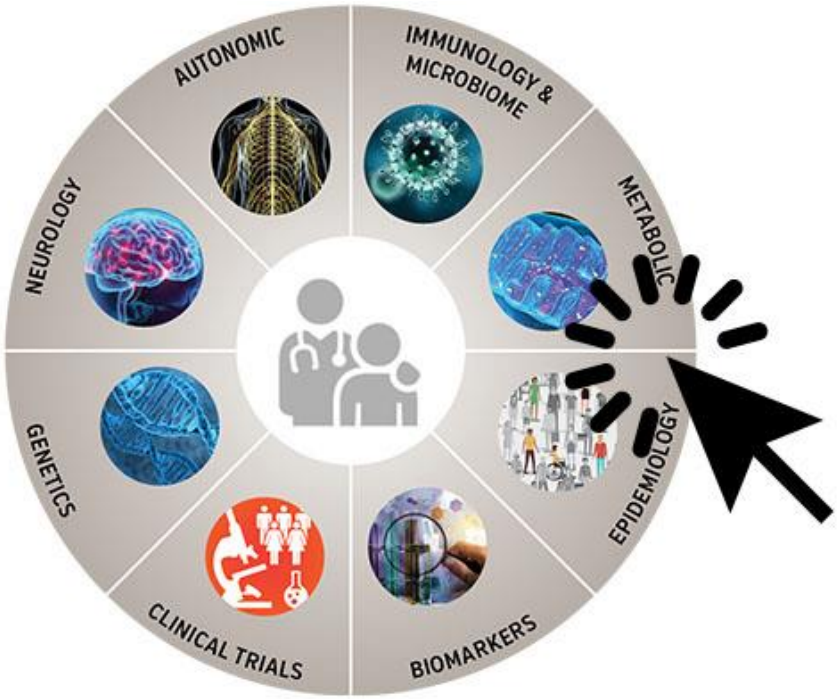
Solve ME/CFS Initiative
Leading the Fight to cure ME/CFS

ME/CFS RESEARCH: THE SECOND QUARTER OF 2019 IN REVIEW

A guide to the promising new discoveries of 2019

By Rochelle Joslyn (PhD)
Edited by Allison Ramiller (MPH)



For an interactive version of this roundup, visit
https://solvecfs.org/me-cfs-research-the-second-quarter-of-2019-in-review/

The second quarter of 2019 brought both an impressive number of ME/CFS publications and highly meaningful content. The momentum in this field is palpable with even a quick glance at this quarter's literature. Importantly, ME/CFS was represented in high-profile, widely read journals. Perhaps most notably, an **entire issue** of *Frontiers in Pediatrics* was devoted exclusively to ME/CFS articles.

Two highly anticipated studies delivered progress on two of the most pressing fronts in the ME/CFS field: objective biomarker identification and

clinical trials. A preliminary description of a novel test provides objective evidence of cellular dysfunction in ME/CFS versus healthy controls with perfect sensitivity and holds promise for the development of a diagnostic test. However, the long-awaited analysis of a failed phase 3 trial of the B-cell depleting antibody rituximab left the ME/CFS community disappointed and scientists scratching their heads over placebo effects and possible responder subgroups.

Encouragingly, sustained progress is apparent in successful follow-up studies that build on prior promising results, expand the range of measurements used with a proven protocol, replicate findings in new cohorts, and tackle comprehensive assessments in large sample sizes. All in all, Q2 has delivered incredibly meaningful discoveries, many pieces of objective evidence of serious disease, and has positioned ME/CFS as bona fide field of study with myriad unanswered questions and tantalizing scientific opportunities.

Immunology & Microbiome

Cliff, et al. examined the presence of antibodies to six herpes viruses and frequencies of several immune cell types in 251 CCC-defined ME/CFS patients, including 54 severely ill, compared with healthy controls and MS patients. While no differences in herpes antibodies were noted between ME/CFS and healthy subjects, the study revealed notable differences in the frequencies of certain types of CD8+ T-cells and elevated frequencies of mucosal-associated invariant T cells (MAIT cells), which were especially high among the severely ill. The group did not find a difference in natural killer (NK) cell abundance or function.

Giannoccaro, et al. tested sera from 50 rituximab trial participants for antibodies targeting neural tissue. While some people with ME/CFS did have neural autoantibodies and their presence was associated with shorter disease duration and higher disease severity, the study overall failed to find evidence of a specific neuronal autoimmune target associated with ME/CFS.

Morris, et al. refined their prior computational model of immune and endocrine regulatory networks in ME/CFS to incorporate data from measurement of circulating cytokines before, during and after submaximal exercise testing in 88 CCC-defined ME/CFS subjects. Following this revision to improve the accuracy of its representation of ME/CFS, the model predicted downregulated hypothalamic-pituitary-adrenal (HPA) axis, upregulated hypothalamic-pituitary-gonadal (HPG) axis, and a major

influence of the cytokines IL-8 and IL-23. The model also provides a simulation platform for characterizing the predicted effects of clinical trial interventions such as Ampligen and Rituxan.

Cabanas, et al. replicated the group's prior work identifying impaired NK cell TRPM3 ion channel function in a second cohort of 6 CCC-defined ME/CFS patients.

Groven, et al. found elevated levels of C-reactive protein (CRP) in blood from 49 Fukuda-defined CFS patients compared to healthy controls, as well as comparably elevated CRP levels in Fibromyalgia patient blood. The authors noted a correlation between CRP levels and body mass index (BMI), but CFS and FM groups showed elevated CRP even after adjusting for BMI.

