IACFS/ME

Dedicated to research, education, treatment and finding a cure for ME/CFS

12th Biennial International Conference

Emerging Science and Clinical Care

October 27-30, 2016

Westin Fort Lauderdale Beach Resort

Fort Lauderdale, Florida, USA

Conference Syllabus

iacfsme.org

International Association for
IACFS/ME
Chronic Fatigue Syndrome

Dedicated to research, education, treatment and finding a cure for ME/CFS

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Welcome To the Fort Lauderdale IACFS/ME Conference!

On behalf of the board of directors of IACFS/ME, I would like to warmly welcome you to our international research and clinical conference. We have an exciting program of research and clinical talks, innovative workshops, and compelling master speakers. And we've reserved plenty of time for Q and A—a must for a field with so many disparate lines of scientific research.

On our speakers list, we have an impressive roster of international CFS/ME experts representing a wide range of biomedical and behavioral disciplines. And our professional workshops promise to offer the latest information on good clinical practice.
Our keynote speaker, Vicky Whittemore, PhD, is a major player at the National Institutes of Health (NIH) with respect to new CFS/ME research initiatives. She is expected to give an in-depth view of plans and programs for CFS/ME with perhaps some surprising new developments (pending NIH approvals). We also have Norwegian physician and researcher, Øystein Fluge, MD as our plenary speaker, who was the principal investigator of the two published rituximab trials that show promise as an intervention for CFS/ME. His collaborator, Olav Mella, MD will also have a speaking role on the subject.

Pragmatic clinical focus
In keeping with feedback from the last conference, a pragmatic clinical focus will be present throughout the conference with informative workshops (e.g., orthostatic intolerance, acute and chronic enteroviral infection, CFS/ME diagnosis and management) and a two hour difficult clinical cases seminar chaired by Nancy Klimas, MD with an invited panel of high profile ME/CFS clinicians. In addition, our treatment studies session will include clinical practice issues. We are asking all presenters to include a "clinical implications" slide (as appropriate) so that our clinical professionals can consider the presented research with respect to their patients.

NIH and CDC presentations
Vicky Whittemore, PhD, our keynote, will also be chairing a Friday evening session titled: "Common Data Elements (CDEs) for Standardized Testing and Clinical Studies." In addition, Beth Unger, MD, PhD, Chief of the Chronic Viral Diseases Branch at the Centers for Disease Control and Prevention (CDC), will play an important role in this meeting with talks during the public health research session as well as a 90-min lunch panel focusing on the CDC's Multi-site Clinic Assessment of ME/CFS.

Travel awards for new investigators
For the first time, IACFS/ME has received a NIH conference grant that is funding six early stage investigators to attend the meeting. This is exceedingly important as we have very few new researchers on the horizon showing interest in CFS/ME research. Please say hello to our six awardees who will be identified on their badges.

Revamped patient meeting
We have also made our patient meeting day into a combined patient and professional meeting with direct benefits to patients (and their families). Our keynote speaker is scheduled for this day and our afternoon session will be devoted to several 1 hr 45 min workshops on patient issues (self-management skills such as meditation and pacing), as well as combined patient and professional workshops on ME/CFS legal issues, global advocacy, and educating students who have ME/CFS.

Finally, please know that your ongoing support helps to sustain our organization and the benefits we provide to you including a peer review journal, newsletter, a practice primer, and timely IACFS/ME position statements on critical issues (e.g., PACE Trial).

With best regards,

Fred
Fred Friedberg, PhD
President
International Association for Chronic Fatigue Syndrome/Myalgic Encephalomyelitis (IACFS/ME)
www.iacfsme.org

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About
International Association for CFS/ME

The mission of the IACFS/ME is to promote, stimulate and coordinate the exchange of ideas related to CFS, ME and fibromyalgia (FM) research, patient care and treatment. In addition, the IACFS/ME periodically reviews the current research and treatment literature and media reports for the benefit of scientists, clinicians and patients. The IACFS/ME also conducts and/or participates in local, national, and international scientific conferences in order to promote and evaluate new research and to encourage future research ventures and cooperative activities to advance scientific and clinical knowledge of these illnesses.

The IACFS/ME shall at all times be organized and operated exclusively for charitable, scientific, literary or educational purposes as a qualified exempt organization described under section 501 (c) (3) of the Internal Revenue code of 1986 and the regulations promulgated thereunder as they may now exist or as they may be hereafter amended.

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In Appreciation

The International Association for CFS/ME (IACFS/ME) gratefully acknowledges those who provide support for our commitment to education for researchers, clinicians and patients.

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R.E.D. Laboratories – your partner of choice for specialty tests

WHO WE ARE: R.E.D. Laboratories (**www.redlabs.be**) develops and performs specialty tests for chronic immune disorders, intestinal dysfunctions, tick-borne diseases and multifactorial afflictions such as autism and chronic fatigue syndrome (CFS).

HOW WE WORK: We are continuously developing new tests according to the specific needs of health care providers. Our focus is to offer tests that are either rarely or not available elsewhere. All of our tests are developed according to the scientific method.

WHAT WE OFFER: We offer SPECIALTY TESTS. Based on the most current scientific literature and through extensive collaborations with prominent physicians, we have developed state-of-the-art diagnostic panels that allow the clinician to effectively manage their patients who have complex immune disorders. Our specialty diagnostics are grouped according to disease or custom-designed Testing Panels. Among the factors that may contribute to the onset or maintenance of a chronic inflammatory condition such as CFS, the scientists at R.E.D. Laboratories pay special emphasis to immune dysregulation (a hallmark of CFS), in the context of intestinal and metabolic dysfunctions as well as chronic infections (with a special focus on tick-borne diseases) and/or persistent viral infections.

WHY TO COLLABORATE WITH US: In order to offer the most relevant and useful testing possible, we at R.E.D., Laboratories leverage the collective knowledge of those physicians, with whom we maintain close collaborations. By collaborating with us, you can contribute to this scientific knowledge base and promote the development of laboratory diagnostics that will benefit your patients.

HOW TO CONTACT US: Please visit our booth or contact us at info@redlabs.be or requests@redlabs.be (USA).

Conference Function and Room Locator

Function	Location
Conference Registration	Las Olas Foyer
Professional Conference Workshops (Thursday Morning)	Atlantic Ballroom III – Workshop 1 Atlantic Ballroom IV – Workshop 2 Oceanside II – Workshop 3
Professional Conference Workshops (Thursday Afternoon)	Atlantic Ballroom III – Workshop 4 Atlantic Ballroom IV – Workshop 5 Oceanside II – Workshop 6
Patient Conference AM	Las Olas Ballroom
Patient Workshops (PM)	
Moving ME/CFS Forward Internationally	Las Olas Ballroom
Legal Issues with ME/CFS – Myths and Reality	Rio Vista I
Pacing Approaches, Healing Time, and Other Techniques to help Lessen ME/CFS Symptoms	Rio Vista II
Mindfulness, Meditation, Movement, and Merriment	Oceanside I
Educating students suffering from ME/CFS—a Global Perspective	Bonnet I
Advocacy Roundtable	Atlantic Ballroom III
Free movie screening - "Forgotten Plague"	Las Olas Ballroom
General Sessions	Las Olas Ballroom
Exhibits – Networking Center	Las Olas Foyer
Poster Presentations – Networking Center	Atlantic I-II-V-VI
Breaks, Refreshments – Networking Center	Las Olas Foyer
Patient Relaxation Room	Bonnet II
Lunch Option	Waves Restaurant
Special Interest Meetings (Friday – Bring your own lunch)	
ME/CFS Studies at the Centers for Disease Control and Prevention	Atlantic Ballroom III
Special Interest Meeting (Saturday – Bring your own lunch)	
International Research Networks	Atlantic Ballroom III
Mitochondrial Dysfunction: A Potential Etiology for ME/CFS?	Atlantic Ballroom III
Friday Evening Session	
Common Data Elements (CDEs) for Standardized Testing and Clinical Studies	Las Olas Ballroom
IACFS/ME Business Meeting (Saturday)	Atlantic Ballroom III
IACFS/ME Reception (Saturday)	Las Olas Foyer
IACFS/ME Banquet (Saturday)	Las Olas Ballroom
Restrooms	Las Olas Foyer

IACFS/ME Awards Banquet

Saturday, October 29, 2016

Westin Fort Lauderdale Beach Resort

Reception

6:00 pm

Las Olas Foyer

Dinner

7:00 pm

Las Olas Ballroom

Banquet Ticket Required for Admission

Awards Ceremony & Keynote Presentation

Governor Rudy Perpich Memorial Award

Lucinda Bateman, M.D.

Nelson Gantz Clinician Award

Rosamund Vallings, M.B., B.S.

Junior Investigator Award

Sharni Hardcastle, Ph.D.

Special Service Award

David Tuller, DrPH

Cort Johnson, M.S.

Master of Ceremonies

Fred Friedberg, Ph.D., President, IACFS/ME

Accreditation

This activity has been planned and implemented in accordance with the Essential Areas and Policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint providership of the Foundation for Care Management (FCM) and International Association for Chronic Fatigue Syndrome/Myalgic Encephalomyelitis (IACFS/ME).

The Foundation for Care Management (FCM) is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians.

FCM designates this educational activity for a maximum of *26 AMA PRA Category 1 Credits*™. Physicians should only claim credit commensurate with the extent of their participation in this activity.

The Foundation for Care Management is an approved provider of The Washington State Nurses Association WSNA-CNE, an accredited approver of Continuing Nursing Education.

Learning Objectives IACFS/ME October 2016

Upon completion of this learning activity, the participant will be able to:

1. Discuss the new research findings regarding the etiology of CFS as well as fibromyalgia and other associated pain, depression, and sleep disturbances.
2. Describe current and emerging pharmacologic treatments for pain, fibromyalgia, GI disturbances, depression, and sleep problems.
3. Utilize music, movement, and meditation in the treatment of CFS.
4. Diagnose and Treat Orthostatic Intolerance both pharmacologically and non-pharmacologically.
5. Teach other HCPs about ME/CFS, Fibromyalgia and Multiple Chemical Sensitivities/Environmental Sensitivities: Office Assessment and Management.
6. Manage Acute and Chronic Enteroviral infection in ME/CFS.
7. Discuss the latest research on immunology, genetics, and microbiome in CFS/ME.
8. Discuss the uses of cardiopulmonary exercise testing and cognitive behavioral therapy in CFS/ME.
9. Describe allergic disorder phenotypes in CFS/ME.
10. Utilize new research findings to inform new ideas for studies and to enhance practice skills.

