THE NATIONAL FORUM

The National CFIDS Foundation

Vol. 28, No. 2 – Winter 2022

U.S. NEEDS NEW $100 MILLION RESEARCH PROGRAM TO STUDY HEALTH EFFECT OF EXPOSURE TO LOW DOSES OF RADIATION, SAYS NEW REPORT

News Release, June 2, 2022

WASHINGTON — The U.S. should establish a new coordinated research program to investigate the impacts of exposure to low doses of radiation on human health, says a new report from the National Academies of Sciences, Engineering, and Medicine. The report estimates $100 million annually for the next 15 years would be required to conduct epidemiological and biological research, and to establish an infrastructure for research. This coordinated program should study how low doses of radiation affect cancer risks, cardiovascular disease risk, neurological disorders, and other disease - and try to establish causal links to health conditions. Research should also better define the impacts of radiation doses, dose rates, types of radiation, and exposure duration.

Radiation exposure at low doses (below 100 milligray) or low-dose rates (less than 5 milligray per hour) occurs in a wide range of medical, industrial, military, and commercial settings. The effects of exposure at these levels are not fully understood, the report says, and there are long-standing concerns that such exposure could negatively affect human health. Although

cancer has been linked to low-dose radiation exposure for decades, there is increasing evidence that it may also be associated with cardiovascular disease, neurological disorders, immune dysfunction, and cataracts.

Concerns about the health effects of low doses of radiation raise questions as to whether the public and workers are adequately protected from exposures from medical diagnostics procedures such as CT scans, legacy exposures from nuclear weapons production and nuclear waste management, and new sources of exposure such as rare earth element and lithium mining, among others. The report says research on the health effects of low-dose radiation in the U.S. is limited and fragmented, lacking leadership, central coordination, and an overarching strategic agenda. While this research was managed in the past by the U.S. Department of Energy's Office of Science, the office's focus has been redirected.

"There is much we don't know about the impacts of low-dose radiation exposures on our health – but recent advances in research, new tools, and a coordinated multidisciplinary research program could help us fill those gaps," said Joe W. Gray, professor emeritus of laboratory medicine at the University of California, San Francisco, and chair of the committee that wrote the report. "This is especially important as science seeks to provide answers to concerned individuals and to communities that have been involuntarily exposed to radiation, including Indigenous communities, atomic veterans, nuclear workers, and others impacted by the legacy of U.S. nuclear weapons testing and production."

A Coordinated Research Program:

Significant investments over a sustained period spanning more than a decade will be required in order to develop and maintain a low-dose radiation research program, with periodic reassessments based on how research is progressing. The $5 million appropriated for the DOE's low-dose radiation program in 2021 and 2022 is not sufficient even to initiate a coordinated federal research program, the report says. With adequate funding, DOE could implement most of the research program's essential elements identified in the report within two years.

The research agenda proposed by the report extends beyond any single agency's capabilities at present, and would involve coordination across federal agencies and national and international partners. The committee supported leadership of this coordination by both DOE and the National Institutes of Health - with DOE leading a portion of the strategic research related to computational and modeling research, and NIH leading the epidemiological and biological research.

The report notes concerns raised by some communities about DOE's inherent conflicts because of its work with the nuclear weapons program and its role in promoting nuclear technologies, as well as concerns from the research community about DOE's shortcomings related to management of the previous program. NIH is widely trusted by the scientific community, has

well-established and transparent processes for funding research, and has no perceived conflicts of interest. Within NIH, the National Institute of Allergy and Infectious Diseases' Radiation and Nuclear Countermeasures Program, the National Cancer Institute, and the newly conceptualized Advanced Research Projects Agency for Health (ARPA-H) could contribute to innovative low-dose radiation research leadership.

The report also recommends elements of a research program that should be incorporated into management of the low-dose program including a long-term commitment to the research, scientific independence, and transparency and engagement with impacted communities.

Research Priorities:

The report sets priorities for epidemiological and biological research on low-dose radiation, as well as for establishing a research infrastructure. A revitalized radiation research program would be able to leverage recent scientific breakthroughs - such as greater computing power, genetic research, and data sharing systems - that previous research did not.

Epidemiological research should improve our estimation of the risks for cancer and other health outcomes, determine factors that can modify these effects - such as genetics or lifestyle - and develop better analytical tools.

Biological research should define the dose-response relationships for low radiation exposure, linking specific doses of radiation to health effects on the cellular level and the progression of disease. This research should also identify the effects of radiation on cellular and molecular features in order to establish causal links to adverse health effects, among other priorities.

Developing a research infrastructure should include creating tools for sensitive detection of radiation and precise characterization of cell and tissue changes, harmonizing research databases, and ensuring researchers' access to low-dose exposure facilities.

New information gleaned by the research program can help inform estimates of the economic impact of possible changes to radiation protection standards and guidance. As there are no comprehensive estimates of the economic impact of current regulations, the committee was not able to estimate those of the proposed radiation research program.

The study, undertaken by the Committee on Developing a Long-Term Strategy for Low-Dose Radiation Research in the United States, was sponsored by the U.S. Department of Energy.

Reference: https://www.nationalacademies.org/news/2022/06/u-s-needs-new-100-million-research-program-to-study-health-effects-of-exposure-to-low-doses-of-radiation-says-new-report

"Most long-COVID victims are suffering from post-viral chronic fatigue syndrome (CFS)."

~ Jacob Teitelbaum, MD

PRESIDENT'S MESSAGE

By Gail Kansky – Copyright 2023

When Dr. Anthony Fauci announced in August that he planned to retire from his high-profile positions as President Biden's top medical advisor and as director of the National Institute of Allergy and Infectious Diseases (NIAID) for the past 38 years, the story of his many successes could be found mentioned in most news alerts around the world. Few, if any, mentioned how he purposely ignored the millions of ME/CFIDS patients which he believed were merely psychologically affected and certainly not a serious immune disease that has been scientifically proven since.

More than two decades ago, Fauci encouraged the NIH to withdraw support of the research centers for ME/CFIDS and the amount of funding for the disease could be found only at the bottom of the Congressional level of expense. Since then, there have been many others who have tried to explain to Fauci how serious the illness was, such as the brilliant Dr. Ian Lipkin, but it was a disease that remained unmentioned by him as he continued to ignore it. Only the recent pandemic has begun to change this as long-haulers of the coronavirus emerged and were found to resemble ME/CFIDS. For decades, Fauci never even mentioned ME/CFIDS at any time and he continued this even after the pandemic began and many stories of long-haulers were written and mentioned the comparisons between the two illnesses. After months of articles were published on Long-Covid, by 2020 Fauci finally spoke about it and mentioned the similar symptoms and included what he called "chronic fatigue syndrome" although he separated CFS from ME as if they were two separate illnesses.

In 2021 Robert F. Kennedy, Jr. published a book entitled "The Real Anthony Fauci: Bill Gates, Big Pharma, and the Global War on Democracy and Public Health". It was very critical book that was very truthful and Fauci called the author "a very disturbed individual." The book has been purchased by over one million people to date. However, no book can solve the problems of how the illness was perceived and the underlying consequences that patients were subjected to live with. Another book that was published years before that by Charles Ortleb, "Fauci: The

Bernie Madoff of Science and the HIV Ponzi Scheme that Concealed the Chronic Fatigue Syndrome Epidemic". Ortleb wrote, "November 2, 1984 was an especially tragic day in the Chronic Fatigue Syndrome/AIDS epidemic. That was the day Anthony Fauci became the Director of the National Institutes of Allergy and Infectious Diseases..." Chuck wrote several more books about ME/CFS and I read and enjoyed the truthfulness of every one of them.

Fauci has been the highest paid member of our national government. He has been paid a higher salary than anyone else including the president, Just days after he announced he would be leaving his government position, Florida's Gov. Ron DeSantis said at a GOP meeting, “Someone needs to grab that little elf and chuck him across the Potomac!”. There are many patients who have been suffering from ME/CFIDS for decades and know how Fauci wiped his hands of our illness and how he was responsible for the loss of research funds which sent work on this illness tumbling into darkness. Luckily, this never stopped the NCF as all donations to our charity go toward finding answers that will be benefit all PWCs. We don't sponsor galas; we don't have anyone work for a salary. We often paid for research via donations since we knew little to no funding would be available for this disease that has stolen most of our lives. But nothing could ever stop Fauci from continually believing that the majority of ME/CFIDS patients were psychologically depressed by an underlying mental illness. Nobody at the NCF will miss him.

DR. JOHN GOFMAN

By The National CFIDS Foundation, February 2023 – Copyright 2023

John William Gofman was a college graduate from Oberlin College, a Ph.D. Graduate from the University of California at Berkeley and an M.D. Degree from the University of California at San Francisco. He was the man who elaborated the dangers of ionizing radiation and how low levels bring on chromosomal damage along with the risk of cancer.

In the 1960's, Dr.Gofman established the Biomedical Research Division at the Livermore National Laboratory where his team researched how cancer was related to chromosomal damage. In one of the books he authored, he explained that medical x-rays were the source of nearly 75 percent of breast cancer and mammography screens were responsible for the increase found in both the United States and France.

