Guildford ME/CFS Support Group
(& West Surrey)

Newsletter

December 2018

Drawing by CFS sufferer Shantel Palmer
Credit for the original concept of the drawing in our June newsletter goes to
Mike Payne Studio - Pinterest

Future dates

Open to all members and carers

For details of the upcoming meetings please email:
GuildfordME@hotmail.co.uk

Could crippled Herpesviruses be contributing to ME/CFS and other diseases?

Source: http://simmaronresearch.com/2018/11/crippled-herpesviruses-contributing-chronic-fatigue-syndrome-mecfs-diseases/

Cort Johnson 17th November 2018

"We provide evidence…. that herpesviruses dUTPases…(have) unique immunoregulatory functions that can alter the inflammatory microenvironment and thus exacerbate the immune pathology of herpesvirus-related diseases including myalgic encephalomyelitis/chronic fatigue syndrome, autoimmune diseases, and cancer." Williams et. al.

Most people are exposed to herpesviruses such as Epstein-Barr virus (EBV) early in their lives and carry the viruses in latent form in their B cells. Sometimes – particularly when the body is under stress – the immune system slips a bit and the viruses reactivate, causing anything from no symptoms at all to – more rarely – being associated with such devastating disorders as autoimmune diseases and cancer. One study suggests that glucocorticoids released during stress tell EBV to come out of hibernation.

Herpesviruses have a long enough history in ME/CFS for the disease to have been referred to as chronic Epstein-Barr virus syndrome by some in the 1980's. However, over thirty years later, the role herpesviruses play in ME/CFS is unclear. Are they simply a common trigger of ME/CFS or do they play a more fundamental role? Several studies have found no evidence of herpesvirus reactivation while others suggest immune problems exist that could allow the virus to wreak havoc in some patients.

The Ohio State University team lead by Maria Ariza and Marshall Williams believes researchers have missed an obvious possibility. They don't believe the virus per se is the problem. (If they're right, you can basically throw out all the viral load studies.)

It's not that the virus is reactivating; in fact, they believe the virus may be most dangerous in ME/CFS when it fails to reactivate properly and produces kind of a very low-level, smouldering infection. Even as the immune system in people with ME/CFS is mostly smothering EBV, the virus is producing a protein that's causing harm.

"Surprisingly, none of these studies have approached the possibility that virus encoded proteins, rather than the viruses themselves, may act as drivers of/contribute to the pathophysiological alterations observed in a subset of patients with ME/CFS." Authors

It turns out that in herpesviruses a failure to replicate produces something called "abortive lytic replication". As it does that, it produces proteins that get ejected into the blood stream or get inserted in vesicles called exosomes, which then travel through the blood. These exosomes are now believed to play important roles in cell to cell communication. (Maureen Hanson is now studying exosomes in ME/CFS).

The protein released during abortive lytic replication is an enzyme called deoxyuridine triphosphate nucleotidohydrolase or EBV-dUTPase. The unusual herpesvirus dUTPase saga at Ohio State University began way back in 1985 with a Williams/Glaser study. It gathered force in the mid-2000's with a series of papers suggesting the protein might be a good target for chemotherapy, produced "sickness behaviour" in mice, and triggered pro-inflammatory cytokine production.

In 2010 Ronald Glaser won an NIH grant to study the protein titled STRESS EFFECTS ON VIRUS PROTEIN INDUCED INFLAMMATION AND SICKNESS BEHAVIOR and the hunt was on to determine dUTPase's effects in ME/CFS. (This long standing grant continues today under Ariza and Williams' name.)

A 2013 paper suggested dUTPase might provide a way to reconcile the studies which had not found herpesvirus reactivation in ME/CFS with others suggesting that the virus could be having profound effects. It found that even under conditions of low viral load, herpesvirus dUTPases were able to trigger a pro-inflammatory response strong enough to promote atherosclerosis and perhaps even precipitate a heart attack. In 2012, Williams, Ariza , Glaser and Martin Lerner and Lenny Jason produced the first direct evidence that dUTPases may be producing problems in ME/CFS. The small study found a prolonged antibody response to the protein in a large subset of ME/CFS patients.