Faculty – Oral Presentations

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The following faculty intend to reference unlabeled/unapproved uses of drugs or products in their presentation:
No faculty reported

The following faculty have disclosed a financial interest or affiliation with one or more of the commercial organizations offering financial support, equipment, or educational grants for this Continuing Medical Education activity, or the IACFS/ME and commercial organizations which do not support this activity but in the interest of full disclosure wish to make attendees aware of a relationship which should be considered in evaluating individual presentations:

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Nurse Practitioner, Institute for Neuro-Immune Medicine, Nova Southeastern University, Fort Lauderdale, FL

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Clinical Research Coordinator, South Florida VA Foundation for Research and Education, Inc., Miami VA Medical, Miami, FL

Leonor Sarria
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Wakiro Sato, Ph.D.
Section Chief, National Center of Neurology and Psychiatry, National Institute of Neuroscience, Department of Immunology, Tokyo, Japan

Alfred Slonim, MBBS
Professor Emeritus, Columbia University, New York, NY

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Psychiatrist in Private Practice, *Assistant Clinical Professor*, University of Calgary, Calgary, Alberta

David R. Strayer, M.D.
Chief Scientific Officer, Hemispherx Biopharma, Inc., Philadelphia, PA

Kimberly Sullivan, Ph.D.
Research Assistant Professor, Boston University School of Public Health, Boston, MA

Eiren Sweetman
Ph.D. Candidate, Department of Biochemistry, Otago School of Medical Sciences, Division of Health Sciences, University of Otago, Dunedin, New Zealand

Karen Tanguay, MSc, M.D., FRCPC
Consultant Psychiatrist, University of Calgary, Calgary, Canada

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Ph.D. Student, Newcastle University, Newcastle Upon-Tyne, UK

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Jr. Matlab Developer, Institute for Neuro-Immune Medicine, Nova Southeastern University, Fort Lauderdale, FL

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John Whiting
Physician, Specialist in Internal Medicine & Infectious Diseases, Brisbane, Australia

Michael Zeineh, M.D., Ph.D.
Assistant Professor of Radiology, Stanford University, Stanford, CA

Marcie Zinn, Ph.D.
Research Project Director for Electrophysiology, Center for Community Research, DePaul University, Chicago, IL

Mark Zinn
Research Project Assistant for Electrophysiology, Center for Community Research, DePaul University, Chicago, IL

Agenda – Thursday, October 27
Patient Agenda

8:00 am – 8:20 am
Welcome & Introduction
Fred Friedberg, Ph.D.
President, IACFS/ME
Research Associate Professor, Stony Brook University
Founder and Editor, *Fatigue: Biomedicine, Health, and Behavior*
Nova Southeastern University and local officials, to be determined

8:20 am – 9:15 am (last 15 min.: Q and A)
New ME/CFS Developments at the National Institutes of Health
Keynote Speaker: Vicky Whittemore, Ph.D.
Program Director, Channels, Synapses and Circuits
National Institute of Neurological Disorders and Stroke

9:15 am – 10:00 am (last 15 min.: Q and A)
Rituximab and Emerging Treatments
Daniel Peterson, M.D.
Sierra Internal Medicine
Øystein Fluge, MD
Chief Physician, Department of Oncology,
Haukeland University Hospital, University of Bergen, Norway
Olav Mella, MD
Department director/professor, Haukeland University Hospital, Oslo, Norway

10:00 am – 10:30 am
Break/Visit Exhibits

10:30 am – 11:00 am (last 10 min.: Q and A)
Ensuring effective and efficient medical appointments: What can patients and caregivers do?
Lily Chu, M.D.
Independent Consultant
Co-Vice President, IACFS/ME

11:00 am – 11:45 am (last 10 min.: Q and A)
If not opioids, then what?
Jarred Younger, Ph.D.
Associate Professor
University of Alabama at Birmingham

11:45 am – 1:15 pm
Lunch Break/Visit Exhibits

1:15 pm – 3:00 pm
Patient workshops (run concurrently; attendees select one only)

Legal Issues with ME/CFS--Myths and Reality (Joint Patient and Professional Workshop)
Steven Krafchick, J.D., M.P.H.
Krafchick Law Firm
IACFS/ME Board Member

Educating students suffering from ME/CFS—a Global Perspective (Joint Patient and Professional Workshop)
Faith Newton, Ed.D.
Associate Professor of Education
Delaware State University

Moving ME/CFS Forward Internationally (Joint Patient and Professional Workshop)
Margaret Parlor
President, National ME/FM Action Network (Canada)
Mary Dimmock, Advocate and Author

Mindfulness, Meditation, Movement, and Merriment (Patient Workshop)
Judy-Anne Wilson
Educator and artist
Treasurer, ME Society of Edmonton, Canada

Pacing Approaches, Healing Time, and Other Techniques to Help Lessen ME/CFS Symptoms (Patient Workshop)
Jon Kaiser, M.D.
University of California, San Francisco

4:00 pm – 5:00 pm (last 15 min. Q and A)
Fibromyalgia Update
Lucinda Bateman, M.D.
Fatigue Consultation Clinic
Jarred Younger, Ph.D.
Associate Professor
University of Alabama at Birmingham

Following each talk, speakers will field questions written on cards by the audience as time permits

5:00 pm – 6:00 pm
Advocacy Roundtable
Everyone is welcome to participate.

6:00 pm – 8:00 pm
Free screening of "Forgotten Plague" directed by Ryan Prior and Nicole Castillo, presented by the Blue Ribbon Foundation

Agenda – Thursday, October 27
IACFS/ME Professional Workshops

9:30 am – 12:30 pm
Professional workshops (run concurrently; attendees select one only)

Review of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome, Fibromyalgia and Multiple Chemical Sensitivities/Environmental Sensitivities: Office Assessment and Management
Alison Bested, M.D., F.R.C.P.C.
Clinical associate professor, Department of Medicine, University of British Columbia

Learn to diagnose and treat the patients with complex chronic medical conditions in your office.

Acute and Chronic Enteroviral Infection
John Chia, M.D.
UCLA School of Medicine

The workshop entitled "Acute and Chronic Enterovirus Infection" is for professionals who would are interested in these virus infections and association with ME/CFS. Nurses, nurse practitioners, physician assistants, physicians, researchers, epidemiologist will gain basic knowledge to recognize and diagnose these medical conditions and learn to associate these infections with ME/CFS.

How Cardiopulmonary Exercise Testing Informs Pathology and Treatment
Mark Van Ness, Ph.D.
Department of Health, Exercise, and Sport Science, University of the Pacific
Christopher Snell, Ph.D.
Scientific Advisor, Workwell Foundation
Betsy Keller, Ph.D.
Department of Exercise and Sport Sciences, Ithaca College

Cardiopulmonary exercise testing (CPET) is a data collection paradigm that accurately and objectively describes the post-exertional response that ME/CFS patients experience. CPET will be described, including its utility for understanding ME/CFS pathology. Information will be presented about how the post-exertional state is particularly useful for data collection pertaining to immunological, neurological and hormonal conditions.

12:30 pm – 1:30 pm
Lunch Break/Visit Exhibits

1:30 pm – 4:30 pm
Professional workshops (run concurrently; attendees select one only)

Behavioral Assessment and Treatment of ME/CFS and Fibromyalgia
Fred Friedberg, Ph.D.
President, IACFS/ME
Research Associate Professor, Stony Brook University
Founder and Editor, *Fatigue: Biomedicine, Health and Behavior*
Leonard A. Jason, Ph.D.
Professor, DePaul University

In this introductory workshop on CFS/ME and fibromyalgia (FM), participants will learn about practical methods of behavioral assessment and individualized treatment strategies. Our approach consists of self-management focused interventions and non-pharmacologic strategies for clinicians that can offer realistic hope for improvement in

these patients. This workshop will benefit clinicians who work with CFS/ME and FM patients.

Diagnosing and Treating Orthostatic Intolerance
Peter Rowe, M.D.
Johns Hopkins University School of Medicine

Postural tachycardia and hypotension in response to orthostatic stress are common in those with ME/CFS. These circulatory disturbances contribute to ME/CFS symptoms and lower quality of life. This workshop will help clinicians identify and treat common forms of orthostatic intolerance in their patients with ME/CFS.

NIH Grant Writing Workshop
Vicky Whittemore, Ph.D.
Program Director, Channels, Synapses and Circuits
National Institute of Neurological Disorders and Stroke

The NIH Grant Writing Workshop will review skills that are critical for becoming a successful grant applicant.

5:00 pm – 6:00 pm
Advocacy Roundtable
Everyone is welcome to participate.

6:00 pm – 8:00 pm
Free screening of "Forgotten Plague" directed by Ryan Prior and Nicole Castillo, presented by the Blue Ribbon Foundation

Agenda – Friday, October 28
12TH International IACFS/ME Biennial Conference
Emerging Science and Clinical Care

8:00 am – 8:15 am
Welcome and Introduction
Fred Friedberg, Ph.D.
President, IACFS/ME
Research Associate Professor, Stony Brook University
Founder and Editor, *Fatigue: Biomedicine, Health and Behavior*

8:15 am – 9:00 am (last 15 min. are Q and A)
Plenary Session
B-lymphocyte depletion and disease mechanisms in ME/CFS
Øystein Fluge, M.D.
Chief Physician, Department of Oncology, Haukeland University Hospital, University of Bergen, Norway

Paper Sessions *following short paper presentations each 12 minutes in length, presenters will field questions written on cards by the audience and given to the chair as time permits.*

9:00 am – 10:15 am
Session 1: The Latest Research in Immunology and the Microbiome
Session Chair: Mady Hornig, M.D.
Mailman School of Public Health, Columbia University Medical Center

A panel of biomarkers accurately identifies CFS/ME patients and contributes to the understanding of the pathophysiology of the disorder
Kenny L. De Meirleir, M.D., Nevada Center for Biomedical Research at University of Nevada

A profile of circulating cytokines is associated with disease severity in chronic fatigue syndrome patients
Jose G. Montoya, M.D., Stanford University School of Medicine

Alterations in the enteric bacterial and viral microbiome in ME/CFS
Ludovic Giloteaux, Ph.D., Department of Molecular Biology and Genetics, Department of Microbiology, Cornell University

10:15am – 10:45 am
Break/Visit Exhibits

10:45 am – 12:15 pm
Session 2: Treatment Studies and Clinical Practice
Chair: Daniel Peterson, M.D.
Griffith University, Gold Coast, Australia
Owner, Sierra Internal Medicine, Incline Village, Nevada

Reflections on the rituximab trials
Olav Mella, M.D., Department director/professor, Haukeland University Hospital, Oslo, Norway

Synergy Trial for CFS – a phase 2 study of low-dose methylphenidate plus mitochondrial support
Lucinda Bateman, M.D., Bateman Horne Center of Excellence

N-Acetylcysteine alleviates cortical glutathione deficit and improves symptoms in CFS: An *in vivo* validation study using proton magnetic resonance spectroscopy
Dikoma Shungu, **Ph.D.,** Departments of Radiology, Neurology and Neuroscience, Weill Cornell Medicine

A re-examination of the cognitive behavioral theory of CFS
Madison Sunnquist, DePaul University

Potential for an immunosignature assay to aid in classification and prediction of rituximab response in ME/CFS
David Patrick, M.D., FRCPC, MHSc, University of British Columbia School of Population and Public Health

12:15 pm – 1:45 pm
Lunch Break/Visit Exhibitors

Special Lunch Sessions

1. ME/CFS studies at the Centers for Disease Control and Prevention
Multi-site Clinic Assessment of ME/CFS (MCAM)
Chair: Elizabeth R. Unger, M.D., Ph.D.
Chief, Chronic Viral Diseases Branch
Centers for Disease Control and Prevention (CDC)

Study design of the multi-site clinic assessment of ME/CFS (MCAM)
Elizabeth R. Unger, M.D., Ph.D.
Jin-Mann S. Lin, Ph.D., Senior statistician/epidemiologist, US Centers for Disease Control and Prevention

Data on cognitive function from Multi-Site Clinical Assessment of Myalgic Encephomyelitis/Chronic Fatigue Syndrome (MCAM) – Preliminary Analysis
Gudrun Lange, Ph.D., Consulting Clinical Neuropsychologist, Mount Sinai Beth Israel Pain and Fatigue Study Center