Dr. Gofman raised questions about the safety of low-level radiation and the harm of it as well as atomic energy and was a leader of the movement against nuclear reactors. Indeed, he suggested atomic bomb tests be done underground but said even the small leakage from them would reach above ground and be a source of harm. In spite of others who were against his speeches and books, he remained adamant of the harms of radiation health effects that continue to this day and just one of the many harmful illnesses that it causes is found worldwide and is known as chronic fatigue syndrome, myalgic encephalomyalitis, CFIDS (chronic fatigue immune dysfunction syndrome), and other names.

John Gofman led the scientific community to acknowledge the Linear No-Threshold (LNT) model that allows a way for low-level radiation to lead to cancer and led to international guidelines to adopt his discoveries. As we have let others know, we had used all donations in the past to test patients for radiation. They were all positive. Our hero, John Gofman, died at age 88 in 2007.

NEW TECHNOLOGY

By Kathy Collett (Twitter: @kathycollett7) – Copyright 2023

Last year in November l was listening to the radio when l heard an interview calling out for patients to be tested at SPIN, a neurological research department at the Edith Cowan University Campus in Joondalup, Perth, Western Australia. They specifically wanted patients with neurological problems to contact them. l naturally got very interested and emailed them.

Knowing how some neurologists have been dismissive of Myalgic Encephalomyelitis despite WHO classifying ME as a neurological disease in 1969, l felt it was a great opportunity to take part. Previously I had been diagnosed by Dr Jay A. Goldstein in California. He identified ME with Fibromyalgia and Repetitive Strain Injury as overlapping.

l informed them l would prefer to be involved during the cooler months as l am worse in the heat and they were accommodating. l received a phone call to take part in their program

including testing upper muscles on Kinarm, an interactive, robotic machine. I was also tested for balance, sleep patterns, cognitive function and I had a DNA blood test.

Everything went smoothly and five vials of blood were collected to be sent away for DNA analysis. They will send them away later as they build on their collection from patients.

Amongst the information they provided, I was asked to write a diary on my sleep pattern over a week. I wore an Actigraph device - like a watch strapped to my wrist - which recorded my sleep quality. As patients know sleep disturbances are a major problem so I wasn't surprised when the results came back. I have been told I am at a high risk of sleep apnea and my sleep pattern should be investigated.

Footnote: SPIN indicated they will test patients again in 12 months' time and will be in contact if there are other developments. They hope to expand the department and apply for research grants for neurological problems and will be linking up with other clinicians from other medical areas.

[Kinarm is the robotic interactive machine used for testing my muscle performance. This was of great interest to me. Not only may it be the only one of its type in Australia (it was at one stage) but I knew I had muscle weakness and I was therefore not surprised when the report identified my upper limb function is not within normal range for my age and suggested I speak to my GP. She said she wouldn't be able to understand it and decided not to read it.]

JUST ASK!

By Alan Cocchetto, NCF Medical Director – Copyright 2023

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.

The NCF has placed a copy of a new paper titled, "A proposed new model to explain the role of low dose non-DNA targeted radiation exposure in Chronic Fatigue and Immune Dysfunction Syndrome," currently in peer-review, on their homepage at www.ncf-net.org . This work establishes an important connection between radiation exposure in CFIDS/CFS/ME patients and the development of melanoma.

The NCF's core CFIDS cohort consists of patients with internal radiation exposure to alpharadionuclides (uranium, thorium, polonium etc.); chromosome damage (translocations, aneuploidy, karyotype abnormalities, defective mitotic figures, chromosome fragmentation, chromosome condensation, genome chaos etc.); and eNOX2 protein generation (ecto-NOX disulfide-thiol exchanger 2, tNOX) as identified in cancer cells. These patients were also positive for Mab-CTX (Monoclonal antibody to ciguatera toxin, Hokama) reactivity. In addition, many patients were found to have STAT1 protein defects and were kappa-lambda light chain positive (MGUS). Neurodegenerative tauopathy has been identified which may result from chronic radiation sickness. Furthermore, bone marrow suppression has been seen and may manifest as a myelodysplastic syndrome or a pre-leukemia/lymphoma condition.

This paper provides a new systems biology model for our patient cohort who have been exposed to radiation. Furthermore, this exposure suggests an association with melanoma and subsequent hematopoietic dysregulation based upon previously identified patient biomarkers. A systems diagram is provided outlining these key characteristics. This paper and its contents will be discussed in detail in the next Forum.

IMPORTANT NOTE TO NCF FORUM READERS:

Did you develop cancer after you were formally diagnosed with CFIDS/ME?

If you would like to participate in an informal patient survey, please drop us an anonymous note stating what type of cancer you had at gailronda@aol.com. We thank you for your participation!

ASK BERNIE THE ATTORNEY

By Bernard A. Kansky, Esq. – Copyright 2023

Q. I am scheduled for an SSDI (disability benefit) hearing before an Administrative Law Judge and my physician has delayed preparing a comprehensive report which will be needed if I have any chance of being awarded the disability benefits which I so desperately need. In addition, if I do not succeed at this SSA level, I have great concern that my long-term disability benefits will be terminated based upon my having been denied SSDI benefits by the Administrative Law Judge. What can I do?

A. First and foremost, you should have completed for your attorney or representative, a detailed form containing a schedule of every symptom from which you have suffered and which in any way causes and/or contributes to your inability to work full-time for at least 5 or more consecutive days a week, week after week, and year after year. In addition, you should have been tested by an experienced SSA occupational expert who understands that even if, on occasion, you may be able to perform some tasks for a short period of me, but that notwithstanding, you are never able to maintain a regular and consistent full-time work schedule. The extensive tests which he or she performed upon you, and which support his or her opinion, should be described in the occupational expert's lengthy and detailed report along with an attachment of his or her curriculum vitae.

Further, your attorney or representative should also arrange to have you tested by a Cardiopulmonary Exercise Test, (abbreviated as CPET). Have that expert prepare a detailed Evaluation Report, based upon testing on two consecutive days in a row and the written results of that two-day test should also be included in your file. In addition, you should undergo the NASA 10-minute Lean Test with any adverse results also included in writing in your file.

When the foregoing has been accomplished, your treating physician must provide a report incorporating all of the foregoing. If MD is overwhelmed by this, then your attorney or representative, keeping in mind what most Administrative Law Judges rely upon to award disability benefits, might offer to prepare a sample form report for your treating physician to use as a guideline (your attorney or representative being sure to prepare a sample format not inconsistent with the reports previously submitted by that physician, unless newer and more recent test results require otherwise). The treating physician should also attach to this ultimate opinion report a copy of his or her own curriculum vitae.

In preparation for the hearing before the Administrative Law Judge, it would be ideal if the treating physician could be present and testifying. In addition, the treating physician could also add input to the form of the key question asked of SSA's occupational expert by the Administrative Law Judge to ensure that the Administrative Law Judge does not omit a crucial symptom or symptoms and in the question to the SSA expert, asks it correctly and includes all relevant limitations which prohibit fulltime work. Finally keeping in mind the phrase, “the more the merrier,” bring in as many people as possible who can legitimately testify under oath and can confirm how very limited and different the applicant has become since the onset of symptoms; including how vibrant the applicant used to be compared to the time of onset of the horrific symptoms, and since, up to and including the present. And the testimony of the clergy, and close family members and friends who can and do speak frankly and honestly is always most persuasive. Do not use the term "disabled," in the reports or at the hearing. That term is the key issue to be decided by the Administrative Law Judge after hearing all of the evidence and reading all of the reports. If you have any questions about any of the foregoing, contact Attorney Kansky at (781) 925-5336.

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!

A PRESENT FOR A PATIENT?

By The National CFIDS Foundation, February 2023 – Copyright 2023

A very special thing this year was an article entitled “Commonalities in the Features of Cancer and Chronic Fatigue Syndrome (CFS): Evidence for Stress-Induced Phenotype Instability”. This is an article you'll love to share with your own doctor and other interested people. It was published this year in the International Journal of Molecular Sciences by our Medical Director and Canada's radiation experts at McMaster University. You can get the article at a medical library or just request it from us this winter before spring is here. Make sure you include your address and a minimum of $3.00 to help cover the expense of copying and postage and use our new address of 285 Beach Ave., Hull, MA 02045.

BITS AND PIECES

By The National CFIDS Foundation, February 2023 – Copyright 2023

June 2, 2022

A report issued by the National Academies of Sciences, Engineering and Medicine stated that the U.S. should investigate what impact low doses of radiation would have on the health of people. The study should include the risk of cancer as well as the risk of cardiovascular problems in neurologival diseases. Joe Gray, a professor emeritus at a California university, was the project's chairman of the report and said, “There is much we don't know about the impacts of low-dose radiation on our health but recent advances in research, new tools, and a coordinated multidisciplinary research program could help us fill in those gaps.”

June 29, 2022

In a controlled clinical trial done by Terra Biological LLC, both Long-haulers and ME/CFIDS patients had reduced fatigue using a nutritional/medical supplement of Anhydrous (AOE) for six weeks. Everyone has oxaloacetate, a metabolite, in their body but studies have found that PWCs have a lower amount. A smaller dose is sold over the counter, the higher dose used in this study requires medical help. The peer-reviewed trial results can be found in the Journal of Translational Medicine.