Kristiansen, et al. examined adolescents with and without chronic fatigue following EBV infection, noting higher symptom scores, elevated C-reactive protein, T-cell frequency, norepinephrine, and epinephrine, as well as disturbed heart rate variability measures among those with chronic fatigue versus those without.

Kerr found that 38-55% of ME/CFS patients show elevated expression of a gene (EBI2) induced by EBV infection, as well as reduced levels of an EBV antibody (EBNA1 IgG).

Autonomic

Garner and Baraniuk assessed heart rate and prevalence of orthostatic intolerance (OI) symptoms during submaximal exercise testing in reclined and standing postures in 39 CCC-defined ME/CFS subjects and 25 sedentary healthy controls. The study found that 41% of ME/CFS subjects experienced OI symptoms while reclining and 72% while standing, with those who experienced symptoms in both positions (termed “persistent OI”) also reporting higher symptom severity.

Kemp, et al. tested the effectiveness of the DePaul Symptom Questionnaire (DSQ) in capturing patients' symptomatic reports of autonomic dysfunction by comparing DSQ responses with physical heart rate variability measurement. The authors noted significant correlations between self-report and objective measures, supporting accuracy in patient self-reporting and the validity of the DSQ in capturing features of autonomic dysfunction.

Raijmakers, et al. compared monocyte gene expression between people with ME/CFS and Q fever fatigue syndrome, noting decreased levels of

mitochondrial genes humanin and MOTS-c in both groups relative to healthy and non-fatigued Q fever controls.

Stemming from prior studies identifying antibodies to the EBV dUTPase protein in ME/CFS patients, Williams, et al. tested the ability of dUTPase to induce gene expression changes in mouse brain tissue and in cultured human neural cells, identifying significant change in expression of many genes that could contribute to neuroinflammation.

Neurology

Josev, et al. measured processing speed following cognitive exertion by fMRI in 25 CCC-defined adolescents, noting elevated reports of fatigue and underperformance on processing speed, attention and learning among ME/CFS patients versus healthy controls.

Metabolic

Lien, et al. measured blood lactic acid levels during repeated exertion challenges (2-day CPET) in 18 mild-moderate CCC-defined ME/CFS patients and found that ME/CFS lactate levels were higher on test 2 than test 1, whereas healthy control levels decreased at test 2. This finding demonstrates that while exertion from the prior test improved healthy control performance, it worsened ME/CFS patients' capacity for subsequent exertion.

Xu, et al. applied single cell Raman spectroscopy, a technique which captures the unique molecular composition of a cell, to blood cells from 5 CFS patients. The profiles reflected increased phenylalanine (a building block for proteins) in patient cells versus healthy controls, consistent with mitochondrial dysfunction and as was observed in control cells with known mitochondrial deficiency. Computational predictions were also highly sensitive in distinguishing patients versus controls based on the phenotypic profiles.

Through analysis of laboratory tests in 272 CCC-defined ME/CFS patients, Nacul, et al. found that people with severe disease had lower levels of creatine kinase in their blood versus those with more mild disease and healthy controls.

Genetics

Perez, et al. analyzed commercial genetic data supplied by 383 people with ME/CFS, finding 5,693 genetic variants that were present in at least 10% of the cohort and 10 variants present in >70% of the cohort. Most of the variants were in genes related to immune, endocrine, metabolic, or cellular interface functions, and 517 are among the 10% most deleterious (harmful or disease-associated) variants known in humans.

Clinical Trials

Fluge, et al. published the long-awaited results of a phase 3 trial of use of the anti-CD20 B-cell depleting antibody, rituximab, to treat ME/CFS. Phase 2 results had shown promise, but the authors report that of 151 people with CCC-defined ME/CFS randomly assigned to 6 rituximab or placebo infusions, only 26% showed a response to rituximab and 35% responded to placebo as measured by fatigue and function scores in the subsequent 24 months. The authors note a major study limitation in its reliance upon self-reported rather than objective outcome measures.

Using a validated objective trial analysis tool, Ahmed, et al. performed a systematic and comprehensive assessment of the methodological quality of studies on the use of graded exercise therapy (GET) and cognitive behavioral therapy (CBT) as treatments for ME/CFS, including 14 clinical trials. The tool identified a high risk of bias in most study designs with regard to features such as selection, blindedness, outcome assessment, reporting and sample size. The authors noted major deficiencies in the use of subjective outcome measures, ill-defined cut-off scores, a near total absence of adverse event reporting, and selection of patients using criteria which do not require PEM, concluding that these methodological flaws undermine claims of CBT/GET effectiveness.

Biomarkers

Esfandyarpour, et al. demonstrated 100% effectiveness of distinguishing CCC-defined ME/CFS patient from healthy control cells using a novel nanoelectronic device that measures electrical impedance in cell cultures following addition of a chemical stressor (salt) which triggers metabolic upregulation. This preliminary study tested only 20 moderate-severely ill people with ME/CFS and did not measure the specificity of the assay in

distinguishing ME/CFS from other diseases, but shows promise in its perfect sensitivity as an objective measure of disease status.

Epidemiology

Castro-Marrero, et al. found high rates of unemployment (58%) among people living with ME/CFS, identifying disease features which associate with work disability.

An epidemiologic study from the CDC found that endometriosis is a common comorbidity, reported by 36% of women in a small CFS cohort meeting the Fukuda criteria.

Note: the use of ME/CFS or CFS is in accordance with the criteria used to include cases in the study