Exercise testing data from the Multi-Site Clinic Assessment of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (MCAM) Study
Dane Cook, Ph.D., Professor of Kinesiology, University of Wisconsin-Madison

Salivary test data from the Multi-site Clinic Assessment of Myalgic Encephomyelitis/Chronic Fatigue Syndrome (ME/CFS) (MCAM) Study
Jin-Mann S. Lin, Ph.D., Senior statistician/epidemiologist, US Centers for Disease Control and Prevention

Pilot study evaluating impact of sample processing and assay format on measured natural killer cell function
Troy Querec, Ph.D., Associate Service Fellow, US Centers for Disease Control and Prevention

Description of the Multi-site Clinic Assessment of ME/CFS (MCAM) Study
Mangalathu Rajeevan, Ph.D., Research Microbiologist, US Centers for Disease Control and Prevention

2. Mitochondrial Dysfunction: A Potential Etiology for ME/CFS?
Moderator: **Jon D. Kaiser, MD**, University of California Medical School, San Francisco

Speaker Panel:
Ron Davis, MD, Stanford University Medical School
Nancy Klimas, MD, Neuro Immune Institute, NOVA Southeastern
Dikoma Shungu, PhD, Departments of Radiology, Neurology and Neuroscience, Weill Cornell Medicine

Mitochondrial dysfunction is an etiologic mechanism that may explain the multisystem range of symptoms experienced by CFS patients. Electron micrographs of muscle biopsies have revealed abnormal mitochondrial degeneration. Evidence of oxidative damage and increased activity of antioxidant enzymes have also been chemically detected in muscle specimens of CFS patients. The classic presentation for an illness manifesting mitochondrial dysfunction is one that involves multiple symptoms spanning many domains. These typically include fatigue, cognitive impairment and other brain-related challenges, muscle weakness, exercise intolerance, and gastrointestinal problems. The broad symptoms profile found in ME/CFS is consistent with this description of a mitochondrial dysfunction disease.

Each panelist will share their perspective on this topic for ten minutes, including an overview of their own investigations, to be followed by a Q&A session.

1:45 pm – 2:45 pm
Session 3: Gulf War Illness
Session Co-chairs:
Kristy Lidie, Ph.D., US Department of Defense
Victor Kalisinsky, Ph.D., US Department of Veterans Affairs
Gulf War Illness Program Officers

Gulf war illness and chronic fatigue syndrome: lessons learned
Presenter: Lea Steele, Ph.D., Professor and Yudofsky Chair in Behavioral Neuroscience, Baylor College of Medicine

Brain Immune Interactions in Gulf War Illness: Cytokines and Cognition in US Military Veterans
Kimberly Sullivan, Ph.D., Boston University Medical

Campus

Genomic approach to find mechanisms of Gulf War Illness pathobiology
Lubov Nathanson, Ph.D., Institute for Neuro Immune Medicine, Nova Southeastern University

Using gene expression signatures to identify novel treatment strategies in Gulf War Illness
Travis Craddock, Ph.D., Department of Psychology & Neuroscience, Nova Southeastern University

2:45 pm – 3:15pm
Break/Visit Exhibits

3:15 pm – 5:15 pm
Session 4: Diagnosing CFS/ME; Difficult Clinical Cases: Focus on Fatigue and Pain
Session Chair: Nancy Klimas, M.D.
Immediate Past President, IACFS/ME
Professor of Medicine & Director, Nova Southeastern University
Director, Miami VAMC Gulf War Illness & ME/CFS Research Program

Panel:
Lucinda Bateman, M.D., Bateman Horne Center of Excellence, Utah
John Chia, M.D., UCLA School of Medicine
Charles Lapp, M.D., Hunter-Hopkins Center, North Carolina
Dan Peterson, M.D., Sierra Internal Medicine, Incline Village, Nevada
Katherine Rowe, M.D., Royal Children's Hospital, Australia
Peter Rowe, M.D., Johns Hopkins University School of Medicine

5:15 pm – 6:00 pm
Visit Poster Presentations/Exhibits

Evening Session
6:30 pm – 8:30 pm
Common Data Elements (CDEs) for Standardized Testing and Clinical Studies
Chair: Vicky Whittemore, Ph.D.
Program Director, Channels, Synapses and Circuits National Institute of Neurological Disorders and Stroke

The National Institute of Neurological Disorders and Stroke (NINDS), National Institutes of Health and the Center for Disease Control and Prevention (CDC) will partner to develop common data elements (CDEs) for standardized testing and common data elements to be recorded in clinical studies/trials of individuals with myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS). The development of CDEs for ME/CFS will facilitate the comparison of results across studies and help to standardize analysis. The session will be led by NINDS and CDC Program Staff to discuss the timeline and process for developing the CDEs and to obtain feedback and input from ME/CFS stakeholders.

Agenda – Saturday, October 29

8:00 am – 9:00 am
Session 5: CFS, SEID, ME Case Definitions: Clinical vs. Research Criteria
Presenter: Leonard Jason, Ph.D.
Professor, DePaul University*, Director of the Center for Community Research*

Discussants:
Lucinda Bateman, M.D.
Chief Medical Officer
Bateman Horne Center of Excellence
Salt Lake City, Utah

Jon Kaiser, M.D.
IACFS/ME Board Member
University of California, San Francisco

9:00 am – 10:00 am
Session 6: Symptom Provocation Studies I
Chair: Staci Stevens, M.A.
Founder, Workwell Foundation

Cardiopulmonary exercise testing demonstrates post-exertional chronotropic incompetence
Mark Van Ness, Ph.D., Department of Health, Exercise, and Sport Science, University of the Pacific

Post-exertional malaise: multiple and unexpected symptoms, sometimes delayed, often prolonged
Lily Chu, M.D., Stanford University School of Medicine

Cognitive function in adolescents with chronic fatigue syndrome/myalgic encephalomyelitis: A novel paradigm
Sarah Knight, Ph.D., Murdoch Children's Research Institute, Australia

10:00 am – 10:30 am
Break/Visit Exhibits

10:30 am – 12:15 pm
Session 7: Public Health Research
Chair: Steve Krafchick, MPH, JD
IACFS/ME Board Member

Estimating rates of pediatric chronic fatigue syndrome and myalgic encephalomyelitis in a community-based sample
Leonard A. Jason, Ph.D., DePaul University

Two year follow-up of impaired range of motion in adolescent chronic fatigue syndrome
Peter C. Rowe, M.D., Johns Hopkins University School of Medicine

Allergic disorder phenotypes in ME/CFS and patterns of medical comorbidity and clinical dysfunction
Susan Levine, M.D., Cornell Medical Center, New York City

Exploring the role of sex hormones in driving symptom severity in ME/CFS
Gordon Broderick, Ph.D., Department of Medicine, University of Alberta

Nurses' acute fatigue predicts sickness absence in the workplace: a 1-year retrospective cohort study
Knar Sagherian, RN, MSN, University of Maryland School of Nursing

Examining the accuracy of a physical diagnostic technique for chronic fatigue syndrome/myalgic encephalomyelitis: a blind controlled study
Ray Perrin, DO, Ph.D., Honorary Senior Lecturer: Allied Health Professions Research Unit, University of Central Lancashire, UK

Demographics of young people diagnosed with CFS in Victoria Australia
Katherine Rowe, M.B.B.S., M.D., Royal Children's Hospital, Melbourne, Australia

12:15 pm – 1:45 pm
Lunch Break/Visit Exhibits

Lunch Panel
Special Interest Groups: International Research Networks
David Patrick, Ph.D., Moderator
Professor and Director
School of Population and Public Health
University of British Columbia, Canada

European network on myalgic encephalomyelitis/chronic fatigue syndrome (EUROMENE)
Eliana Lacerda, M.D., Ph.D., Assistant Professor, London School of Hygiene & Tropical Medicine

The case for stratification in ME/CFS: Experience from the UK ME/CFS Biobank
Luis Nacul, M.D., Ph.D.
London School of Hygiene & Tropical Medicine

1:45 pm – 2:45 pm
Session 8: Research on Autonomic Functioning and Comorbidities
Chair: Peter Rowe, M.D., Johns Hopkins University School of Medicine

Postural tachycardia in chronic fatigue syndrome induced by exercise
Madison Keefe, B.S., Georgetown University

Distribution of dolorimetry in CFS, FM, GWI and control women
Rakib Rayhan, M.S., Department of Medicine, Georgetown University

Truncal ataxia is an unrecognized cause of orthostatic intolerance in patients with myalgic encephalomyelitis
Kunihisa Miwa, M.D.
Miwa Naika Clinic, Japan

2:45 pm – 3:45 pm
Session 9: Advances in Brain Research and Neurological Studies
Chair: Anthony L. Komaroff, M.D., *Professor of Medicine,* Harvard Medical School (retired)

Assessment of neurobiological dysfunction in chronic fatigue syndrome
Ben Natelson, M.D.
Pain & Fatigue Study Center, Mount Sinai Beth Israel

Disrupted functional connectivity in Gulf War illness (GWI)
James N. Baraniuk, M.D., Department of Medicine, Georgetown University

Functional neural consequences of post-exertion malaise in myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS)
Dane B. Cook, Ph.D., University of Wisconsin-Madison

3:45 pm – 4:00 pm
Break/Visit Exhibits

4:00 pm – 5:00 pm
Visit Poster Presentations/Exhibits

5:00 pm – 6:00 pm
IACFS/ME Membership Business Meeting

6:00 pm – 7:00 pm
IACFS/ME Social/Cocktails Hour

7:00 pm – 8:00 pm
IACFS/ME Banquet Dinner

8:00 pm – 9:00 pm
Awards Presentation

Agenda – Sunday, October 30
12TH International IACFS/ME Biennial Conference
Emerging Science and Clinical Care

8:00 am – 9:15 am
Session 10: Symptom Provocation Studies II
Chair: Betsy Keller, Ph.D.
Department of Exercise and Sport Sciences, Ithaca College

Blood lactate increases more rapidly after a previous exercise challenge in patients with chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME) than in healthy subjects
Katarina Lien, M.D., Ph.D., University of Oslo

Subsets of ME/CFS patient responses to a 2-day CPET
Betsy Keller, Ph.D., Department of Exercise and Sport Sciences, Ithaca College

Neuromuscular Strain Increases Symptom Intensity in Chronic Fatigue Syndrome
Peter Rowe, M.D, Johns Hopkins University School of Medicine

Polar Metabolites Distinguish ME/CFS Patients and Controls
Maureen Hanson, Ph.D., Department of Molecular Biology and Genetics, Cornell University

9:15 am – 10:30 am
Session 11: Genetics Research
Chair: Jose Montoya, M.D.
Professor of Medicine, Stanford University Medical Center

Single nucleotide polymorphisms in myalgic encephalomyelitis: possible genetic factors influencing pathophysiology
Benjamin Eike, B.A., Nova Southeastern University, College of Osteopathic Medicine

Using gene expression modules to identify gender specific treatments in myalgic encephalomyelitis/chronic fatigue syndrome
Mary G. Jeffrey, Institute for Neuro-Immune Medicine, Nova Southeastern University

Epigenetic modifications and glucocorticoid sensitivity in myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS)
Wilfred de Vega, Ph.D. Can.
University of Toronto

ME/CFS miRNA analysis, mRNA in-situ hybridization and STAT1 localization upon stress trigger
Paula A. F. Waziry, Ph.D., Institute of Neuro Immune Medicine, Nova Southeastern University

Genomics of chronic fatigue syndrome reveals systemic inflammatory response
Jose G. Montoya. M.D., Stanford University School of Medicine

10:30 am – 10:45 am
Break

10:45 am – 12:15 pm
Session 12: Panel Discussion
"Nothing about us without us:" How community-engaged research can accelerate progress in the field of ME/CFS
Moderator: **Lily Chu, M.D., MSHS,** Co-Vice President, IACFS/ME; Collaborator, Stanford ME/CFS Initiative

Speaker: William Elwood, Ph.D., Expert, community-engaged research, US National Institutes of Health (NIH) Member, Trans-NIH Working Group for ME/CFS

Panelists
Jin-Mann Lin, Ph.D., Senior statistician/epidemiologist, US Centers for Disease Control and Prevention
Leonard Jason, Ph.D., Professor of community psychology, DePaul University (Chicago, Illinois)
Sonya Chowdhury, Chief Executive, Action for M.E.; Member, United Kingdom ME/CFS Research Collaborative
Jennifer Spotila, J.D., www.occupyme.net, former chairman of Solve ME/CFS Initiative

12:15 pm – 1:15 pm
Lunch/Visit Exhibits
Networking Lunch - Offering an opportunity for clinicians to network and talk about assessment and treatment issues.