A 2014 study indicated that during EBV's last gasp while undergoing lytic replication, the virus was pouring enough dUTPase into exosomes to produce major immune effects that supported or promoted the establishment/maintenance of further EBV infections.

The 2017 ME/CFS Study
J Med Virol. 2017 Mar 17. doi: 10.1002/jmv.24810. [Epub ahead of print] Myalgic Encephalomyelitis/Chronic Fatigue Syndrome and Gulf War Illness patients exhibit increased humoral responses to the Herpesviruses-encoded dUTPase: Implications in disease pathophysiology. Halpin P1, Williams MV1,2, Klimas NG3,4, Fletcher MA3,4, Barnes Z3,5, Ariza ME1,2.

Then, in an expanded version of the 2012 study, the group in 2017 (which also included Nancy Klimas and Mary Fletcher) presented stronger evidence that herpesvirus produced dUTPases were present and could be causing harm in a subset of ME/CFS patients. The study looked for evidence that herpesvirus produced dUTPases were tweaking the immune systems of 74 ME/CFS patients – and found it.

The fact that antibodies to dUTPases produced by both EBV and HHV-6 were found in almost fifty percent of the ME/CFS patients in the study suggested that the two herpesviruses may be reactivating each other in ME/CFS – a feature also found in immune suppressed states such as organ transplant patients and drug induced hypersensitivity syndrome (DRSS).
Plus, for the first time, autoantibodies to the human dUTPases (humans produce a dUTPase as well) were found in ME/CFS – at much higher levels than in healthy controls (39% vs. 5%).
The authors suggested the Loebel's 2014 study, which uncovered problems that ME/CFS patients' T cell's were having in suppressing EBV, could account for the evidence of multiple herpesvirus reactivations.

The immune system does ultimately jump in and suppress the virus in most people with ME/CFS, but it takes its time to do that. That delay appears to give herpesviruses the time they need to spill immune altering dUTPases into the bloodstream and slip them into exosomes to travel through the body.

Besides the immune alterations possibly caused by herpesvirus produced dUTPases, they may be contributing to numerous symptoms including flu-like symptoms, fatigue, cognitive problems, anxiety, etc. in ME/CFS.

Plus, because failed herpesvirus reactivations commonly occur alongside actual herpesvirus reactivations, herpesvirus encoded dUTPases could end up being an excellent biomarker for herpesvirus reactivations.

This strange model of partial viral reactivation could end up playing a role in ME/CFS, Gulf War Syndrome and other diseases in several ways. It could be actually driving ME/CFS in a subset of patients, or it could, along with other possibly related immune issues, be exacerbating it.

Next Steps
However it all works out, it's clear that the Ohio State University team's long embrace of this novel protein is paying off. The more work they do with herpesvirus-encoded dUTPases, the more evidence they seem to find of its role in ME/CFS and other diseases. They have an 8-year continuing NIH grant under their belts – a grant that looks like it and the herpesvirus-dUTPase-ME/CFS saga will likely continue in the foreseeable future.

If the findings hold up, it may even provide a treatment option – the authors have published a paper alerting drug-makers to the potential this escaped protein may hold in treating herpesvirus infections.

Dr. Williams reported that the group has "some exciting data" concerning the potential role dUTPase plays in autoantibody production and the neurological effects the protein may be having in people with ME/CFS. The manuscripts are being written up now and will be submitted shortly.

GET paper withdrawal shocks CBT/GET proponents – emboldens ME/CFS advocates

The overturning of CBT/GET recommendations for ME/CFS are starting to add up
Source: www.prohealth.com/me-cfs/library/get-paper-withdrawal-shocks-cbt-get-proponents-emboldens-cfs-advocates-87251

By Cort Johnson 24th October 2018

Our mission is to promote evidence-informed health decision-making by producing high-quality, relevant, accessible systematic reviews and other synthesized research evidence. Our work is internationally recognized as the benchmark for high-quality information about the effectiveness of health care. ~Cochrane

The Cochrane Reviews are the gold standard – highly respected and valued – they're the go-to reviews doctors and medical websites use to get beyond the hype and learn how effective treatments really are.