August 11, 2022

Griffith University's researchers in Australia previously reported on specific ion channels in ME/CFIDS using electrophysiology which is a technique they pioneered. The channels allow tons such as calcium to flow in and out of the body's cells in patients. For example, depending on the particular cells affected, a patient may suffer different symptoms such as brain fog or, perhaps, muscle pain. The director of this special team, Professor Sonya Marshall-Gradisnik, believes some new methods may help with Long Covid as well as ME/CFIDS according to the University's news published on this date.

August 31, 2022

Two universities, one from Berlin, Germany as well as the Max Delbrick Center for Molecular Medicine found that “SARS-CoV-2 can trigger chronic fatigue syndrome. The Canadian Consensus Criteria for a diagnostic entity. Half the patients were positive and the other half that were negative had much milder symptoms. None had been vaccinated. Those that fit that criteria had symptoms that were severe and symptoms that lasted much longer and got weaker which suggests muscle weakness caused by impaired blood supply. One director, Professor

Scheibenbogen, said, “Our data also provide further evidence that ME/CFS is not a psychosomatic disorder but a severe physical disease which can be measured and diagnosed using objective methods.” This study was published in the journal entitled Nature Communications.

September 14, 2022

A U.K.-based company reported that they found a genetic link to ME/CFIDS. That information could lead to faster way to diagnose the disease as well as better medication and better treatments. The company, PrecisionLife, also announced they discovered that 14 genes found in the same disease were associated with 199 single nucleotide polymorphisms in 91% of PWCs. These findings could lead to the very first therapeutic option and could make our lives so much better! This same study also found some similarities with genes associated with Long-COVID and with multiple sclerosis. This exciting work is due to be published in a medical journal. More information can be found at www.precisionlife.com. The future results will help to change the way PWCs have been mistreated, misdiagnosed and, all too often, misbelieved.

September 19, 2022

Joyce Frieden, the Washington editor of *MedPage Today*, had an online article published that came to the White House to express their frustration over the federal government spending so little money and not much attention to Long Covid and ME/CFIDS. The two illnesses have had little to no real support and get little to no help from the NIH. Joyce mentioned an ME/CFIDS patient from Texas who has been sick for 17 years but didn't get diagnosed for 15 years! Sadly, that’s not uncommon as most doctors don’t know about the illness and it still isn't taught at most medical schools. The only reason that the woman from Texas got diagnosed was due to a nurse practitioner in that office with the disease. The protesters want doctors to be educated, economic support, dedicated clinics, services provided for patients that include housing, transportation assistance, food purchasing help, and education for the unaffected as well. One of the chants the protesters proclaimed was “History will recall, Biden did nothing at all.”

September 21, 2022

Mount Sinai's Icahn School of Medicine reported that people who lost about an hour and a half sleep consistently can actually lead to inflammation as well as diseases since it actually alters one's DNA.

September 24, 2022

The Journal of Translational Medicine came out with an article reporting on neuromuscular problems of SARS-Covid and the similarities it has with ME/CFIDS. One can look at Pub Med for further information.

September 24, 2022

Another medical journal (PMID) had an article that reported on what actually happens when a PWC exercises and the actual damage that takes place via the microglia. This preprint can be seen on Pub Med. Another article tells of gut microbiota.

October 6, 2022

President Biden, while addressing an audience in New York, said, “We have not faced the prospect of Armageddon since Kennedy and the Cuban Missile Crisis.” This quotation was first mentioned by the New York Times since we are now facing a similar situation as that crisis was averted 60 years ago. It is now a problem that is happening in Ukraine and a nuclear crisis must be defused. It is a problem we’re facing today as the Russians continue bombing and the radiation involved can hurt the world as there is no simple way to control a speck of radiation that can travel anywhere. Anyone, anywhere could unknowingly ingest that speck by simply inhaling and become another victim of ME/CFIDS. Of course, the president was not referring to ME/CFIDS, but it is one of the many problems taking place today.

October 17, 2022

News reports via print as well as television and radio about radioactive waste was found at an elementary school in Florissant, MO. It was found only after so many children in the school got sick. The school was built in a space that, during World War II, was used for nuclear waste dumping. That was found only after dozens of children began to get sick as well as some teachers. While the Associated Press stated, “Inhaling or ingesting these radioactive materials can cause significant injury,” no mention of having these children getting sick for the rest of their lives, which has been found and proven, was not part of what these unfortunate kids will have to endure.

October 18, 2022

An article via the Future of Health was put online talking about a woman who was working for the U.S. Department of Transportation who got a Covid-19 infection in 2020 and continued to have impaired thinking and pain, fatigue, seizures, and headaches. This year, her doctor suggested low doses of the drug, Naltrexone which is used to treat alcohol and opioid addiction. The article stated that the drug was also used for “myalgic encephalomyelitis/chronic fatigue syndrome” but I wonder if the woman really has that illness but was not diagnosed correctly. Many PWCs take it for the same problems.

November 1, 2022

An article from Yale was written by Isabella Backman entitled “Will Long COVID Research Provide Answers for Poorly Understood Diseases Like ME/CFS?” Isabella mentions, “an unfortunate name” which was explained by a worker at a college of how the name of “CFS” just

defines it by a single symptom. But the article doesn't mention how the government chose this name and how one scientist objected and told patients to call it CFIDS which is for “Chronic Fatigue and Immune Dysfunction Syndrome” The article does give other good information about our disease.

November 9, 2022

The Sunshine Coast News reported that the UniSC's Thompson Institute will study the neurobiological origin of ME/CFIDS in order to find better treatments and a way of diagnosing the illness. This clinical study has registered with the Australian New Zealand Registry.

November 13, 2022

Miriam Stoppord wrote a story about a genetic study of ME that the British researchers will undertake using about 23,000 DNA samples. It intends to be the largest genetic study of ME ever done and is being helped by the University of Edinburgh and UK charities.

November 16, 2022

BottomLine Personal (Volume 43, Number22) has an article about Long Covid and how it can be treated like “Post-Viral CFS” by Jacob Teitelbaum, MD. Among several things we didn't agree with, the worst was telling patients to, “Exercise...as best you can.” If he recited this in a classroom, he'd be told to go stand in the corner of the room!

November 24, 2022

Posted by the World Health Net, “Feeling Fatigue? Finding Possible Causes” that said, “Researchers have not yet found an effective way to diagnose or treat ME.CFS”. As many long-term PWCs know, that is not true but our government has helped some to get well and to move such as the late Dr. Jay Goldstein as well as Mark Iverson who established the first national group for patients.

November 25, 2022

The article, written by Francis Stead Sellers, was in The Washington Post and found Covid long haulers had tried many unproven treatments and spent a huge amount of money but none had found any of them helpful.

November 29, 2022

“What it's like to live with brain fog” was another from The Washington Post and this one was written by Lindsey Bever. Some have it following chemotherapy and call it “chemo brain”, It mentions affecting those “with myalgic encephalomyelitis.”

MEDICAL JOURNAL SUMMARIES

Stress-Induced Transcriptomic Changes in Females with Myalgic Encephalomyelitis/Chronic Fatigue Syndrome Reveal Disrupted Immune Signatures

Derek J Van Booven, Jackson Gamer, Andrew Joseph, Melanie Perez, Oskar Zarnowski, Meha Pandya, Fanny Collado, Nancy Klimas, Elisa Oltra, Lubov Nathanson; Int J Mol Sci 2023 Jan 31;24(3):2698.

Abstract: Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) is a chronic, complex multiorgan illness characterized by unexplained debilitating fatigue and post-exertional malaise (PEM), which is defined as a worsening of symptoms following even minor physical or mental exertion. Our study aimed to evaluate transcriptomic changes in ME/CFS female patients undergoing an exercise challenge intended to precipitate PEM. Our time points (baseline before exercise challenge, the point of maximal exertion, and after an exercise challenge) allowed for the exploration of the transcriptomic response to exercise and recovery in female patients with ME/CFS, as compared to healthy controls (HCs). Under maximal exertion, ME/CFS patients did not show significant changes in gene expression, while HCs demonstrated altered functional gene networks related to signaling and integral functions of their immune cells. During the recovery period (commonly during onset of PEM), female ME/CFS patients showed dysregulated immune signaling pathways and dysfunctional cellular responses to

stress. The unique functional pathways identified provide a foundation for future research efforts into the disease, as well as for potential targeted treatment options.

Altered Fatty Acid Oxidation in Lymphocyte Populations of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome

Jessica Maya, Sabrina M Leddy, C Gunnar Gottschalk, Daniel L Peterson, Maureen R Hanson; Int J Mol Sci . 2023 Jan 19;24(3):2010.