1:15 pm – 2:30 pm
Session 13: Medical Education Proposals for ME/CFS
Panel Chair: Susan Levine, M.D., Visiting Fellow, Cornell University, Ithaca, NY

Fellowship program for CFS/ME research (I)
Mady Hornig, M.D., Columbia University Medical Center

A fellowship training program for ME/CFS (II)
Anthony Komaroff, M.D., Harvard Medical School (retired)

Fellowship opportunity in ME/CFS (III)
Daniel Peterson, M.D., Simmaron Research

2:30 pm – 3:00 pm
Summary of the Conference
Anthony L. Komaroff, M.D.

3:00pm
Conference Concludes

Abstracts
IACFS/ME Professional Workshops
Thursday, October 27, 2016

Workshop 1
Review of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome, Fibromyalgia and Multiple Chemical Sensitivities/Environmental Sensitivities: Office Assessment and Management
Alison Bested, M.D., F.R.C.P.C.

Learn to diagnose and treat the patients with complex chronic medical conditions in your office.

Workshop 2
Acute and Chronic Enteroviral Infection
John Chia, M.D.

The workshop entitled "Acute and Chronic Enterovirus Infection" is for professionals who would are interested in these virus infections and association with ME/CFS. Nurses, nurse practitioners, physician assistants, physicians, researchers, epidemiologist will gain basic knowledge to recognize and diagnose these medical conditions and learn to associate these infections with ME/CFS.

Workshop 3
How Cardiopulmonary Exercise Testing Informs Pathology and Treatment
Mark Van Ness, Ph.D., **Christopher Snell, Ph.D., Betsy Keller, Ph.D.**

Cardiopulmonary exercise testing (CPET) is a data collection paradigm that accurately and objectively describes the post-exertional response that ME/CFS patients experience. CPET will be described, including its utility for understanding ME/CFS pathology. Information will be presented about how the post-exertional state is particularly useful for data collection pertaining to immunological, neurological and hormonal conditions.

Workshop 4
Behavioral Assessment and Treatment of ME/CFS and Fibromyalgia
Fred Friedberg, Ph.D., **Leonard A. Jason, Ph.D.**

In this introductory workshop on CFS/ME and fibromyalgia (FM), participants will learn about practical methods of behavioral assessment and individualized treatment strategies. Our approach consists of self-management focused interventions and non-pharmacologic strategies for clinicians that can offer realistic hope for improvement in these patients. This workshop will benefit clinicians who work with CFS/ME and FM patients.

Workshop 5
Diagnosing and Treating Orthostatic Intolerance
Peter Rowe, M.D.

Postural tachycardia and hypotension in response to orthostatic stress are common in those with ME/CFS. These circulatory disturbances contribute to ME/CFS symptoms and lower quality of life. This workshop will help clinicians identify and treat common forms of orthostatic intolerance in their patients with ME/CFS.

Workshop 6
NIH Grant Writing Workshop
Vicky Whittemore, Ph.D., Cheryl Kitt, PhD., Joseph Breen, Ph.D.

The NIH Grant Writing Workshop will review skills that are critical for becoming a successful grant applicant.

Abstracts
General Session
Friday, October 28, 2016

Session 1: The Latest Research in Immunology and the Microbiome

Session Chair: Mady Hornig, M.D.

Mailman School of Public Health, Columbia University Medical Center

A panel of biomarkers accurately identifies CFS/ME patients and contributes to the understanding of the pathophysiology of the disorder

Kenny L. De Meirleir[1,2], Tatjana Mijatovic[3], Eugene Bosmans[3], Nossa Van den Vonder[2], Vincent Lombardi[1]

1. *Nevada Center for Biomedical Research at University of Nevada, Reno, USA*
2. *Himmunitas vzw, Brussels, Belgium*
3. *RED Laboratories NV, Zellik, Belgium*

Background

CFS/ME is a debilitating illness for which no specific biomarkers have been identified, although several immune abnormalities including neuroinflammation have been described. The goal of this study was to assemble a panel of immune and inflammatory markers, with the ability to accurately identify CFS/ME cases.

Objectives

From observations made in clinical practice, four markers were selected (immune and inflammatory). These markers were initially investigated to establish differences between CFS/ME cases and controls. We then evaluated their potential usefulness as a diagnostic biomarker by establishing their specificity and sensitivity.

Methods

Venous blood was collected from 70 male and 70 female CFS/ME patients (mean age 43 and 44 years, respectively - Fukuda case definition was used) as well as 70 male and 70 female healthy controls (mean age 43.5 and 44.5 years, respectively). Serum Interleukin 8 (IL-8), soluble CD14 (sCD14, a surrogate marker for bacterial LPS), and prostaglandin E2 (PGE2) were measured for all subjects as were absolute CD3- / CD57+ lymphocytes counts (CD57+ lymph), according to accepted clinical laboratory techniques.

We then established median values for all analysed parameters; independent sample t-test, Mann-Whitney test and ROC curve analysis were used to investigate difference linked to gender and age.

Results

ROC Statistics (area under the ROC curve) revealed a significant difference between CFS/ME cases and controls ($p < 0.001$) for the four parameters separately, both in the male and female cohorts. Sensitivity was 74.3 - 80 % (females) and 52.1 - 85.9 % (males). Specificity was 57.1 - 98.1 (females) and 65.7 - 88.6 (males).

Logistic regression analysis for the combination of parameters in our panel (IL-8, sCD14, PGE2 and CD57+ lymph) correctly predicted in 89.36 % of male CFS/ME cases and in 97.14 % of female CFS/ME cases.

Conclusions

This panel differentiates CFS/ME cases from controls with high sensitivity and specificity and therefore represents a potential tool in selecting CFS/ME subjects for clinical studies.

Each of these four biological markers relate strongly to the disorder. PGE2 activates dendritic cells and suppresses their ability to attract T cells. It also suppresses the function of macrophages and neutrophils as well as Th1, CTL-, NK-cell mediated type 1 immunity (e.g. CD3- / CD57+ lymphocytes). PGE2 additionally promotes Th2, Th17 and Tregs and also modulates chemokine production (e.g. IL-8). When taken together, these data suggest that lipopolysaccharide (LPS), likely from gut bacteria, plays an important role in the pathophysiology of CFS/ME.

This screening panel represents an initial step toward identifying biomarkers to broadly diagnose subjects with CFS/ME. Subsequent markers will be required to subcategorize CFS/ME subjects in order to tailor therapeutic solutions.

Presenting authors:

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Funding of the work: Himmunitas vzw (non profit organisation), Brussels, Belgium
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A Profile of Circulating Cytokines is Associated with Disease Severity in Chronic Fatigue Syndrome Patients (CFS)

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Background: Symptoms suggestive of inflammation are often observed in Chronic Fatigue Syndrome (CFS). Cytokine studies may substantiate an overactive immune system, but results have provided limited and sometimes, contradictory data.

Objectives: To determine whether a profile of circulating cytokines (out of 51) could be associated with CFS and correlate with disease severity.

Methods: 192 CFS patients and 392 healthy controls (HC) had serum cytokines measured using a 51-multiplex array on the Luminex 200 IS system (Affymetrix; Santa Clara, CA). Median fluorescence intensity (MFI) data were pre-processed for each cytokine through sequence of averaging over duplicate wells per plate, natural-logarithm transformation, isolation/removal of plate effects, and centering/scaling. Multidimensional fatigue inventory (MFI-20) scores were recorded. Each cytokine's pre-processed data were regressed on CFS severity (control vs. tertiles on MFI-20) plus covariates for age, gender, race, and nonspecific binding via distribution-free generalized maximum entropy estimation. Post hoc estimates of trend (orthogonal linear and quadratic contrasts) across severity tertiles were obtained. All p-values were adjusted through an adaptive two-stage linear step-up procedure to control false discovery rate at 5% across 51 cytokines.

Results: Average age (± 1 SD) was 49.9 ± 12.7 years (cases) and 50.1 ± 12.5 years (controls). Proportion of female subjects was 76.6% (cases) and 77.3% (controls). In cases, TGF-β was elevated ($p = 0.0076$) and resistin was lower ($p = 0.0076$, with a non-linear trend $p = 0.0362$). Seventeen cytokines had a statistically significant upward linear trend that correlated with CFS severity: **CCL11**, **G-CSF**, **CXCL1, CXCL10, GM-CSF, IFN-γ, IL-4, IL-5, IL-7, IL-12p70, IL-13, IL-17F, leptin,** LIF, NGF, SCF, and TGF-α. P-values for the linear trend ranged from 0.0062 to 0.0366.

Conclusion: Out of 17 cytokines that correlated with severity, 13 (bolded) are pro-inflammatory, likely substantiating many of the symptoms experienced by patients and the immune nature of the disease.

Alterations in the enteric bacterial and viral microbiome in ME/CFS

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Background: Gastrointestinal disturbances are among symptoms commonly reported by individuals diagnosed with Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS). However, whether ME/CFS is associated with an altered microbiome has remained uncertain and little information is known about the virome in this disease.

Objectives: To determine whether the gut microbiome, comprising both bacterial and viral populations, differs from healthy individuals in a ME/CFS population from the New York City area.

Methods: Stool and blood samples were collected from a cohort of 48 patients with ME/CFS and 39 healthy controls from the New York City region. Markers of inflammation and microbial translocation were measured in plasma. Bacterial populations were characterized by sequencing amplicons of the V4 region of 16S rRNA genes after DNA extraction. Viral DNA and RNA were enriched, extracted and amplified from stool samples prior to sequencing using the Illumina platform.

Results: We observed elevated levels of Lipopolysaccharide (LPS), LPS Binding Protein (LBP), and sCD14 in ME/CFS subjects. Levels of LBP correlated with LPS and sCD14 and LPS levels correlated with sCD14. The bacterial diversity was decreased in the ME/CFS specimens compared to controls, in particular, a reduction in the relative abundance and diversity of members belonging to the Firmicutes phylum. Specific genera such as *Faecalibacterium* and *Bifidobacterium*, known to be beneficial, were decreased in the ME/CFS population. We observed that the enteric virome of ME/CFS patients is abnormal in comparison to healthy individuals with an expansion of members of the Caudovirales bacteriophages. The predicted hosts of the identifiable phages and prophages were members of the Firmicutes and Bacteroidetes; these phyla, and in particular the families Ruminococcaceae, Lachnospiraceae and Bacteroidaceae, constituted the most abundant bacterial families in the sampled fecal microbial communities, as defined by 16S rRNA gene analysis.