In David Tuller's superb Sept. 2018 piece Trial By Error: The Cochrane Controversy he pointed out how important a role the reviews play in bucking up the biopsychosocial view of ME/CFS, stating that "the CBT/GET ideological brigades and their enablers regularly cite Cochrane's systematic reviews". As long "as CBT/GET promoters can hide behind Cochrane's skirts", Tuller said, the biopsychosocial influence on ME/CFS research and treatment will continue.

Now in a potentially major event, the Cochrane is temporarily withdrawing the 2017 Cochrane Review on graded exercise in ME/CFS. That's not the authors choice – they're spitting mad at that idea – it's coming straight from the Cochrane editors.

Several factors make this temporary withdrawal noteworthy – and suggest it might not be so temporary after all.

1. Cochrane is withdrawing the review over the authors' objections – an unusual occurrence.
   Review withdrawal is usually based on new scientific evidence – but not in this case.
2. The Cochrane editors appear to have decided that there's a good chance that the original analysis was faulty.

Ironically, the review was not particularly laudatory. It concluded that GET was more effective at reducing fatigue than pacing, or no treatment at all, and did not worsen symptoms. It did not find evidence, though, that GET helped with pain, self-perceived changes in overall health, use of health service resources, and made little or no difference in physical functioning, depression, anxiety and sleep. The fact that the authors could not say that GET lessened an ME/CFS patient's use of health care was important as one of the justifications for employing CBT or GET is that it will reduce doctor visits.

The CBT/GET field's success is sowing the seeds of its decline. Years of federal funding from the U.K. and the Netherlands have produced enough studies to conclude that the therapies have limited efficacy at best. Why the U.K. or the Netherlands or anyone else would pour enormous amounts of money into a treatment with such little efficacy is baffling.

The Cochrane authors' conclusion that further research is needed to determine the kinds of exercise that could be most helpful could, however, potentially set the stage for years of expensive studies. More money which could have gone to getting at the cause of ME/CFS being thrown down the GET rabbit hole.

The authors probably didn't help themselves with their rather tortured attempts to find benefits. After stating in the main results section that:
"We observed little or no difference in physical functioning, depression, anxiety and sleep, and we were not able to draw any conclusions with regard to pain, self-perceived changes in overall health, use of health service resources and drop-out rate." Authors

They reported in their conclusions section that:
"A positive effect with respect to sleep, physical function and self-perceived general health has been observed, but no conclusions for the outcomes of pain, quality of life, anxiety, depression, drop-out rate and health service resources were possible. Authors

Obfuscation in Full Force
Calling the decision "disprortionate and poorly justified", the authors were not surprisingly rather upset to see their work removed from publication. A critic of the withdrawal responded to it in much the same way that Queen Mary's College responded to ME/CFS advocates' attempt to get at the PACE data: by ignoring the central issue – whether the original analysis was flawed – and going after the patient activists and then accusing the journal of folding to them.

Medscape reported that Colin Blakemore, a professor of neuroscience and philosophy at London University, said the withdrawal decision was basically a perversion of science that was done to mollify the "opinions of activists" and their "unsubstantiated views". He accused Cochrane of capitulating to lobbying from small numbers of vocal patient groups.

Medscape, to its discredit, missed the bad science theme and jumped on the angry patient theme, stating that, "Scientists conducting studies on potential therapies say they are often harassed and verbally abused by groups that disagree with their approach."

The Cochrane editors fought back, stating that it's decision was based on "extensive feedback" and a "formal complaint" which they felt raised "important questions". Given how rare a withdrawal of a study over the authors' objections from the Cochrane Library is, one can guess that the Cochrane editors felt substantial issue, indeed, had been raised.

Given the importance the huge PACE trial with its 640 participants must have played in the original analysis, any diminishment in that controversial trial's effects might alone be enough to pretty well negate the already pretty mediocre conclusions the authors came to regarding GET. Earlier this year a re-analysis of the PACE trial data from a group which included David Tuller and other advocates such as Tom Kindlon and Alem Mathees cast doubt on virtually every major finding from the trial.

Plus a highly critical paper which re-analysed the Cochrane Review study data problems sharpened the Cochrane Editors' focus a bit. It's probably not often that the august Cochrane Reviews receive such an overt challenge. In July of this year, Mark Vink's and Alexandra Vink-Niese of the Soerabaja Research Centre in the Netherlands re-analysis of the GET studies used in the Cochrane review concluded that the Cochrane GET review was wrong and that the studies do not show that GET is safe, and in fact the suggest that GET is "ineffective".