Abstract: Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) is a disabling multisystem illness in which individuals are plagued with fatigue, inflammatory symptoms, cognitive dysfunction, and the hallmark symptom, post-exertional malaise. While the cause of this disease remains unknown, there is evidence of a potential infectious component that, along with patient symptoms and common onsets of the disease, implicates immune system dysfunction. To further our understanding of the state of ME/CFS lymphocytes, we characterized the role of fatty acids in isolated Natural Killer cells, CD4+ T cells, and CD8+ T cells in circulation and after overnight stimulation, through implicit perturbations to fatty acid oxidation. We examined samples obtained from at least 8 and as many as 20 subjects for immune cell fatty acid characterization in a variety of experiments and found that all three isolated cell types increased their utilization of lipids and levels of pertinent proteins involved in this metabolic pathway in ME/CFS samples, particularly during higher energy demands and activation. In T cells, we characterized the cell populations contributing to these metabolic shifts, which included CD4+ memory cells, CD4+ effector cells, CD8+ naïve cells, and CD8+ memory cells. We also discovered that patients with ME/CFS and healthy control samples had significant correlations between measurements of CD4+ T cell fatty acid metabolism and demographic data. These findings provide support for metabolic dysfunction in ME/CFS immune cells. We further hypothesize about the consequences that these altered fuel dependencies may have on T and NK cell effector function, which may shed light on the illness's mechanism of action.

No Causal Effects Detected in COVID-19 and Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: A Two Sample Mendelian Randomization Study

Wangzi Xu, Yu Cao, Lin Wu; Int J Environ Res Public Health 2023 Jan 30;20(3):2437.

Abstract: New clinical observational studies suggest that Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) is a sequela of COVID-19 infection, but whether there is an exact causal relationship between COVID-19 and ME/CFS remains to be verified. To investigate whether infection with COVID-19 actually causes ME/CFS, this paper

obtained pooled data from the Genome Wide Association Study (GWAS) and analyzed the relationship between COVID susceptibility, hospitalization and severity of COVID and ME/CFS, respectively, using two-sample Mendelian randomization (TSMR). TSMR analysis was performed by inverse variance weighting (IVW), weighted median method, MR-Egger regression and weighted mode and simple mode methods, respectively, and then the causal relationship between COVID-19 and ME/CFS was further evaluated by odds ratio (OR). Eventually, we found that COVID-19 severity, hospitalization and susceptibility were all not significantly correlated with ME/CFS (OR:1.000,1.000,1.000; 95% CI:0.999-1.000, 0.999-1.001, 0.998-1.002; p = 0.333, 0.862, 0.998, respectively). We found the results to be reliable after sensitivity analysis. These results suggested that SARS-CoV-2 infection may not significantly contribute to the elevated risk of developing CFS, and therefore ME/CFS may not be a sequela of COVID-19, but may simply present with symptoms similar to those of CFS after COVID-19 infection, and thus should be judged and differentiated by physicians when diagnosing and treating the disease in clinical practice.

Impact of Misdiagnosis in Case-Control Studies of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome

João Malato, Luís Graça, Nuno Sepúlveda; Diagnostics (Basel) 2023 Feb 1;13(3):531.

Abstract: Misdiagnosis of myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) can occur when different case definitions are used by clinicians (relative misdiagnosis) or when failing the genuine diagnosis of another disease (misdiagnosis in a strict sense). This problem translates to a recurrent difficulty in reproducing research findings. To tackle this problem, we simulated data from case-control studies under misdiagnosis in a strict sense. We then estimated the power to detect a genuine association between a potential causal factor and ME/CFS. A minimum power of 80% was obtained for studies with more than 500 individuals per study group. When the simulation study was extended to the situation where the potential causal factor could not be determined perfectly (e.g., seropositive/seronegative in serological association studies), the minimum power of 80% could only be achieved in studies with more than 1000 individuals per group. In conclusion, current ME/CFS studies have suboptimal power under the assumption of misdiagnosis. This power can be improved by increasing the overall sample size using multi-centric studies, reporting the excluded illnesses and their exclusion criteria, or focusing on a homogeneous cohort of ME/CFS patients with a specific pathological mechanism where the chance of misdiagnosis is reduced.

Symptom-based clusters in people with ME/CFS: an illustration of clinical variety in a cross-sectional cohort

Anouk W Vaes, Maarten Van Herck, Qichen Deng, Jeannet M Delbressine, Leonard A Jason, Martijn A Spruit; J Transl Med 2023 Feb 10;21(1):112.

Abstract: Background: Myalgic encephalomyelitis (ME)/chronic fatigue syndrome (CFS) is a complex, heterogenous disease. It has been suggested that subgroups of people with ME/CFS exist, displaying a specific cluster of symptoms. Investigating symptom-based clusters may provide a better understanding of ME/CFS. Therefore, this study aimed to identify clusters in people with ME/CFS based on the frequency and severity of symptoms.

Methods: Members of the Dutch ME/CFS Foundation completed an online version of the DePaul Symptom Questionnaire version 2. Self-organizing maps (SOM) were used to generate symptom-based clusters using severity and frequency scores of the 79 measured symptoms. An extra dataset (n = 252) was used to assess the reproducibility of the symptom-based clusters.

Results: Data of 337 participants were analyzed (82% female; median (IQR) age: 55 (44-63) years). 45 clusters were identified, of which 13 clusters included ≥ 10 patients. Fatigue and PEM were reported across all of the symptom-based clusters, but the clusters were defined by a distinct pattern of symptom severity and frequency, as well as differences in clinical characteristics. 11% of the patients could not be classified into one of the 13 largest clusters. Applying the trained SOM to validation sample, resulted in a similar symptom pattern compared the Dutch dataset.

Conclusion: This study demonstrated that in ME/CFS there are subgroups of patients displaying a similar pattern of symptoms. These symptom-based clusters were confirmed in an independent ME/CFS sample. Classification of ME/CFS patients according to severity and symptom patterns might be useful to develop tailored treatment options.

Deficient butyrate-producing capacity in the gut microbiome is associated with bacterial network disturbances and fatigue symptoms in ME/CFS

Cheng Guo, Xiaoyu Che, Thomas Briese, Amit Ranjan, Orchid Allicock, Rachel A Yates, Aaron Cheng, Dana March, Mady Hornig, Anthony L Komaroff, Susan Levine, Lucinda Bateman, Suzanne D Vernon, Nancy G Klimas, Jose G Montoya, Daniel L Peterson, W Ian Lipkin, Brent L Williams; Cell Host Microbe 2023 Feb 8;31(2):288-304.

Abstract: Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) is characterized by unexplained debilitating fatigue, cognitive dysfunction, gastrointestinal disturbances, and orthostatic intolerance. Here, we report a multi-omic analysis of a geographically diverse cohort of 106 cases and 91 healthy controls that revealed differences in gut microbiome diversity, abundances, functional pathways, and interactions. Faecalibacterium prausnitzii and Eubacterium rectale, which are both recognized as abundant, health-promoting butyrate producers in the human gut, were reduced in ME/CFS. Functional metagenomics, qPCR, and metabolomics of fecal short-chain fatty acids confirmed a deficient microbial capacity for butyrate synthesis. Microbiome-based machine learning classifier models were robust to geographic variation and generalizable in a validation cohort. The abundance of Faecalibacterium prausnitzii was inversely associated with fatigue severity. These findings demonstrate the functional nature of gut dysbiosis and the underlying microbial network disturbance in ME/CFS, providing possible targets for disease classification and therapeutic trials.

Multi-'omics of gut microbiome-host interactions in short- and long-term myalgic encephalomyelitis/chronic fatigue syndrome patients

Ruoyun Xiong, Courtney Gunter, Elizabeth Fleming, Suzanne D Vernon, Lucinda Bateman, Derya Unutmaz, Julia Oh; Cell Host Microbe 2023 Feb 8;31(2):273-287.

Abstract: Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) is a complex, debilitating disorder manifesting as severe fatigue and post-exertional malaise. The etiology of ME/CFS remains elusive. Here, we present a deep metagenomic analysis of stool combined with plasma metabolomics and clinical phenotyping of two ME/CFS cohorts with short-term (<4 years, n = 75) or long-term disease (>10 years, n = 79) compared with healthy controls (n = 79). First, we describe microbial and metabolomic dysbiosis in ME/CFS patients. Short-term patients showed significant microbial dysbiosis, while long-term patients had largely resolved microbial dysbiosis but had metabolic and clinical aberrations. Second, we identified phenotypic, microbial, and metabolic biomarkers specific to patient cohorts. These revealed potential functional mechanisms underlying disease onset and duration, including reduced microbial butyrate biosynthesis and a reduction in plasma butyrate, bile acids, and benzoate. In addition to the insights derived, our data represent an important resource to facilitate mechanistic hypotheses of host-microbiome interactions in ME/CFS.

Potential molecular mechanisms of chronic fatigue in long haul COVID and other viral diseases

Carl Gunnar Gottschalk, Daniel Peterson, Jan Armstrong, Konstance Knox, Avik Roy; Infect Agent Cancer 2023 Feb 7;18(1):7.