Conclusion: Our results indicate dysbiosis of the gut microbiota in this disease and further suggest an increased incidence of microbial translocation, which may play a role in inflammatory symptoms in ME/CFS. Our data also support the hypothesis in which changes in the virome may contribute to intestinal inflammation and bacterial dysbiosis.

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Conflicts of Interest: none

Session 2: Treatment Studies and Clinical Practice

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Reflections on the rituximab studies

Olav Mella

Till now we have received most attention for attempting to find a drug treatment for CFS/ME. Our efforts are just as much directed at understanding the disease mechanisms. As newcomers in this research field, we were struck by the similarity in clinical presentation among patients. Our advantage is the possibility to correlate laboratory findings with clinical manifestations and response to interventional treatment. Our philosophy has been that symptoms the patients describe mostly will have a molecular counterpart. Also, postulated mechanisms that cannot account for the various symptoms so typical for CFS/ME are at best partial explanations. CFS/ME has different disease triggers before coming manifested, probably on an underlying genetic susceptibility. What we have seen as the result of immune manipulation (rituximab, cyclophosphamide) makes an immunological malfunction plausible as a starting point in a hierarchy of reactions, ending in effector systems that manifest the subjective symptoms patients experience, also in objective tests that demonstrate diversity compared to healthy individuals. Material from previous intervention studies, the ongoing double-blind, placebo controlled RituxME 5-center study with 151 patients, and the CycloME with 40 patients have given clinical data and a biobank, which is the basis of most ongoing analysis, both in-house/nationally and in collaboration with research groups in other countries. These studies comprise hunting autoantibodies, alterations in immune cells and immunoglobulins after intervention, changes in ability to regulate arterial blood flow and in anaerobic threshold during exertion, studies particularly addressing the energy metabolism and other relevant metabolomic pathways, and in vitro work elucidating mechanisms deduced from the clinical samples. We have also studied autopsy material from 4 patients who have died with or from CFS/ME and are conducting genetic studies on families that have a high occurrence of ME cases. Our aim is to find unifying concepts pointing at possible disease mechanisms.

The Synergy Trial for CFS – A Phase 2 Study of Low-Dose Methylphenidate plus Mitochondrial Support in Patients with Chronic Fatigue Syndrome

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Background

CNS stimulants have been utilized to treat CFS symptoms though their benefits are often limited and their tolerability is uncertain. Evidence of mitochondrial dysfunction in CFS patients has also been identified in several publications. Micronutrient support has been shown to improve mitochondrial function. One open-label trial in CFS patients has been published showing a significant benefit to combining these two treatment modalities.

Objectives

This Phase 2 multicenter, double-blinded, placebo-controlled trial (n=128) was performed at four US research clinics to examine the clinical effects and safety profile of combining low-dose methylphenidate plus mitochondrial micronutrient support in patients with CFS.

Methods

128 CFS patients (1994 Fukuda criteria) were randomized in double-blinded fashion to two parallel arms: a double treatment group (methylphenidate + mitochondrial support) and a double placebo group to investigate the potential synergistic effect of this combination. Fatigue and concentration disturbance symptoms were measured at baseline, 4 weeks, and 12 weeks using two clinically validated tools: Checklist Individual Strength (CIS) and Visual Analog Scale (VAS). The primary objective of the study was to measure the treatment's safety as well as its efficacy utilizing the change in CIS total score.

Results

At twelve weeks there was a change in the mean CIS total score of -16.9 in the treatment group and -13.8 for the placebo group when compared to baseline (P = 0.36). In the PP population, there was a change in the mean CIS total score of -20.9 in the treatment group and -12.6 for the placebo groups at Day 84 (P = 0.19). The change in the mean VAS score for fatigue from baseline was -18.2 in the treatment group and -11.1 in the placebo group (P = 0.19). Adverse events were not significantly different between the two groups.

Conclusion

Treatment with low-dose methylphenidate plus mitochondrial micronutrient support in CFS patients was well tolerated during this trial. Using a validated patient reported outcome measurement tool, overall CFS symptoms

decreased in a majority of the treatment subjects. Though statistical significance was not achieved in this Phase 2 trial, all analyses revealed an advantage to the treatment group. Further investigation is warranted.

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- This trial was sponsored by K-PAX Pharmaceuticals, Mill Valley, CA
- No conflicts of interest.

N-Acetylcysteine Alleviates Cortical Glutathione Deficit and Improves Symptoms in CFS: An *In Vivo* Validation Study using Proton Magnetic Resonance Spectroscopy

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OBJECTIVES
We previously reported a robust 36% deficit of occipital cortex glutathione (GSH) – the primary tissue antioxidant – in patients with CFS compared to healthy comparison (HC) subjects, a finding that implicated oxidative stress in the disorder. The primary objective of the present study was to assess whether supplementing CFS patients with the GSH synthetic precursor N-acetylcysteine (NAC) daily for 4 weeks would spur *in situ* synthesis and significant elevation of cortical GSH compared to baseline, as assessed *in vivo* with proton magnetic resonance spectroscopy (^{1}H MRS).

METHODS
For this pilot clinical study, we recruited 16 medication-free patients meeting the CDC criteria for CFS and 15 HC subjects. Following baseline measurement of occipital cortex GSH with ^{1}H MRS and administration of a battery of clinical assessments, both CFS and HC participants received a 4-week supplement of 1800mg NAC/day. After 4 weeks, identical ^{1}H MRS scan and clinical assessments were conducted to determine the effect of NAC on cortical GSH levels and on CFS symptoms as assessed with the CDC CFS symptom inventory.

RESULTS
At baseline, controlling for age and race, cortical GSH levels were 15% lower in CFS than in HC (95%CI: -0.0005,0; p=0.04, one-tailed as the differences and direction of changes were postulated *a priori*). Following 4 weeks of daily NAC supplementation, cortical GSH levels rose significantly relative to baseline (95%CI: 0.0001,0.0006; p=0.004, one-tailed) in CFS patients to match those in HC, which did not differ compared to baseline (95%CI: -0.0002,0.0003; p=0.33, one-tailed). Lastly, NAC supplementation markedly improved symptoms in CFS patients, with significant decreases in CDC CFS symptom inventory *total scores* (95%CI: -51.5-9.6; p=0.006), *case definition scores* (95%CI: -28.2-2 .0; p=0.03) and *"other symptoms" scores* (95%CI: -24.0-7.3; p<0.001). However, GSH levels did not correlate with any clinical measure.

CONCLUSION
The results of this study have provided the very first direct evidence that NAC crosses the blood-brain barrier to spur *in situ* synthesis and elevation of cortical GSH. Significantly, increasing cortical GSH levels with NAC ameliorated symptoms in CFS patients. Future studies evaluating the clinical efficacy, and optimal dose and treatment duration of NAC are warranted.

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A reexamination of the cognitive behavioral theory of CFS

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Background: Cognitive behavioral theories of chronic fatigue syndrome (CFS) suggest that cognitions and behaviors perpetuate the fatigue and impairment that individuals with CFS experience. The first empirical study of this theory resulted in a model that was supportive of the cognitive behavioral framework (Vercoulen et al., 1998). However, an attempt to replicate this model resulted in inadequate fit statistics for a well-characterized group of individuals with CFS, though the model fit well for individuals with chronic fatigue from primary psychiatric disorders (Song & Jason, 2005). These studies differed in the case definitions applied and the examination of psychiatric disorders, indicating that these factors may have contributed to the discrepant findings.
Objectives: The current study sought to reexamine the behavioral pathway of the cognitive behavioral model of CFS: activity level as a mediator between individuals' causal attribution for their illness (i.e., belief in a physical or psychological cause) and their degree of impairment. Moderators were examined to investigate reasons for previous studies' discrepant results.
Methods: Second-stage conditional process modeling (i.e., moderated mediation) was conducted on a sample of 990 individuals with CFS to reevaluate the model's behavioral pathway. Additionally, participants were classified by case definition [Oxford (Sharpe et al., 1998; Canadian ME/CFS (Carruthers et al., 2003); ME Ramsay (as operationalized by Jason et al., 2012)], and case definition fulfillment was entered as a moderator of the relation between activity level and impairment.
Results: Results were inconsistent with the cognitive behavioral theory of CFS. Activity level did not significantly mediate the relation between causal attribution and impairment (R^2 = 0.002, p = 0.175). An interaction between case definition fulfillment and activity predicted impairment (β = 0.588, p < 0.001); when individuals met less stringent case definitions, the relation between activity level and impairment was stronger.
Conclusion: These findings suggest that individuals do not reduce activity level due to illness beliefs, as proposed by the cognitive behavioral theory of CFS. Additionally, as the relation between activity level and impairment attenuated with increased case definition specificity, exercise-based interventions lack empirical justification and may not be appropriate.

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3. Conflicts of Interest:
None to report

Potential for an Immunosignature Assay to aid in Classification and Prediction of Rituximab Response in ME/CFS

Background: Immunosignatures (IMS) employ a microarray of 125,000 random-sequence peptides to interrogate serum antibodies in a broad, unbiased fashion. They have been applied to cancer detection, diagnosis of infections and interrogation of vaccine response.
Objectives: To search for IMS signatures to aid in classification, understanding pathogenesis and predicting treatment response for ME/CFS.
Methods: ME/CFS (n=25) and matched control (n=25) sera were obtained from a Canadian study. ME/CFS

Rituximab responder (n=18) and non-responder (n=7) sera were obtained from the Phase 1/2 Norwegian trials. Samples were diluted 1:1 with glycerol and 0.025% sodium azide. Microarrays were blocked with 1mM PBS, 3% BSA, 0.05% Tween 20, 0.014% mercaptohexanol for 1 h at 25 °C, then sera were diluted 1:1500 in 3% BSA, 1 mM PBS, 0.05% Tween 20 pH 7.2 and allowed to bind for 1 h at 37°C at 20 RPM. Slides were washed 3x5' with 1mM TBS, 0.05% Tween20 pH 7.2, 3x with DW water then centrifugation dried. Images were recorded using the Innoscan 910 AL scanner.

Results: Canadian cases and controls were tested for a disease signature. 200 peptides were selected that represented the disease state with the best balance between sensitivity and specificity. Cross-validation was used to predict how well the signature could predict samples. 10% (n=5) samples were randomly left out of the training. 200 peptides were re-selected, and the left-out samples were predicted. On average, the blinded samples were correctly identified 77.8% of the time. A separate and distinct signature was observed in baseline (time=0) sera from the Norway Rituximab trial. 200 peptides differentiated responders from non-responders 92% of the time. The signature was also evident in 10/25 Canadian CFS and 9/25 controls.

Conclusions: We hypothesize that the IMS assay may be useful in identifying subclasses of ME/CFS and in identifying patients most likely to benefit from B-cell depletion with anti-CD20 therapy. The predictive value of these signatures should be tested in larger studies and in the context of a phase 3 randomized controlled trial of Rituximab. Immunologic and bioinformatic investigation of key IMS peptide motifs may provide further insight into pathogenesis.