A "Common Mental Disorder" No More

Let's dispense with one issue right away: This illness should not be housed in the Common Mental Disorders group. Whatever the historical reasons for this arrangement, it undoubtedly must lead observers to assume that Cochrane as an organization endorses the framing of CFS as a psychiatric illness. David Tuller

Last year Tuller pointed out that Cochrane is aware of the PACE controversy; aware enough to have first given another ME/CFS exercise review to reviewers outside the Common Mental Disorders division (yes, Cochrane classified ME/CFS as a "common mental disorder") who reportedly ripped it to shreds.

Cochrane just responded to Tuller's and others complaints by moving the responsibility for reviewing these trials outside of their "Common Mental Disorders" division.

Tide Turning?

The biopsychosocial field has had a rough year. But is it enough to turn off the spigot that provides the funding which keeps the field alive?

This is just one in a series of wins by ME/CFS advocates seeking more relevant research and better treatment options than the biopsychosocial field offers. The overturning of CBT/GET recommendations for ME/CFS- they are starting to add up. It's been a rough year for the biopsychosocial field….

- After Queen Mary University of London was ordered to release the raw data from the PACE trial, a re-analysis confirmed that the PACE authors reconfigured the trial in ways that produced dramatically better results
- A re-analysis by the U.S. Agency for Healthcare Research and Quality (AHRQ) of CBT/GET studies left it unable to recommend them for ME/CFS
- That prompted the Centres for Disease Control to remove recommendations for CBT/GET from its website.
- Remarkably, this year the Dutch Health Council, of all groups, recommended that GET not be used to treat ME/CFS
- In August of this year, a letter signed by over 100 academics, ten members of Parliament, and 70 patient and advocacy organizations urging an unbiased reanalysis of the PACE trial data was sent to Lancet.
- An editorial appeared in the London Times regarding that letter.
- Earlier this year Geraghty and Blease (who hails from the Harvard Medical School) argued that the "biopsychosocial framework currently applied to ME/CFS is too narrow".
- Last year Geraghty used huge patient's surveys to argue that CBT helps only a small percentage of people with ME/CFS and that GET often produces large negative outcomes.
- Last year the Journal of Health Psychology devoted an entire issue to the discussion of the PACE trial.
- In 2017 White published mediocre results from the 200 plus person GETSET trial. (Other than the Rituximab trial no non-behavioural therapy trial has been able to come close to matching the size of the huge CBT/GET trials that litter ME/CFS treatment literature.)

The Journal of Health Psychology's decision to devote an entire issue to the problems of the PACE trial raised the question when, if ever, a journal has devoted an entire issue to debunking a single trial? Citing the unwillingness of the PACE authors to engage with their critics at all, the editor of the the Journal of Health Psychology stated that "the unwillingness of the co-principal

investigators of the PACE trial to engage in authentic discussion and debate….(it) leads one to question the wisdom of such a large investment from the public purse (£5million) on what is a textbook example of a poorly done trial."

Lancet, the publisher of the original PACE trial and the recent GETSET trial and others, under the editorship of Richard Horton, is at the epicenter of a veritable storm of protest. No one, it seems, can plausibly or convincingly stand up for the study. That Horton is willing to continue to subject his lauded Lancet to such ridicule is beyond puzzling.

It bears mentioning that Horton has been editor-in-chief of Lancet for over 20 years – longer than any editor since the 1940's. He won't be there forever. Perhaps Lancet will tire of his fact defying embrace of the PACE trial, decide he's been in the chair long enough and give the editorship to a fresher face.

If the huge PACE study falls it will take others with it. The damage to the reputations of the authors – who have played a major role in the establishment of the biopsychosocial paradigm of ME/CFS and who have been so unyielding in their defence of the tarnished study – will likely be significant.