Abstract: Historically, COVID-19 emerges as one of the most devastating diseases of humankind, which creates an unmanageable health crisis worldwide. Until now, this disease costs millions of lives and continues to paralyze human civilization's economy and social growth, leaving an enduring damage that will take an exceptionally long time to repair. While a majority of infected patients survive after mild to moderate reactions after two to six weeks, a growing population of patients suffers for months with severe and prolonged symptoms of fatigue, depression, and anxiety. These patients are no less than 10% of total COVID-19 infected individuals with distinctive chronic clinical symptomatology, collectively termed post-acute sequelae of COVID-19 (PASC) or more commonly long-haul COVID. Interestingly, Long-haul COVID and many debilitating viral diseases display a similar range of clinical symptoms of muscle fatigue, dizziness, depression, and chronic inflammation. In our current hypothesis-driven review article, we attempt to discuss the molecular mechanism of muscle fatigue in long-haul COVID, and other viral diseases as caused by HHV6, Powassan, Epstein-Barr virus (EBV), and HIV. We also discuss the pathological resemblance of virus-triggered muscle fatigue with myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS).

Circulating microRNA expression signatures accurately discriminate myalgic encephalomyelitis from fibromyalgia and comorbid conditions

Evguenia Nepotchatykh, Iurie Caraus, Wesam Elremaly, Corinne Leveau, Mohamed Elbakry, Christian Godbout, Bita Rostami-Afshari, Diana Petre, Nasrin Khatami, Anita Franco, Alain Moreau; Sci Rep 2023 Feb 2;13(1):1896.

Abstract: Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS), and fibromyalgia (FM) are two chronic complex diseases with overlapping symptoms affecting multiple systems and organs over time. Due to the absence of validated biomarkers and similarity in symptoms, both disorders are misdiagnosed, and the comorbidity of the two is often unrecognized. Our study aimed to investigate the expression profiles of 11 circulating miRNAs previously associated with ME/CFS pathogenesis in FM patients and individuals with a comorbid diagnosis of FM associated with ME/CFS (ME/CFS + FM), and matched sedentary healthy controls. Whether these 11 circulating miRNAs expression can differentiate between the two disorders was also examined. Our results highlight differential circulating miRNAs expression signatures between ME/CFS, FM and ME/CFS + FM, which also correlate to symptom severity between ME/CFS and ME/CFS + FM groups. We provided a prediction model, by using a machine-

learning approach based on 11 circulating miRNAs levels, which can be used to discriminate between patients suffering from ME/CFS, FM and ME/CFS + FM. These 11 miRNAs are proposed as potential biomarkers for discriminating ME/CFS from FM. The results of this study demonstrate that ME/CFS and FM are two distinct illnesses, and we highlight the comorbidity between the two conditions. Proper diagnosis of patients suffering from ME/CFS, FM or ME/CFS + FM is crucial to elucidate the pathophysiology of both diseases, determine preventive measures, and establish more effective treatments.

Endothelial dysfunction in ME/CFS patients

Miriam Kristine Sandvik, Kari Sørland, Elisabeth Leirgul, Ingrid Gurvin Rekeland, Christina Særsten Stavland, Olav Mella, Øystein Fluge; PLoS One 2023 Feb 2;18(2):e0280942.

Objective: A few earlier studies have found impaired endothelial function in patients with Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS). The present study investigated large-vessel and small-vessel endothelial function in patients with ME/CFS.

Study design: The study was a substudy of the RituxME trial, a national, multicenter, randomized, double-blind, placebo-controlled phase III study on the effect of rituximab vs. placebo in ME/CFS patients in Norway. Flow-mediated dilation (FMD) and post-occlusive reactive hyperemia (PORH) was measured at baseline and after 18 months of treatment in 39 patients and compared with healthy controls. Other outcome measures were symptom severity and various physical function measures.

Results: ME/CFS patients had markedly reduced FMD compared to healthy controls at baseline (5.1% vs. 8.2%, $p< 0.0001$, adjusted for arterial diameter and sex), and significantly lower microvascular regulation measured by PORH than healthy controls (1354 PU vs. 2208 PU, $p = 0.002$). There were no differences between the treatment and placebo groups in symptom changes or vascular measures. As a group, the ME/CSF patients experienced a slight, but significant improvement in clinical symptoms after 18 months. PORH, but not FMD, was similarly improved (1360 to 1834 PU, $p = 0.028$). There was no significant correlation between FMD and PORH. There were non-significant tendencies towards associations between symptom severity/physical function measures and lower FMD and PORH, and a significant correlation between PORH and steps per 24 hours at baseline.

Conclusions: ME/CFS patients had reduced macro- and microvascular endothelial function, indicating that vascular homeostasis may play a role in the clinical presentation of this disease.

Gastric dysmotility and gastrointestinal symptoms in myalgic encephalomyelitis/chronic fatigue syndrome

Elisabeth K Steinsvik, Trygve Hausken, Øystein Fluge, Olav Mella, Odd Helge Gilja; Scand J Gastroenterol 2023 Feb 2;1-8.

Background: Gastrointestinal symptoms are common in ME/CFS, but there is a knowledge gap in the literature concerning gastrointestinal motility features and detailed symptom description.

Objective: In this study, we aimed to characterize gastric motility and gastric symptoms in response to a liquid meal.

Methods: We included 20 patients with ME/CFS with abdominal complaints who were recruited to a double-blind randomized placebo-controlled trial of Rituximab. The patients of this sub study were examined with an ultrasound drink test, and gastrointestinal symptoms were evaluated using the Rome III questionnaire and Irritable Bowel Syndrome Symptom Severity Scale (IBS-SSS) questionnaire.

Results: We found that patients commonly reported fullness/bloating (75%), abdominal pain (45%) and nausea (35%). Ultrasound measurements revealed lower proximal measurements of the stomach after a meal ($p < 0.01$) and larger fasting antral area ($p = 0.019$) compared to healthy controls. The patients had a stronger symptomatic response to the liquid meal compared to healthy controls regarding epigastric pain, discomfort and nausea ($p < 0.05$).Ninety percent of the patients reported bowel movement frequencies within the normal range but scored high on bowel habit dissatisfaction and life disruption.

Conclusion: The patients presented with fullness/bloating, nausea and epigastric pain, showed signs of impaired gastric accommodation and visceral hypersensitivity, showing that the gastrointestinal symptoms of ME/CFS patients are similar to functional dyspepsia.Key summary Gastrointestinal symptoms are common in ME/CFS, but there is a knowledge gap in the literature concerning gastrointestinal motility features and detailed symptom description. • In this study, patients with ME/CFS had signs of impaired gastric accommodation after a liquid meal. • Out of 20 patients, 15 patients reported fullness/bloating, 9 reported abdominal pain, and 7 reported nausea. The patients showed signs of visceral hypersensitivity on a drink test. • Our findings suggest that patients with ME/CFS share many similarities with patients with Functional Dyspepsia. The findings were not typical for Irritable Bowel Syndrome.

The Link Between Empty Sella Syndrome, Fibromyalgia, and Chronic Fatigue Syndrome: The Role of Increased Cerebrospinal Fluid Pressure

Mieke Hulens, Wim Dankaerts, Ricky Rasschaert, Frans Bruyninckx, Peter De Mulder, Chris Bervoets; J Pain Res 2023 Jan 25;16:205-219.

Abstract: The etiopathogenesis of fibromyalgia (FM) and chronic fatigue syndrome (CFS) is not yet elucidated. Hypothalamo-pituitary-adrenal (HPA) axis dysfunction is reflected in the hormonal disturbances found in FM and CFS. Some study groups have introduced a novel hypothesis that moderate or intermittent intracranial hypertension may be involved in the etiopathogenesis of FM and CFS. In these conditions, hormonal disturbances may be caused by the mechanical effect of increased cerebrospinal fluid pressure, which hampers blood flow in the pituitary gland. Severe intracranial pressure may compress the pituitary gland, resulting in primary empty sella (ES), potentially leading to pituitary hormone deficiencies. The aim of this narrative review was to explore whether similar hormonal changes and symptoms exist between primary ES and FM or CFS and to link them to cerebrospinal fluid pressure dysregulation. A thorough search of the PubMed and Web of Science databases and the reference lists of the included studies revealed that several clinical characteristics were more prevalent in primary ES, FM or CFS patients than in controls, including increased cerebrospinal fluid pressure, obesity, female sex, headaches and migraine, fatigue, visual disturbances (visual acuity and eye motility abnormalities), vestibulocochlear disturbances (vertigo and neurosensorial hearing loss), and bodily pain (radicular pain and small-fiber neuropathy). Furthermore, challenge tests of the pituitary gland showed similar abnormalities in all three conditions: blunted adrenocorticotropic hormone, cortisol, growth hormone, luteinizing hormone, and thyroid stimulating hormone responses and an increased prolactin response. The findings of this narrative review provide further support for the hypothesis that moderately or intermittently increased cerebrospinal fluid pressure is involved in the pathogenesis of FM and CFS and should stimulate further research into the etiopathogenesis of these conditions.

A description of the current status of chronic fatigue syndrome and associated factors among university students in Wuhan, China

Lunbing Luo, Yutong Zhang, Tao Huang, Fang Zhou, Change Xiong, Yang Liu, Piyong Zhai, Guiping Wang, Jianhua Tan, Chengjun Jiao, Xin Chen, Jiao Yu, Yuhao Qiao, Shuqi Ren, Xiaohui Hu, Jianbo Zhan, Jing Cheng; Front Psychiatry 2023 Jan 12;13:1047014.