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Special Lunch Sessions

1. ME/CFS studies at the Centers for Disease Control and Prevention
Chair: Elizabeth R. Unger, M.D., Ph.D.
Chief, Chronic Viral Diseases Branch
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Study Design of the Multi-site Clinic Assessment of ME/CFS (MCAM)

Elizabeth R. Unger†, Jin-Mann S. Lin, and MCAM Workgroup. Centers for Disease Control and Prevention (CDC), Atlanta, GA

Background: While it is clear that physicians and researchers world-wide recognize an ME/CFS illness with similar features, there are several different case definitions and marked heterogeneity among patients. CDC has

endeavored to collect standardized data on key illness dimensions from ME/CFS patients from multiple clinical practices located throughout the continental United States.

Objectives: The major objectives were to use standardized questionnaires to measure illness domains of ME/CFS and to evaluate patient heterogeneity overall and between clinics; describe the course of illness and identify measures that best correlate with meaningful clinical differences and assess performance of questionnaires as Patient/Person Reported Outcome Measures; describe medication, orders for laboratory and other tests, and management tools used by expert clinicians to care for persons with ME/CFS; collect biospecimens for future hypothesis testing and for evaluation of morning cortisol profile; and identify measures that best distinguish ME/CFS from the comparison groups and identify ME/CFS subgroups that may reflect different underlying causes.

Methods: A key feature was reliance on the clinical experience of physicians who specialize in the identification and management of ME/CFS patients rather than a pre-specified case definition for study enrollment. Healthy persons and those with other illnesses that share some features with ME/CFS were enrolled as comparison groups. The study began in 2012 and enrollment is planned to continue in multiple stages through 2017. The seven collaborating clinics are: Mount Sinai Beth Israel, New York City, NY; Institute for Neuro Immune Medicine, Miami and Ft. Lauderdale, FL; Bateman Horne Center (BHC), Salt Lake City, UT; Hunter-Hopkins Center (HHC), Charlotte, NC; Open Medicine Clinic (OMC), Mountain View, CA; Richard Podell Medical (RPM), Summit, NJ; and Sierra Internal Medicine (SIM), Incline Village, NV. Five clinics (BHC, HHC, OMC, RPM and SIM) collaborated through the coordination of the Open Medicine Institute (OMI) Consortium, Mountain View, CA.

Results and Conclusions: The MCAM study has established a framework to systematically collect data on ME/CFS patients identified by experts in the field. Preliminary results document the severity and heterogeneity of the illness. Few differences in patient characteristics have been identified between clinics.

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The findings and the conclusions in this report are those of the authors and do not necessarily represent the official position of CDC. Authors declare no conflict of interest.

DATA ON CONGNITIVE FUNCTION FROM MULTI-SITE CLINICAL ASSESSMENT OF MYALGIC ENCEPHOMYELITIS/CHRONIC FATIGUE SYNDROME (MCAM) – PRELIMINARY ANALYSIS

G. Lange, JM Lin, ME Cornelius, D Robertson, M Blate, BH Natelson, ER Unger, and the MCAM Study Group

BACKGROUND: Cognitive dysfunction is one of the most common symptoms reported by patients with ME/CFS. Previous studies have shown that cognition in ME/CFS is flawed in several areas including: attention/concentration, learning, speed of information processing, and working memory.

OBJECTIVES: Cognitive function is usually assessed by lengthy neuropsychological evaluations. We wanted to evaluate whether a brief cognitive screening battery focused on the areas of cognitive dysfunction identified in ME/CFS could be useful in a clinical setting to address the presence of cognitive dysfunction especially after exercise.

METHODS: This study used paper and pencil assessments (TOPF, WAIS IV Digit Span Test) as well as a computer-administered cognitive test battery (CogState Brief Battery (CBB)) that are closely correlated with standard neuropsychological tools commonly used to evaluate attention/concentration, learning, speed of information processing, working memory, as well as executive and overall premorbid function. CBB tasks were administered at all 7 clinics within MCAM at 5 time points: during clinic visits before (Baseline) and after (Time 1) exercise (where applicable), from home on the evening of their clinic visit day (Time 2), after 24 (Time 3), and 48 hours (Time 4) after their clinic visit.

RESULTS: Valid records of a total of 250 (out of 275) participants were examined. Premorbid overall intellectual function was similar across all sites ranging from average to high average. Preliminary data analysis revealed that

speed of processing rather than accuracy of performance differentiated ME/CFS patients from a healthy normative group as well as a healthy control group over time.

CONCLUSION: Preliminary data suggest that speed of information processing is slower in ME/CFS patients before and after exercise against the background of normal overall intellectual function.

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Exercise testing data from the Multi-Site Clinic Assessment of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (MCAM) Study

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Background: Exercise testing has proven useful for both determining aerobic fitness and as a physical stressor in ME/CFS. **Objective:** To describe preliminary cardiopulmonary exercise testing data from the MCAM Study. **Methods:** Maximal exercise testing was performed in six clinics using a ramped protocol on a cycle ergometer. Exercise began with a one-minute warm-up. Thereafter, exercise intensity increased at a rate of 15-Watts/min until volitional exhaustion. Oxygen consumption (VO2), carbon dioxide production, ventilation (VE), heart rate (HR) and perceived exertion (RPE) were directly measured using a metabolic cart, HR monitor and RPE scale, respectively. Lactate was measured from blood (finger stick) at baseline, minute-2, peak exercise and minutes 3, 6 and 10 during recovery. Metabolic and perceptual data were independently and blindly assessed to determine peak effort criteria, anaerobic threshold, lactate and perceived exertion responses during exercise. Following blind assessment, data were coded for gender and illness category. Peak exercise effort was determined using American College of Sports Medicine (ACSM) criteria and relaxed criteria for respiratory exchange ratio (RER=1.1) and HR (85%_age-predicted max) Anaerobic threshold was determined using the Vslope method. **Results:** One-hundred and eighty tests were evaluated including 135 (39 male) ME/CFS patients and 45 (18 male) controls. ME/CFS patients were significantly older (ME/CFS: 50.2±13 yrs; control: 42.5±14.5 yrs, $p<0.05$), heavier (ME/CFS: 173.5±41.2 lbs; control: 152.9±33.3 lbs, $p<0.05$) and had higher BMIs (ME/CFS: 27.3±5.8; control: 24.6±4.5, $p<0.05$). Over 80% of the sample achieved peak exercise effort using ACSM criteria. When the criteria were relaxed, 92% of the sample met criteria. Percentages of achieving peak effort were similar for ME/CFS and controls for both ACSM (ME/CFS 81%; control: 78%) and relaxed (ME/CFS: 89%; control: 93%) criteria. Controlling for age and BMI, ME/CFS patients had significantly ($p<0.05$) lower peak VO2, VE, Watts, HR and lactate, but significantly ($p<0.05$) higher RER and RPE. Anaerobic threshold occurred at similar percentages of peak VO2 (ME/CFS: 54%; control: 53%) and peak Watts (ME/CFS: 39%; control: 45%). **Conclusions:** These preliminary data demonstrate the validity of the exercise testing procedures for the multi-site study. Future work will include exercise efficiency assessments and relationships to symptoms and cognitive function.

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The findings and the conclusions in this report are those of the authors and do not necessarily represent the official position of CDC. Authors declare no conflict of interest.

Salivary Test Data from the Multi-site Clinic Assessment of Myalgic Encephomyelitis/ Chronic Fatigue Syndrome (ME/CFS) (MCAM) Study

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Background: Cortisol regulates several functions associated with energy production and could play a role in fatigue and post-exertional malaise (PEM) seen in ME/CFS. Previous studies have shown that lowered cortisol levels are associated with increased fatigue and PEM in ME/CFS.

Objective: To examine whether the awakening response (measured by salivary cortisol and alpha-amylase in the morning) is affected in patients with ME/CFS.

Methods: The MCAM study is being conducted in stages at 7 ME/CFS clinics and biologic sample collection began in Stage 2. ME/CFS enrollment was determined by ME/CFS clinicians rather than a pre-specified case definition. Participants collected saliva samples at home using Salivettes at 4 time-points (awakening and at 30, 45 and 60-minutes after awakening), and transported them to the clinic on cold packs. Cortisol and alpha-amylase testing was performed by Salimetrics. This analysis concerned salivary test results on 472 participants: 293 ME/CFS and 179 Healthy Controls (HC).

Results: Overall, salivary cortisol levels increased quickly (about 40%) after awakening in the morning (from 9.0 to 12.5 nmol/L) and stayed high while alpha-amylase started higher, dropped sharply (from 118 to 71.2 u/mL) and then increased slightly within the first hour of awakening. The mean cortisol and alpha-amylase values in patients with ME/CFS did not differ from healthy controls across 4 time-points. However, there was a wide variation in the cortisol change between awakening and 30-minute time-points in both groups (ME/CFS: mean change= 64.6%, range= -64.2% - 670.1%; HC: mean change= 56.5%, range= -64.6% - 470.53%). A higher proportion of ME/CFS patients than healthy controls had mean change ≥ 50% (42.9% vs. 36.3%, p-value=0.17). Both groups had similar proportions of individuals whose cortisol values decreased from awakening to 30 minutes (~30%). In ME/CFS patients, PEM showed a linearly decreasing trend with cortisol change stratified as “<0%”, “>=0, <50%”, “>=50%” (p-trend=0.0462).

Conclusions: Preliminary analysis showed that the awakening response in ME/CFS patients did not differ significantly from healthy controls. However, the cortisol change in the first 30 minutes after wakening was highly variable in both groups. Subgrouping patients based on awakening cortisol response may be a useful correlate to ME/CFS illness domains.

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Pilot Study Evaluating Impact of Sample Processing and Assay Format on Measured Natural Killer Cell Function

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Background. Impaired natural killer (NK) cell function is one of the most consistent abnormalities reported in ME/CFS patients. The current gold standard assay requires testing on the day of blood collection and few laboratories have this testing capacity. Improving logistics of NK cell function testing is one step towards advancing NK cell function as a clinically useful biomarker.

Objectives. Conduct a pilot study to evaluate the impact of variables involved in sample collection, processing and assay format on reported NK cell function.

Methods. Whole blood (heparin and EDTA) from 31 subjects enrolled from 3 clinics was tested by two laboratories. In total six NK functional assays that varied by blood collection tube (heparin, EDTA), blood processing (whole blood, isolated PBMCs, freezing), NK activation (K652 target cells, PMA/ionomycin), NK functional parameter (cytotoxicity, CD107a upregulation), detection method (^{31}Cr-release, flow cytometry) and data analysis were used. All assays were performed the day after collection, ideally within 24 hours of collection. Delays were noted for potential impact on results. As the gold-standard reference, 11 subjects were also tested the day of collection using whole-blood and ^{31}Cr-release.

Results. Next day analysis of whole blood or frozen PBMCs impaired NK cytotoxicity (median cytotoxicity by ^{31}Cr-release: whole blood/same day = 10.2 versus whole blood/next day = 6.0 and PBMC/next day = 13.0 versus frozen PBMC/same day = 5.8). CD107a expression after PMA/ionomycin had wide dynamic range but did not correlate with cytotoxicity. For next-day testing, measuring cytotoxicity on isolated PBMCs was more reliable than cytotoxicity in whole blood (whole blood/same day versus PBMC/next day: $n = 10$, $R^2 = 0.6$, $p = 0.01$ or versus whole blood/next day: $n = 11$, $R^2 < 0.03$, $p = 0.6$).

