Chronic Fatigue Syndrome

Dominic Stanculescu, Nuno Sepúlveda, Chin Leong Lim, Jonas Bergquist Front Neurol 2021 Dec 13;12:789784. PMID: 34966354

Abstract: We here provide an overview of the pathophysiological mechanisms during heat stroke and describe similar mechanisms found in myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS). Both conditions are characterized by disturbed homeostasis in which inflammatory pathways play a central role. Splanchnic vasoconstriction, increased gut permeability, gut-related endotoxemia, systemic inflammatory response, central nervous system dysfunction, blood coagulation disorder, endothelial-cell injury, and mitochondrial dysfunction underlie heat stroke. These mechanisms have also been documented in ME/CFS. Moreover, initial transcriptomic studies suggest that similar gene expressions are altered in both heat stroke and ME/CFS. Finally, some predisposing factors for heat stroke, such as pre-existing inflammation or infection, overlap with those for ME/CFS. Notwithstanding important differences - and despite heat stroke being an acute condition - the overlaps between heat stroke and ME/CFS suggest common pathways in the physiological responses to very different forms of stressors, which are manifested in different clinical outcomes. The human studies and animal models of heat stroke provide an explanation for the self-perpetuation of homeostatic imbalance centered around intestinal wall injury, which could also inform the understanding of ME/CFS. Moreover, the studies of novel therapeutics for heat stroke might provide new avenues for the

treatment of ME/CFS. Future research should be conducted to investigate the similarities between heat stroke and ME/CFS to help identify the potential treatments for ME/CFS.

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

Xia Li, Per Julin, Tie-Qiang Li Tomography 2021 Nov 1;7(4):675-687. PMID: 34842817

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.

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. We welcome submissions of all ME patients who have died.

Margaret Peggy Calhoun, 82, died on New Year's Eve, December 31, 2021 after suffering with CFIDS for many years. She was born in California and lost her mother to cancer at a young age. She was brought up by two aunts, one in Kansas and the other in California. She worked at a bank but had to retire after CFIDS/ME took over her life. She had two daughters, two cats, and four dogs. She is remembered for her vibrant personality.

Andrea Jennings, 68, a beloved mother of daughters, Andrea had ME for many years. Her final years of life found her fighting both lung and kidney cancer that led to operations for those which added to her back and knee pain. That pain also ended her teaching career. Her suffering became so pronounced that she took her own life on the third of March, 2022.

Graham McPhee died on October 11, 2021 after spending much of his last year in a hospital for sepsis that developed from an abscess on his liver due to ME/CFS. He was known for his great sense of humor and advocating for his community's CFIDS population in the U.K. Graham was a retired math teacher and was working with Dr. Charles Shepherd to create a website to educate doctors on ME/CFS. He inspired many. (Source: ME Association)

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).

GOLDEN BENEFACTOR

Edward Taylor and Family

SILVER BENEFACTOR

Irel Urreiztieta, "In Memory of Dr. Jay Goldstein, MD Compassionate and wonderful physician; brilliant pursuer of help and encyclopedic Renaissance man. We miss you terribly, and wish you eternal rest after your valiant life."

BENEFACTOR

Anonymous, New Mexico

SUPPORTER

Network for Good

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The donations listed above were received after March 18, 2022. Those who donated before that date are not listed as their names. along with all that was to appear in this issue, were stored on a computer that was melted in a fire that destroyed the office of the NCF. If your name was one who generously donated to the NCF, please let us know by emailing our president at gailronda@aol.com or calling us at 781-925-5336.