Introduction: Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) is a group of chronic conscious fatigue that is not easily relieved by rest and is accompanied by corresponding physiological dysfunction and psychological symptoms. However, due to the insufficient understanding of the pathogenesis of ME/CFS, there is currently a lack of effective treatment methods. In addition, there are few surveys on the current status of ME/CFS in the central region of China, and the data on ME/CFS among university students in the central region are lacking.

This group conducted a survey on university students in Wuhan, Hubei Province in 2022 to collect and analyze the current status of ME/CFS among university students in central China for the first time, aiming to understand the current development of ME/CFS among university students, investigate the influencing factors of its prevalence, fill the data gaps, and provide a reliable basis for developing interventions for chronic fatigue syndrome among university students.

Methods: A cross-sectional study was conducted among university students in a university in Hubei province. Data were collected via online questionnaire surveys. The contents included demographic characteristics, lifestyles, disease history, depression, anxiety, sleep, ME/CFS and other associated factors. SAS 9.4 statistical software was used to analyze and estimate the effect of associated factors on ME/CFS.

Results: A total of 1826 subjects were included in the final analysis. The results showed that the prevalence of ME/CFS in university students was 6.25%. Univariate analysis showed that exercise, alcohol consumption, study, overnights, diet, anxiety, depression, and sleep quality were associated with ME/CFS ($P < 0.05$). Multivariate analysis showed that overnights, overeating, anxiety, and sleep quality were independent risk factors, while learning was a protective factor.

Conclusion: College students should pay enough attention to ME/CFS, improve their understanding of ME/CFS, and improve people's ability to understand ME/CFS.

The persistent viral infections in the development and severity of myalgic encephalomyelitis/chronic fatigue syndrome

Santa Rasa-Dzelzkaleja, Angelika Krumina, Svetlana Capenko, Zaiga Nora-Krukle, Sabine Gravelsina, Anda Vilmane, Lauma Ievina, Yehuda Shoenfeld, Modra Murovska; J Transl Med 2023 Jan 18;21(1):33.

Background: Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) is a multifactorial disease with an unexplained aetiology in which viral infections are possible trigger factors. The aim of this study was to determine the involvement of human herpesvirus (HHV)-6A/B, HHV-7, and parvovirus B19 (B19V) in the etiopathogenesis of ME/CFS.

Methods: 200 patients with clinically diagnosed ME/CFS and 150 apparently healthy individuals were enrolled in this study. Single-round, nested, and quantitative real-time polymerase chain reactions (PCR) were used to detect the presence and load of HHV-6A/B, HHV-7, and B19V. HHV-6A and HHV-6B were distinguished by PCR and restriction analysis. Immunoenzymatic assays were applied to estimate the presence of virus-specific antibodies and the level of cytokines.

Results: HHV-6A/B, HHV-7, and B19V specific antibodies were detected among patients and healthy individuals in 92.1% and 76.7%, 84.6% and 93.8%, and 78% and 67.4% of cases. HHV-6B had 99% of HHV-6 positive patients. Latent HHV-6A/B, HHV-7, and B19V infection/co-infection was observed in 51.5% of the patients and 76.7% of the healthy individuals, whereas active-45% of the ME/CFS patients and 8.7% of healthy individuals. HHV-6A/B load in patients with a persistent infection/coinfection in a latent and active phase was 262 and 653.2 copies/106 cells, whereas HHV-7 load was 166.5 and 248.5 copies/106 cells, and B19V-96.8 and 250.8 copies/106 cells, respectively. ME/CFS patients with persistent infection in an active phase had a higher level of pro-inflammatory cytokines (interleukin(IL)-6, tumor necrosis factor-alpha(TNF-α) and IL-12) and anti-inflammatory (IL-10) than with a persistent infection in a latent phase. A significant difference was revealed in the levels of TNF-α, IL-12, and IL-10 among the patient groups without infection, with latent infection/co-infection, active single, double and triple co-infection. The levels of TNF-α, IL-12, and IL-10 are significantly higher in patients with severe compared with a moderate course of ME/CFS.

Conclusions: Significantly more persistent HHV-6A/B, HHV-7, and B19V infection/co-infection in an active phase with a higher viral load and elevated levels of pro- and anti-inflammatory cytokines among patients with ME/CFS than healthy individuals indicate the importance of these infections/coinfections in ME/CFS development. The presence of these infections/co-infections influences the ME/CFS clinical course severity.

ME/CFS and Post-Exertional Malaise among Patients with Long COVID

Leonard A Jason, Joseph A Dorri; Neurol Int 2022 Dec 20;15(1):1-11.

Abstract: This study sought to ascertain the prevalence of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) among a sample of 465 patients with Long COVID. The participants completed three questionnaires: (1) a new questionnaire measuring both the frequency and severity of 38 common symptoms of COVID and Long COVID, (2) a validated short form questionnaire assessing ME/CFS, and (3) a validated questionnaire measuring post-exertional malaise. The population was predominantly white, female, and living in North America. The mean duration since the onset of COVID-19 symptoms was 70.5 weeks. Among the 465 participants, 58% met a ME/CFS case definition. Of respondents who reported that they had ME/CFS only 71% met criteria for ME/CFS and of those who did not report they had ME/CFS, 40% nevertheless did meet criteria for the disease: both overdiagnosis and under-diagnosis were evident on self-report. This study supports prior findings that ME/CFS occurs with high prevalence among those who have persistent COVID-19 symptoms.

Tissue specific signature of HHV-6 infection in ME/CFS

Francesca Kasimir, Danny Toomey, Zheng Liu, Agnes C Kaiping, Maria Eugenia Ariza, Bhupesh K Prusty; Front Mol Biosci 2022 Dec 14;9:1044964.

Abstract: First exposure to various human herpesviruses (HHVs) including HHV-6, HCMV and EBV does not cause a life-threatening disease. In fact, most individuals are frequently unaware of their first exposure to such pathogens. These herpesviruses acquire lifelong latency in the human body where they show minimal genomic activity required for their survival. We hypothesized that it is not the latency itself but a timely, regionally restricted viral reactivation in a sub-set of host cells that plays a key role in disease development. HHV-6 (HHV-6A and HHV-6B) and HHV-7 are unique HHVs that acquire latency by integration of the viral genome into sub-telomeric region of human chromosomes. HHV-6 reactivation has been linked to Alzheimer's Disease, Chronic Fatigue Syndrome, and many other diseases. However, lack of viral activity in commonly tested biological materials including blood or serum strongly suggests tissue specific localization of active HHV-6 genome. Here in this paper, we attempted to analyze active HHV-6 transcripts in postmortem tissue biopsies from a small cohort of ME/CFS patients and matched controls by fluorescence in situ hybridization using a probe against HHV-6 microRNA (miRNA), miR-aU14. Our results show abundant viral miRNA in various regions of the human brain and associated neuronal tissues including the spinal cord that is only detected in ME/CFS patients and not in controls. Our findings provide evidence of tissue-specific active HHV-6 and EBV infection in ME/CFS, which along with recent work demonstrating a possible relationship between herpesvirus infection and ME/CFS, provide grounds for renewed discussion on the role of herpesviruses in ME/CFS.

Genetic risk factors for ME/CFS identified using combinatorial analysis

Sayoni Das, Krystyna Taylor, James Kozubek, Jason Sardell, Steve Gardner; J Transl Med 2022 Dec 14;20(1):598.

Background: Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) is a debilitating chronic disease that lacks known pathogenesis, distinctive diagnostic criteria, and effective treatment options. Understanding the genetic (and other) risk factors associated with the disease would begin to help to alleviate some of these issues for patients.

Methods: We applied both GWAS and the PrecisionLife combinatorial analytics platform to analyze ME/CFS cohorts from UK Biobank, including the Pain Questionnaire cohort, in a case-control design with 1000 cycles of fully random permutation. Results from this study were supported by a series of replication and cohort comparison experiments, including use of disjoint

Verbal Interview CFS, postviral fatigue syndrome and fibromyalgia cohorts also derived from UK Biobank, and compared results for overlap and reproducibility.

Results: Combinatorial analysis revealed 199 SNPs mapping to 14 genes that were significantly associated with 91% of the cases in the ME/CFS population. These SNPs were found to stratify by shared cases into 15 clusters (communities) made up of 84 high-order combinations of between 3 and 5 SNPs. p-values for these communities range from 2.3 × 10-10 to 1.6 × 10-72. Many of the genes identified are linked to the key cellular mechanisms hypothesized to underpin ME/CFS, including vulnerabilities to stress and/or infection, mitochondrial dysfunction, sleep disturbance and autoimmune development. We identified 3 of the critical SNPs replicated in the post-viral fatigue syndrome cohort and 2 SNPs replicated in the fibromyalgia cohort. We also noted similarities with genes associated with multiple sclerosis and long COVID, which share some symptoms and potentially a viral infection trigger with ME/CFS.