Conclusions. NK function measured in PBMCs isolated after one-day shipping can be used when same day testing is not available.

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Description of the Multi-site Clinic Assessment of ME/CFS (MCAM) Study Biorepository

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Background and objectives: The MCAM study aims to improve illness measures and to identify patient subgroups that reflect biologic differences in pathogenesis or response to therapy. Collection and storage of biologic specimens from study participants was added to create a biorepository resource to advance ME/CFS research.
Methods: The study has been conducted in stages at 7 clinical sites following a rolling cohort design. Blood and saliva were collected starting in Stage-2. These were selected because they were the least invasive, and minimized processing at the clinics, to help achieve uniform high quality samples from as many participants as possible. Participants collected saliva at home at 4 time points (immediately after awakening while still in bed, and at 30, 45 and 60 minutes after awakening) using the saliva collection kits (Salimetrics, CA) following instructions provided by the clinic. Whole blood was collected at the clinics via venipuncture, into two tubes to lyse and preserve nucleic acids; Tempus blood RNA tube (Applied Biosystems, CA) and PAXgene blood DNA tube (Qiagen, CA) in that order. In the exercise sub-study, whole blood was collected in EDTA tubes for plasma, and Tempus tubes immediately before and one hour after exercise. Standard operating procedures for collection, labeling, storage and shipping were implemented to assure quality of biospecimens.
Results: As of April 2016, biospecimens were collected from 686 subjects in Stage-2 (417 CFS, 231 healthy controls, 38 ill controls), and 267 subjects in Stage-3 (190 CFS, 55 healthy controls, 14 ill controls, 8 pediatric/adolescent ME/CFS). Pre- and post-exercise samples were collected on 132 ME/CFS subjects. MCAM biorepository consists of a total of 6,717 vials of specimens (3,511 saliva collections, 824 PAXgene DNA blood tubes, 1,079 Tempus blood RNA tubes, and 1,303 plasma aliquots) from a total of 1,085 subjects. Extraction of DNA from PAXgene tube is in

progress. Tempus tube RNA extraction is being optimized for recovery of both messenger and microRNAs. **Conclusions**: The MCAM biorepository is one of the largest collection of biospecimens representing ME/CFS, ill comparison and healthy controls. A Steering Committee and process for evaluation of requests for biospecimens are being established.

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The findings and the conclusions in this report are those of the authors and do not necessarily represent the official position of CDC. Authors declare no conflict of interest.

2. Mitochondrial Dysfunction: A Potential Etiology for ME/CFS?
Moderator: Jon D. Kaiser, M.D., University of California Medical School, San Francisco

Speaker Panel: **Ron Davis, MD**, Stanford University Medical School
Nancy Klimas, MD, Neuro Immune Institute, NOVA Southeastern
Dikoma Shungu, PhD, Departments of Radiology, Neurology and Neuroscience, Weill Cornell Medicine

Mitochondrial dysfunction is an etiologic mechanism that may explain the multisystem range of symptoms experienced by CFS patients. Electron micrographs of muscle biopsies have revealed abnormal mitochondrial degeneration. Evidence of oxidative damage and increased activity of antioxidant enzymes have also been chemically detected in muscle specimens of CFS patients. The classic presentation for an illness manifesting mitochondrial dysfunction is one that involves multiple symptoms spanning many domains. These typically include fatigue, cognitive impairment and other brain-related challenges, muscle weakness, exercise intolerance, and gastrointestinal problems. The broad symptoms profile found in ME/CFS is consistent with this description of a mitochondrial dysfunction disease.

Each panelist will share their perspective on this topic for ten minutes, including an overview of their own investigations, to be followed by a Q&A session.

Session 3: Gulf War Illness

Session Co-chairs:
Kristy Lidie, Ph.D., US Department of Defense
Victor Kalisinsky, Ph.D., US Department of Veterans Affairs
Gulf War Illness Program Officers

Gulf war illness and chronic fatigue syndrome: lessons learned
Presenter: Lea Steele, Ph.D., Professor and Yudofsky Chair in Behavioral Neuroscience, Baylor College of Medicine

The modern era of Chronic Fatigue Syndrome (CFS) research and clinical care began in the late 1980s, with reported outbreaks in Nevada and New York. The problem of "Gulf War Syndrome", now known as Gulf War illness (GWI), first came to light in 1991, as troops returned home from a brief and successful military campaign in the deserts of Southwest Asia. In both scenarios, reports of unexplained illness, characterized by a similar profile of chronic neurocognitive difficulties, fatigue, pain, and associated symptoms, posed major challenges for patients seeking care, healthcare providers, and the federal agencies tasked with addressing these problems.

More than a quarter century later, a great deal has been learned about both conditions, with improved understanding of their occurrence and risk factors, and the biological systems affected. Yet, despite persistent efforts by patients and clinicians, and hundreds of millions of dollars of research expenditures, satisfactory treatments and diagnostic measures have remained elusive. This presentation will provide a brief overview of key findings in both conditions, similarities and differences between CFS and GWI, and a relatively recent shift in federal GWI research that has accelerated efforts to identify effective treatments.

Brain Immune Interactions in Gulf War Illness: Cytokines and Cognition in US Military Veterans

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Background: Identifying objective biomarkers of persistent symptoms in ill US Gulf War veterans (GWI) has been a focus at the Boston Gulf War Illness Consortium (GWIC). Symptoms of GWI include fatigue, pain and cognitive problems. Our prior studies showed cognitive decrements in veterans with GWI compared with healthy veterans.

Objectives: The next step would be to compare these deficits with proinflammatory cytokine biomarkers in healthy and ill GW veterans. This study compared a cognitive battery including attention/executive, memory, visuospatial and motor functions and plasma cytokine biomarkers in veterans with GWI versus healthy GW veterans. Sixteen cytokines were compared between groups.

Methods: Participants included 36 GW veterans including 28 with GWI and 8 healthy controls. Cases and controls did not differ by age, sex or education. The study population had a mean age of 50 years and 15 years of education. Cytokines were evaluated by a high sensitivity chemiluminescent multiplex ELISA assay.

Results: Veterans with GWI had significantly higher mean Conners CPT3 reaction time and Purdue pegboard scores and lower CVLT-II recognition memory scores ($p<.05$). In addition, CPT3 mean reaction time, T scores and commission errors significantly correlated with IL6, IL13, IL1-apha and TNF-alpha and inversely correlated with IL12 ($p<.05$) in GWI cases.

Conclusions: This study is the first to report plasma cytokine biomarker differences and reduced performance on tasks of information processing speed and sustained attention in veterans with GWI. Further study of brain-immune interactions and cognitive outcomes should be conducted in larger cohorts to further validate these cognitive-immune biomarker findings in GWI.

Presenting Author: Kimberly Sullivan, PhD Research Assistant Professor Boston University School of Public Health, 715 Albany Street, T4W, Boston, MA 02118 email: tty@bu.edu

Acknowledgments: This work is supported by a CDMRP GWI consortium award (GW120037) to Dr. Kimberly Sullivan.

Conflicts of Interest: none

Genomic approach to find mechanisms of Gulf War Illness pathobiology

Nathanson L., Rashid H., Sarria L., Collado F., Cash M., Moturu A., Galvez Cabezas K., Fletcher M.A., Klimas N.G.

Background: Gulf War Illness (GWI) is a prominent condition affecting up to 30% veterans of the 1990-91 Persian Gulf deployment with a cluster of chronic debilitating symptoms such as fatigue, cognition difficulties, and disturbances of multiple organ systems. The causes and mechanisms of GWI are unknown, however, the symptoms suggests that GWI is caused by a combination of factors such as genetic predisposition and environmental modifications to genomic profiles, likely due to exposure to toxic chemicals. There are no specific biomarkers for diagnosis or management of GWI and treatment has been symptom-driven. DNA methylation is one of the epigenetic mechanisms that regulate gene transcription without changes in the DNA sequence. It involves the covalent binding of a methyl group to a Cytosine-5 at a C-phosphate-G (CpG) site. Negative associations between methylation and transcription are known to be enriched particularly in promoter regions. It was shown that DNA methylation plays an important role in the transcriptional regulation in cancers, neurological and immune system diseases, however, the role of DNA methylation in GWI remains unknown.
Objectives: The main objective of this research proposal is to identify novel mechanisms of transcriptional regulation in GWI, which will help to better understand GWI pathobiology.
Methods: We evaluated levels of DNA methylation in peripheral mononuclear blood cells isolated from 10 male GWI patients and 10 male healthy controls using Illumina MethylationEPIC BeadChip arrays, controlling for the probes with the low detection, invariant probes and probes overlapping polymorphic sequences. DNA methylation analysis was performed using R software with RnBeads package. The mean difference in means across all sites in a region of the two groups, the mean of quotients in mean methylation and a combined p-value calculated from all site p-values in the region were used to rank the degree of the differential methylation.
Results: We found an increased abundance of hypomethylated promoters of genes participating in signal transduction in the cells from GWI patients. However, there was enrichment in hypermethylated promoters of genes involved in apoptosis and cell differentiation.
Conclusion: This data show that DNA methylation is one of the factors regulating gene expression in GWI.

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The authors declare no conflicts of interest.

Using gene expression signatures to identify novel treatment strategies in Gulf War Illness

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[7]Diabetes Research Institute, University of Miami, Miami, FL, USA

Objective: Gulf War Illness (GWI) is a complex multi-symptom disorder that affects up to one in three veterans of this 1991 conflict and for which no effective treatment has been found. Discovering novel treatment strategies for such a complex chronic illness is extremely expensive, carries a high probability of failure and a lengthy cycle time. Repurposing Food and Drug Administration approved drugs offers a cost-effective solution with a significantly abbreviated timeline.
Methods: Gene expression data from Affymetrix Human U133 2.0 arrays for male GWI subjects (n = 17) defined by the Fukuda definition were compared to healthy sedentary Gulf War era veterans (n = 22) across 4,620 functional modules defined by the human protein-protein interaction network. The absolute average T-score for each gene module was used to capture differential gene module expression at a threshold of 1.5, corresponding to a p-value of < 0.1 chosen as a liberal cutoff value to identify modules affected in GWI. Expression of individual genes from identified affected modules was then compared between the same GWI subjects and healthy controls using an unpaired t –test. After correcting for false discovery genes with a false discovery rate of less than 0.05 were considered significantly expressed. These genes were then cross-referenced with drug atlas and pharmacogenomic databases to identify agents currently used successfully for treatment in other diseases. To explore the clinical use of these drugs in illnesses similar to GWI we compared gene expression patterns in modules that were significantly expressed in GWI with expression patterns in those same modules in other illnesses.
Results: We found 19 functional modules with significantly altered gene expression patterns in GWI. Within these modules, 45 genes were documented drug targets. Illnesses with highly correlated gene expression patterns overlapping considerably with GWI were found in 18 of the disease conditions studied. Brain, muscular and autoimmune disorders composed the bulk of these.
Conclusion: Of the associated drugs, immune-suppressants currently used in treating rheumatoid arthritis, and hormone based therapies were identified as the best available candidates for treating GWI symptoms.
Sponsorship: Funding came from the US Department of Defense Congressionally Directed Medical Research Program (CDMRP) awards (http://cdmrp.army.mil/) GW093042 (Broderick - PI) and GW080152 (Klimas - PI), as well as the U.S. Department of Veterans Affairs (Merit Award, N. Klimas, PI). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Session 4: Diagnosing CFS/ME; Difficult Clinical Cases: Focus on Fatigue and Pain

Session Chair: Nancy Klimas, M.D.
Immediate Past President, IACFS/ME
Professor of Medicine & Director, Nova Southeastern University
Director, Miami VAMC Gulf War Illness & ME/CFS Research Program

Panel:
Lucinda Bateman, M.D., Bateman Horne Center of Excellence, Utah

John Chia, M.D., UCLA School of Medicine
Charles Lapp, M.D., Hunter-Hopkins Center, North Carolina
Dan Peterson, M.D., Sierra Internal Medicine, Incline Village, Nevada
Katherine Rowe, M.D., Royal Children's Hospital, Australia
Peter Rowe, M.D., Johns Hopkins University School of Medicine

Evening Session:

Session Chair: Vicky Whittemore, Ph.D.
Program Director, Channels, Synapses and Circuits
National Institute of Neurological Disorders and Stroke

The National Institute of Neurological Disorders and Stroke (NINDS), National Institutes of Health and the Center for Disease Control and Prevention (CDC) will partner to develop common data elements (CDEs) for standardized testing and common data elements to be recorded in clinical studies/trials of individuals with myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS). The development of CDEs for ME/CFS will facilitate the comparison of results across studies and help to standardize analysis. The session will be led by NINDS and CDC Program Staff to discuss the timeline and process for developing the CDEs and to obtain feedback and input from ME/CFS stakeholders.