Whether these controversies will be enough to get funders in the UK, the Netherlands and elsewhere to point their dollars towards biological causes/treatments is unclear, but the Cochrane editor's temporary withdrawal of their own GET review is a notable event. If that withdrawal becomes permanent or the review's conclusions are dramatically altered, a chink in the biopsychosocial advocates' armour will result. No longer will they be able to refer to a Cochrane review for validation

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ME Association's clinical and research guide

Source: https://www.meassociation.org.uk/shop/books/mecfspvfs-an-exploration-of-the-key-clinical-issues

The 10th edition of our clinical and research guide is a must-have for anyone who has been affected by – or has an interest in – ME/CFS.

It has been written by ME Association medical adviser, Dr Charles Shepherd, and consultant neurologist, Dr Abhijit Chaudhuri, from the Essex Centre for Neurosciences.

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M.E. (myalgic encephalopathy or encephalomyelitis) is a complex multisystem disease with a wide range of disabling symptoms.

M.E. RESEARCH SUMMARY

INTRODUCTION

This leaflet provides a summary of what biomedical research is telling us about M.E. It considers key symptoms, common triggers, and explains how various aspects of disease pathology could be linked to specific symptoms. All references for the research mentioned below, along with more detail, can be found in the ME Association's Clinical and Research Guide.

Key Symptoms

M.E. is diagnosed following a significant reduction in pre-illness activity levels and an inability to return to normal function. The most important diagnostic symptoms are:

- Post-exertional malaise/symptom exacerbation (PEM) – often with a delayed impact, lasting days or weeks before function is restored. PEM can also trigger a relapse;
- Activity-induced muscle fatigue – precipitated by trivially small exertion (physical or mental) relative to the patient's previous activity tolerance;
- Cognitive dysfunction – problems with short-term memory, concentration, word-finding;
- Sleep problems – sleeping too little or too much, vivid dreams, unrefreshing sleep;
- Ongoing flu-like symptoms – including sore throats and enlarged glands, fever-like sweats, lethargy;
- Orthostatic intolerance – problems with pulse and blood pressure control leading to feeling faint/dizzy when upright.

Other common symptoms include: Disturbed thermoregulation (temperature control), sensory disturbances including paraesthesia (abnormal skin sensations), photophobia (sensitivity to light) and hyperacusis (sensitivity to noise), headaches, shakiness, balance problems, nausea, gastrointestinal problems, alcohol intolerance and chemical sensitivities, recurrent sore throats, shortness of breath, vision problems.

Comorbidities

A number of other medical conditions and symptoms appear to be more common:

- Fibromyalgic-type pain
- Atypical facial pain and temporomandibular jaw dysfunction
- Gynaecological conditions - such as pelvic pain unrelated to menstruation, endometriosis and a premenstrual exacerbation of symptoms
- Hypermobility syndromes - such as Ehlers-Danlos Syndrome (EDS)
- Interstitial cystitis/bladder pain syndrome
- Gastrointestinal complaints - including irritable bowel syndrome
- Migraine type headaches
- Postural Orthostatic Tachycardia Syndrome (POTS) – an abnormal increase in heart rate after sitting or standing, which occurs to compensate a drop in blood supply to the brain, resulting in dizziness and/or fainting, along with other symptoms such as fatigue, headaches and shaking

M.E. RESEARCH SUMMARY

Predisposing and Triggering factors

There is no definitive evidence that can explain why people develop M.E. Factors that seem most likely include:

- A genetic predisposition – which may explain why more than one family member can be affected
- An infection – bacterial or viral
- Trauma – physical or emotional
- Exposure to toxins – including mould and pesticides
- Vaccination

Key research explanations for symptoms and disease pathology

Cardiac Function

- Some studies have found results suggesting low cardiac output as an explanation for poor physical stamina and chronic fatigue (as a symptom).
- There is also some evidence of hypotension (low blood pressure), especially on standing, which could explain symptoms such as fatigue, dizziness, cognitive issues, tremors and nausea.

Genetics

- Several gene polymorphisms (variations in DNA sequence) have been identified, which are involved in various processes such as immune modulation, oxidative stress and energy metabolism.
- Under and over-expression of certain genes and miRNAs (small molecules that regulate gene expression) may explain some symptoms and also account for an increased susceptibility to developing M.E. They also represent potential biomarkers for diagnosis and drug treatment targets. Recent findings from Prof Moreau et al. found that miRNAs might be used to place patients into subgroups.