Conclusions: This study provides the first detailed genetic insights into the pathophysiological mechanisms underpinning ME/CFS and offers new approaches for better diagnosis and treatment of patients.

Muscle sodium content in patients with Myalgic Encephalomyelitis/Chronic Fatigue Syndrome

Elisabeth Petter, Carmen Scheibenbogen, Peter Linz, Christian Stehning, Klaus Wirth, Titus Kuehne, Marcus Kelm; J Transl Med 2022 Dec 9;20(1):580.

Background: Muscle fatigue and pain are key symptoms of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS). Although the pathophysiology is not yet fully understood, there is ample evidence for hypoperfusion which may result in electrolyte imbalance and sodium overload in muscles. Therefore, the aim of this study was to assess levels of sodium content in muscles of patients with ME/CFS and to compare these to healthy controls.

Methods: Six female patients with ME/CFS and six age, BMI and sex matched controls underwent 23Na-MRI of the left lower leg using a clinical 3T MR scanner before and after 3 min of plantar flexion exercise. Sodium reference phantoms with solutions of 10, 20, 30 and 40 mmol/L NaCl were used for quantification. Muscle sodium content over 40 min was measured using a dedicated plugin in the open-source DICOM viewer Horos. Handgrip strength was measured and correlated with sodium content.

Results: Baseline tissue sodium content was higher in all 5 lower leg muscle compartments in ME/CFS compared to controls. Within the anterior extensor muscle compartment, the highest difference in baseline muscle sodium content between ME/CFS and controls was found (mean ± SD; 12.20 ± 1.66 mM in ME/CFS versus 9.38 ± 0.71 mM in controls,

p = 0.0034). Directly after exercise, tissue sodium content increased in gastrocnemius and triceps surae muscles with + 30% in ME/CFS (p = 0.0005) and + 24% in controls (p = 0.0007) in the medial gastrocnemius muscle but not in the extensor muscles which were not exercised. Compared to baseline, the increase of sodium content in medial gastrocnemius muscle was stronger in ME/CFS than in controls with + 30% versus + 17% to baseline at 12 min (p = 0.0326) and + 29% versus + 16% to baseline at 15 min (p = 0.0265). Patients had reduced average handgrip strength which was associated with increased average muscle tissue sodium content (p = 0.0319, R2 = 0.3832).

Conclusion: Muscle sodium content before and after exercise was higher in ME/CFS than in healthy controls. Furthermore, our findings indicate an inverse correlation between muscle sodium content and handgrip strength. These findings provide evidence that sodium overload may play a role in the pathophysiology of ME/CFS and may allow for potential therapeutic targeting.

Differences in Symptoms among Black and White Patients with ME/CFS

Leonard A Jason, Chelsea Torres; J Clin Med 2022 Nov 12;11(22):6708.

Abstract: Study samples of patients with myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) have primarily involved White subjects, so the literature on ethnic differences is sparse. The current study identified a sample of 19 Black patients diagnosed with ME/CFS and compared them with White patients with ME/CFS, as well as with healthy controls. The studies used a similar psychometrically sound assessment tool to assess symptoms in all subjects. Findings indicated there were significant differences between patients with ME/CFS versus controls, but few differences between patients who identified as Black or White. The results suggest there might be few symptom differences between patients with ME/CFS in these two ethnic groups. The implications of these findings are discussed.

Saliva antibody-fingerprint of reactivated latent viruses after mild/asymptomatic COVID-19 is unique in patients with myalgic-encephalomyelitis/chronic fatigue syndrome

Eirini Apostolou, Muhammad Rizwan, Petros Moustardas, Per Sjögren, Bo Christer Bertilson, Björn Bragée, Olli Polo, Anders Rosén; Front Immunol 2022 Oct 20;13:949787.

Background: Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) is a chronic disease considered to be triggered by viral infections in a majority of cases. Symptoms overlap largely with those of post-acute sequelae of COVID-19/long-COVID implying common pathogenetic mechanisms. SARS-CoV-2 infection is risk factor for sustained latent virus

reactivation that may account for the symptoms of post-viral fatigue syndromes. The aim of this study was first to investigate whether patients with ME/CFS and healthy donors (HDs) differed in their antibody response to mild/asymptomatic SARS-CoV-2 infection. Secondly, to analyze whether COVID-19 imposes latent virus reactivation in the cohorts.

Methods: Anti-SARS-CoV-2 antibodies were analyzed in plasma and saliva from non-vaccinated ME/CFS (n=95) and HDs (n=110) using soluble multiplex immunoassay. Reactivation of human herpesviruses 1-6 (HSV1, HSV2, VZV, EBV, CMV, HHV6), and human endogenous retrovirus K (HERV-K) was detected by anti-viral antibody fingerprints in saliva.

Results: At 3-6 months after mild/asymptomatic SARS-CoV-2 infection, virus-specific antibodies in saliva were substantially induced signifying a strong reactivation of latent viruses (EBV, HHV6 and HERV-K) in both cohorts. In patients with ME/CFS, antibody responses were significantly stronger, in particular EBV-encoded nuclear antigen-1 (EBNA1) IgG were elevated in patients with ME/CFS, but not in HDs. EBV-VCA IgG was also elevated at baseline prior to SARS-infection in patients compared to HDs.

Conclusion: Our results denote an altered and chronically aroused anti-viral profile against latent viruses in ME/CFS. SARS-CoV-2 infection even in its mild/asymptomatic form is a potent trigger for reactivation of latent herpesviruses (EBV, HHV6) and endogenous retroviruses (HERV-K), as detected by antibody fingerprints locally in the oral mucosa (saliva samples). This has not been shown before because the antibody elevation is not detected systemically in the circulation/plasma.

Orthostatic intolerance and neurocognitive impairment in Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS)

Caroline L Gaglio, Mohammed F Islam, Joseph Cotler, Leonard A Jason; Epidemiol Methods 2022 Oct 10;11(1):20210033.

Objectives: The Institute of Medicine (IOM 2015. Beyond Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: Redefining an Illness. Washington: The National Academies Press) suggested new criteria for Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS), which requires an endorsement of either neurocognitive impairment or orthostatic intolerance (OI) in addition to other core symptoms. While some research supports the inclusion of OI as a core symptom, others argue that overlap with neurocognitive impairment does not justify the either/or option. The current study assessed methods of operationalizing OI using items from the DePaul Symptom Questionnaire (DSQ-1 and -2) as a part of the IOM criteria. Evaluating the relationship between OI and neurocognitive symptoms may lead to a better understanding of diagnostic criteria for ME/CFS.

Methods: Two-hundred and forty-two participants completed the DSQ. We examined how many participants met the IOM criteria while endorsing different frequencies and severities of various OI symptoms.

Results: Neurocognitive impairment was reported by 93.4% of respondents. OI without concurrent neurocognitive symptoms only allowed for an additional 1.7-4.5% of participants to meet IOM criteria.

Conclusions: Neurocognitive symptoms and OI overlap in ME/CFS, and our results do not support the IOM's inclusion of neurocognitive impairment and OI as interchangeable symptoms. Furthermore, our findings highlight the need for a uniform method of defining and measuring OI via self-report in order to accurately study OI as a symptom of ME/CFS.

Biomarkers in the diagnostic algorithm of myalgic encephalomyelitis/chronic fatigue syndrome

Sabine Gravelsina, Anda Vilmane, Simons Svirskis, Santa Rasa-Dzelzkaleja, Zaiga Nora-Krukle, Katrine Vecvagare, Angelika Krumina, Iana Leineman, Yehuda Shoenfeld, Modra Murovska; Front Immunol 2022 Oct 10;13:928945.

Abstract: Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) is a complex disease that is mainly diagnosed based on its clinical symptoms. Biomarkers that could facilitate the diagnosis of ME/CFS are not yet available; therefore, reliable and clinically useful disease indicators are of high importance. The aim of this work was to analyze the association between ME/CFS clinical course severity, presence of HHV-6A/B infection markers, and plasma levels of autoantibodies against adrenergic and muscarinic acetylcholine receptors. A total of 134 patients with ME/CFS and 33 healthy controls were analyzed for the presence of HHV-6A/B using PCRs, and antibodies against beta2-adrenergic receptors (ß2AdR) and muscarinic acetylcholine receptors (M3 AChR and M4 AChR) using ELISAs. HHV-6A/B U3 genomic sequence in whole-blood DNA was detected in 19/31 patients with severe ME/CFS, in 18/73 moderate ME/CFS cases, and in 7/30 mild ME/CFS cases. Severity-related differences were found among those with a virus load of more than 1,000 copies/106 PBMCs. Although no disease severity-related differences in anti-ß2AdR levels were observed in ME/CFS patients, the median concentration of these antibodies in plasma samples of ME/CFS patients was 1.4 ng/ml, while in healthy controls, it was 0.81 ng/ml, with a statistically significant increased level in those with ME/CFS ($p = 0.0103$). A significant difference of antibodies against M4 AChR median concentration was found between ME/CFS patients (8.15 ng/ml) and healthy controls (6.45 ng/ml) ($p = 0.0250$). The levels of anti-M4 plotted against disease severity did not show any difference; however, increased viral load correlates with the increase in anti-M4 level. ME/CFS patients with high HHV-6 load have a more

severe course of the disease, thus confirming that the severity of the disease depends on the viral load-the course of the disease is more severe with a higher viral load. An increase in anti-M4 AchR and anti-ß2AdR levels is detected in all ME/CFS patient groups in comparison to the control group not depending on ME/CFS clinical course severity. However, the increase in HHV-6 load correlates with the increase in anti-M4 level, and the increase in anti-M4 level, in turn, is associated with the increase in anti-ß2AdR level. Elevated levels of antibodies against ß2AdR and M4 receptors in ME/CFS patients support their usage as clinical biomarkers in the diagnostic algorithm of ME/CFS.

Autoimmune gene expression profiling of fingerstick whole blood in Chronic Fatigue Syndrome

Zheng Wang, Michelle F Waldman, Tara J Basavanhally, Aviva R Jacobs, Gonzalo Lopez, Regis Y Perichon, Johnny J Ma, Elyse M Mackenzie, James B Healy, Yixin Wang, Sarah A Hersey; J Transl Med 2022 Oct 25;20(1):486.

Background: Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) is a debilitating condition that can lead to severe impairment of physical, psychological, cognitive, social, and occupational functions. The cause of ME/CFS remains incompletely understood. There is no clinical diagnostic test for ME/CFS. Although many therapies have been used off-label to manage symptoms of ME/CFS, there are limited, if any, specific therapies or cure for ME/CFS. In this study, we investigated the expression of genes specific to key immune functions, and viral infection status in ME/CFS patients with an aim of identifying biomarkers for characterization and/or treatment of the disease.

Methods: In 2021, one-hundred and sixty-six (166) patients diagnosed with ME/CFS and 83 healthy controls in the US participated in this study via a social media-based application (app). The patients and heathy volunteers consented to the study and provided self-collected finger-stick blood and first morning void urine samples from home. RNA from the fingerstick blood was tested using DxTerity's 51-gene autoimmune RNA expression panel (AIP). In addition, DNA from the same fingerstick blood sample was extracted to detect viral load of 4 known ME/CFS associated viruses (HHV6, HHV7, CMV and EBV) using a real-time PCR method.

Results: Among the 166 ME/CFS participants in the study, approximately half (49%) of the ME/CFS patients reported being house-bound or bedridden due to severe symptoms of the disease. From the AIP testing, ME/CFS patients with severe, bedridden conditions displayed significant increases in gene expression of IKZF2, IKZF3, HSPA8, BACH2, ABCE1 and CD3D, as compared to patients with mild to moderate disease conditions. These six aforementioned genes were further upregulated in the 22 bedridden participants who suffer not only from ME/CFS but also from other autoimmune diseases. These genes are involved in T cell, B cell and

autoimmunity functions. Furthermore, IKZF3 (Aiolos) and IKZF2 (Helios), and BACH2 have been implicated in other autoimmune diseases such as systemic lupus erythematosus (SLE) and Rheumatoid Arthritis (RA). Among the 240 participants tested with the viral assays, 9 samples showed positive results (including 1 EBV positive and 8 HHV6 positives).

Conclusions: Our study indicates that gene expression biomarkers may be used in identifying or differentiating subsets of ME/CFS patients having different levels of disease severity. These gene targets may also represent opportunities for new therapeutic modalities for the treatment of ME/CFS. The use of social media engaged patient recruitment and at-home sample collection represents a novel approach for conducting clinical research which saves cost, time and eliminates travel for office visits.

Genetic and epigenetic regulation of Catechol-O-methyltransferase in relation to inflammation in chronic fatigue syndrome and Fibromyalgia

Andrea Polli, Jolien Hendrix, Kelly Ickmans, Jelena Bakusic, Manosij Ghosh, Dora Monteyne, Brigitte Velkeniers, Bram Bekaert, Jo Nijs, Lode Godderis; J Transl Med 2022 Oct 25;20(1):487.

Methods: A case-control study with repeated-measures design was used to reduce the chance of false positive and increase the power of our findings. Fifty-four participants (28 patients with CFS/FM and 26 controls) were assessed twice within 4 days. The assessment included clinical questionnaires, neurophysiological assessment (pain thresholds, temporal summation, and conditioned pain modulation), and blood withdrawal in order to assess rs4818, rs4633, and rs4680 COMT polymorphisms and perform haplotype estimation, DNA methylation in the COMT gene (both MBCOMT and S-COMT promoters), and cytokine expression (TNF-α, IFN-γ, IL-6, and TGF-ß).

Results: COMT haplotypes were associated with DNA methylation in the S-COMT promoter, TGF-ß expression, and symptoms. However, this was not specific for one condition. Significant betweengroup differences were found for increased DNA methylation in the MB-COMT promoter and decreased IFN-γ expression in patients.

Discussion: Our results are consistent with basic and clinical research, providing interesting insights into genetic-epigenetic regulatory mechanisms. MB-COMT DNA methylation might be an independent factor contributing to the pathophysiology of CFS/FM. Further research on DNA methylation in complex conditions such as CFS/FM is warranted. We recommend future research to employ a repeated-measure design to control for biomarkers variability and within-subject changes.

Global prevalence of chronic fatigue syndrome among long COVID-19 patients: A systematic review and meta-analysis

Nader Salari, Yassaman Khodayari, Amin Hosseinian-Far, Hosna Zarei, Shabnam Rasoulpoor, Hakimeh Akbari, Masoud Mohammadi; Biopsychosoc Med 2022 Oct 23;16(1):21.

Background: Chronic fatigue syndrome is a persistent and debilitating disorder. According to several studies, chronic fatigue syndrome has been identified among recovered COVID-19 patients as the most common symptom of long COVID. The aim of this systematic review and meta-analysis study was to obtain the prevalence of chronic fatigue syndrome in long COVID cases.

Methods: In this systematic review and meta-analysis, we analysed reported results of studies that assessed the occurrence of chronic fatigue syndrome among COVID-19 patients four weeks after the onset of symptoms. The study selection was commenced by searching PubMed, Web of Science, Science Direct, Scopus, Embase, and Google scholar using the keywords of Chronic fatigue syndrome, COVID-19, and post-COVID-19 syndrome. The searches were without a lower time limit and until April 2022. Heterogeneity of studies was assessed using the I2 index, and a random effects model was used for analysis. Data analysis was performed within the Comprehensive Meta-Analysis software (version 2).

Results: The pooled prevalence of chronic fatigue syndrome four weeks after the onset of COVID-19 symptoms, in 52 studies with a sample size of 127,117, was 45.2% (95% CI: 34.1-56.9%). Metaregression analysis in examining the effects of the two factors of sample size, and year of study on the changes in the overall prevalence, showed that with increasing sample size, and year of study, the prevalence of chronic fatigue syndrome among long COVID patients ($p < 0.05$).

Conclusion: Our results show that the overall prevalence of chronic fatigue syndrome as a long COVID symptom is 45.2%. Chronic fatigue after infection with COVID-19 can negatively affect personal and social lives. Given such significant negative consequences caused by the syndrome, it is recommended that health policymakers allocate funds to reduce the adverse effects of this syndrome, by creating programs to support long COVID patients.

Exosome-associated mitochondrial DNA from patients with myalgic encephalomyelitis/chronic fatigue syndrome stimulates human microglia to release IL-1β

Irene Tsilioni, Benjamin Natelson, Theoharis C Theoharides; Eur J Neurosci 2022 Nov;56(10):5784-5794.

Abstract: Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) is a debilitating disease that presents with fatigue, sleep disturbances, malaise, and cognitive problems. The pathogenesis of ME/CFS is presently unknown, and serum levels of potential biomarkers have been inconsistent. Here, we show that mitochondrial DNA (mtDNA) associated with serum exosomes, is increased in ME/CFS patients only after exercise. Moreover, exosomes isolated from patients with ME/CFS stimulate significant release of IL-1ß from cultured human microglia. These results provide evidence that activation of microglia by serum-derived exosomes may serve as a potential novel pathogenetic factor and target for treatment of ME/CFS.

IN MEMORIUM

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

Ruby Hokana, 95, died at her assisted living home in Moorhead, Minn. on November 2, 2022. She had worked as a Sunday School teacher for 25 years, sang in a choir and worked as a librarian at a junior high school for a couple of decades. She and her husband Archie were married for 75 years and had a daughter and a son. Ruby loved to sing, play bridge, and take long walks. In her later years, her physical activities became limited by ME/CFIDS.

Maeve Boothby O'Neill, 27, passed away in October of 2021 after extreme suffering for nearly half her life. She lived with her parents, Sarah and Sean, in Exeter, Devon UK. Maeve needed a feeding tube during her last year alive and went to The Wonford Hospital where her severe disease was dismissed as they believed the PACE trial nonsense, told to them by a psychiatrist that it was just mental and CBT and GET would help. Maeve was highly intelligent and creative, but the severity of the illness was mishandled and brought on her demise.

DONATIONS

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

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The Edward Taylor Family & the Dr. Ed Taylor Family

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