Immunological Dysfunction

- Activated immune system – studies have shown cytokine-mediated, low-level immune system activation, in the blood and cerebrospinal fluid. This results in low-grade inflammation and a general 'sickness response', involving decreased appetite, wanting to sleep a lot and flu-like malaise and pain. Several studies have demonstrated altered levels of inflammatory markers, called cytokines, and activated immune cells, such as lymphocytes.
- Poor cellular function – reduced Natural Killer (NK) cell activity is a common research finding. NK cells are a type of white blood cell that comprise part of the immune system and act like security guards, circulating round the body looking for potential threats.

- Autoimmune component – some studies have found activated T- and B-cells, as well as an increased incidence of autoantibodies (immune cells, that attack tissues of your own body, instead of targeting foreign cells, such as bacteria).

Metabolomics

- Recent studies have found abnormalities in several metabolic (chemical) pathways, particularly those involved in glucose metabolism suggesting that there may be problems in converting glucose to energy.

Microbiome

- Researchers are currently investigating the role of the microbiome (the collection of different types of microbes, such as bacteria in the gut), with findings indicating gut dysbiosis (an imbalance of gut flora – not enough beneficial bacteria and an overgrowth of bad bacteria). This might contribute to general inflammation and to symptoms like fatigue and gastrointestinal symptoms.

M.E. RESEARCH SUMMARY

Muscle research: mitochondrial dysfunction, cellular bioenergetics and exercise physiology

■ There is growing evidence of mitochondrial dysfunction. Mitochondria (often called the powerhouse of the cell) are specialised structures responsible for the production of most of our cellular energy.

■ Muscle biopsies have shown evidence of mitochondrial degeneration, deletions of mitochondrial DNA (DNA, located inside the mitochondria, which is inherited from your mother) and reduction of mitochondrial activity.

■ Research suggests problems in energy metabolism pathways, such as functional impairments involving an enzyme (a type pf protein that acts as a catalyst for chemical reactions in the body) called pyruvate dehydrogenase and impairments in the activation of another enzyme called AMPK (adenosine monophosphate-activated protein kinase), leading to impaired glucose uptake.

■ Recent research from Newcastle University presented at the 2018 CMRC conference have also shown reduced mitochondrial function.

■ A number of other muscle abnormalities have been reported, including defects in muscle energy metabolism, changes in muscle fibre types and demonstrating PEM using repetitive isometric quadriceps exercise testing. These findings demonstrate that muscle symptoms cannot be due to inactivity/ deconditioning.

■ Exercise physiology research has demonstrated that a two-day cardiopulmonary exercise test (CPET) can objectively confirm the presence of PEM and could be used as a diagnostic test. This testing method has determined that PEM cannot be due to inactivity or deconditioning.

Neurology and neuroendocrinology

■ Neuroinflammation – several studies support the presence of neurobiological and spinal fluid abnormalities, some of which are consistent with low level neuroinflammation.

■ Central Nervous System – defects have been found in the basal ganglia pathways (areas of the brain which are extremely sensitive to cytokines). Post-mortem research has also found dorsal root ganglionitis (inflammation in a part of the peripheral nervous system).

■ Cerebrospinal fluid – studies have shown abnormalities in proteins and white blood cells.

■ Neuroimaging – studies have demonstrated a number of structural and functional abnormalities, including differences in the volume of white and grey matter in the brain, reduced cerebral blood flow and neuroinflamation. This could help to explain symptoms of cognitive dysfunction, as well as pain.

■ Autonomic nervous system (ANS) dysfunction – studies have shown disturbances in the autonomic regulation of cardiovascular reflexes in a subgroup of patients. POTS (Postural orthostatic tachycardia syndrome – represented by an abnormal increase in heart rate upon sitting or standing) is often also diagnosed or Neurally-mediated hypotension. The ANS also controls circulation, which may help to explain why patients experience problems with cold extremities, and temperature regulation. ANS dysfunction may also explain why irritable bowel and bladder symptoms are very common.

■ Hypothalamic-pituitary-adrenal (HPA) Axis – studies have found disturbances involving the HPA axis, mainly demonstrating defects in the output of the hormone cortisol from the adrenal glands. This could explain key symptoms such as fatigue, sleep dysfunction and also temperature regulation.