Abstracts
General Session
Saturday, October 29, 2016

Session 5: CFS, SEID, ME Case Definitions: Clinical vs. Research Criteria

Presenter: Leonard Jason, Ph.D.
Professor, DePaul University*, Director of the Center for Community Research*

Discussants:
Lucinda Bateman, M.D.
Chief Medical Officer
Bateman Horne Center of Excellence
Salt Lake City, Utah

Jon Kaiser, M.D.
IACFS/ME Board Member
University of California, San Francisco

Session 6: Symptom Provocation Studies I

Session Chair: Staci Stevens, M.A.
Founder, Workwell Foundation

Cardiopulmonary Exercise Testing Demonstrates Post-Exertional Chronotropic Incompetence

Bettencourt, Haylee[1]; Davenport, Todd E.[2];Stevens, Jared[3]; Stevens, Staci R.[3]; Snell, Christopher R.[3] and **Van Ness, J. Mark[1]**

1. Department of Health, Exercise, and Sport Science, University of the Pacific, Stockton, CA, United States. 2. Department of Physical Therapy, University of the Pacific, Stockton, CA, United States. 3. Workwell Foundation, Ripon, CA, United States.

Background : Chronotropic incompetence (CI) is the inability of the heart to increase its rate commensurate with increased functional demands. CI is common in patients with cardiovascular disease, and associated with exercise intolerance that impairs quality of life. In previous studies we've demonstrated that patients with CFS/ME experience post-exertional exercise intolerance. **Objective**: This study examined the heart rate response to exercise to determine whether CI is associated with post-exertional exercise intolerance. **Methods**: 39 females with CFS/ME and 39 age- and weight-matched control subjects (CON). Subjects performed a graded exercise test to volitional fatigue on a cycle ergometer (Test 1). A subset of 17 subjects with CFS/ME and 18 CON subjects repeated a second exercise test 24 hours later to examine the exercise heart rate response in the post-exertional state (Test 2). Heart rate (HR) was collected continuously throughout the exercise test. Data were analyzed for resting (Rest), at anaerobic threshold (AT), and at peak exercise (Peak). Only subjects that reached criteria for maximal effort were included in the analysis. Repeated measures ANOVA was used to compare HR measurements between groups and tests. **Results** : HR in the CON group was not significantly different between Test 1 and 2 at

any exercise intensity (Rest: 88±11 vs 89±19; AT: 126±17 vs 121±12; and Peak: 182±12 vs 180±15; values expressed as mean ± standard deviation). The CFS/ME group responses were not significantly different from CON on Test 1 (rest: 90±15; AT: 120±13; Peak: 170±10). However, the CFS/ME group demonstrated significantly lower Peak heart rate values on Test 2 (Rest: 100±18; AT: 116±10; Peak: 165±10; $p<.05$) compared to Test 1. HR measurements were not significantly different between groups or exercise tests for any group except the diminished peak value during the second exercise test in subjects with CFS/ME group. **Conclusion** : Patients with CFS/ME appear to display post-exertional reductions in the peak HR response to exercise, which could contribute to exercise intolerance and observed reductions in oxygen consumption during post-exertional malaise. The combination of elevation in resting heart rate and reduction in peak exercise heart rate may contribute to the impaired quality of life.

Post-exertional malaise: multiple and unexpected symptoms, sometimes delayed, often prolonged

Chu L, Norris JL, Valencia IJ, Garvert DW, Montoya JG.

Background: Post-exertional malaise (PEM) is considered to be the hallmark symptom of myalgic encephalomyelitis/ chronic fatigue syndrome (ME/CFS) and is included in most case definitions. Yet, patients have rarely been asked in formal studies to describe their experience of PEM.

Objectives: To describe the time course of and symptoms associated with PEM

Methods: 150 subjects, diagnosed via the 1994 Fukuda CFS criteria, completed a survey concerning 11 symptoms they could experience after exposure to two different types of triggers. We also inquired about onset and duration of PEM and included space for subjects to write in any additional symptoms. Results were summarized with descriptive statistics; McNemar's, paired t-, and chi-square goodness-of-fit tests were used to compare symptom presentation and time course.

Results: 129 (89%) subjects experienced PEM with both physical/ cognitive exertion and emotional distress. Almost all were affected by the former trigger but 14 (10%) reported no effect with the latter trigger. Exertion precipitated significantly more symptoms than emotional distress (7±2.8 vs. 5±3.3 symptoms (median, standard deviation), $p<0.001$). Fatigue was the most commonly exacerbated symptom but cognitive difficulties, sleep disturbances, headaches, muscle pain, and flu-like feelings were cited by over 30% of subjects. 61% of subjects experienced at least one inflammatory/ immune-related symptom. Subjects also cited gut-, orthostatic-, and mood-related symptoms. Except for sleep disturbances, exertional stressors were significantly more likely than emotional distress to provoke symptoms ($p<0.004$). The onset and duration of symptoms varied for most patients. However, 11% reported a consistent post-trigger delay of at least 24 hours before PEM began and 23% endured PEM for 3 or more days.

Conclusions: Our results confirm patient and clinician accounts of PEM. PEM involves exacerbation of multiple symptoms, including many not traditionally associated with exertion, is occasionally delayed, and persists for extended periods. In the future, researchers should inquire about the wide range of PEM symptoms and build into their study designs flexibility to capture the varying time courses of PEM that subjects experience.

Lily Chu, MD, MSHS; Stanford ME/CFS Initiative Community Advisory Board, lchu1@stanford.edu. **Portions of this work were funded by the Stanford ME/CFS Initiative. Dr. Chu has no conflicts of interest to disclose.**

Cognitive function in adolescents with chronic fatigue syndrome/myalgic encephalomyelitis: A novel paradigm

Sarah Knight[1,2,3], Elisha Josev[1], Adam Scheinberg[1,2,4], Adrienne Harvey[1,3], Kathy Rowe[2], Lionel Lubitz[2], Marc Seal[1,3]

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[3]Department of Paediatrics, The University of Melbourne, Melbourne, Australia
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Background

Cognitive dysfunction following mental or physical exertion is commonly reported in paediatric Chronic Fatigue Syndrome/Myalgic Encephalomyelitis (CFS/ME), and can impact on schooling and social functioning. However, cognitive functioning has rarely been measured objectively in this population.

Objective

This study aimed to evaluate cognitive performance and subjective fatigue in adolescents with CFS/ME in comparison with healthy adolescents, before and after a period of cognitive exertion.

Methods

A pre-test/post-test design was used (i.e., before and after a 30-minute academic assessment). 23 adolescents (mean age=15.5 ± 1.4 years) diagnosed based on the Pediatric Case Definition at the Royal Children's Hospital CFS/ME Clinic were recruited, as well as a convenience sample of 20 healthy controls (mean age=15.5 ± 1.9 years). A CogState Research battery measuring processing speed, sustained attention, working memory and new learning, and a Visual Analogue Scale (VAS) of subjective fatigue severity were completed before and after a 30-minute period of academic tasks (i.e., cognitive exertion). Paired sample t-tests and regression analyses were used to investigate mean between-group differences before and following cognitive exertion.

Results

There were no group differences in age, sex, or intelligence. Prior to cognitive exertion, adolescents with CFS/ME demonstrated significantly poorer performance on measures of processing speed ($p<0.05$) and sustained attention ($p<0.05$), and reported greater subjective fatigue ($p<0.001$) compared with controls. Following cognitive exertion, poorer performance on processing speed and sustained attention measures ($p<0.05$), and greater subjective fatigue ($p<0.001$), were maintained by the CFS/ME group. Poorer performance on the working memory task ($p<0.05$) also emerged post-exertion. However, no significant group differences were observed in the magnitude of change between groups over time. There was no association between changes in subjective fatigue over time and cognitive performance.

Conclusions

These findings suggest that adolescents with CFS/ME are slower to process information and have less capacity to sustain their attention compared with healthy adolescents, before and following cognitive exertion. It is important for clinicians and school staff to be aware that adolescents with CFS/ME are at heightened risk for experiencing cognitive difficulties. Considering how these cognitive weaknesses can best be supported in the school environment is an imperative.

Session 7: Public Health Research

Session Chair: Steve Krafchick, MPH, JD
IACFS/ME Board Member

Estimating Rates of Pediatric Chronic Fatigue Syndrome and Myalgic Encephalomyelitis in a Community-based Sample

Leonard A. Jason[1], Ben Z Katz[2], Cynthia Mears[3], Rachel Jantke[1], Abby Brown[1], Madison Sunnquist[1], Kelly O'Connor[1], DePaul University[1], Lurie Children's Hospital at Northwestern University[2], Advocate Health Care[3]

Objectives: There is a need to examine the prevalence of pediatric chronic fatigue syndrome (CFS) and Myalgic Encephalomyelitis (ME) in the general community. We describe an ongoing NIH-funded study, which uses a multiple-stage design, beginning with a brief screening for CFS- and ME-like symptomatology, followed by a more rigorous medical and psychiatric diagnostic evaluation.

Methods: The present community-based sample is generated in two stages. In Stage 1, we contact households in the Chicago metropolitan area and screen for CFS and ME-like profiles in children and youth. The screening questionnaire thus creates 2 groups: pre-screen positives and pre-screen negatives/controls. Children participating in Stage 2 have a comprehensive physical examination, including a structured medical history assessment, blood work, urine analysis, and a salvia sample taken. In addition, both the parent/legal guardian and the child fill out several questionnaires related to the child's health and activity levels, as well as self-report measures of behavior and psychosocial functioning. Next, a psychiatric interview is completed with the parent/legal guardian and the child separately to determine the child's overall mental health functioning. Finally, the child is asked to wear an actigraph monitor for 24 hours to measure their activity levels.

Results: In our ongoing study, we have examined youth who present with a wide range of reasons for their impairment, and different case definitions select different youth. We are using three case definitions including the Fukuda et al. (1994) criteria, the IOM (2015) clinical criteria, and a pediatric criteria based on the Canadian Consensus Criteria (2003). Findings will be presented at the conference.

Conclusions: We continue to deal with diagnostic challenges in categorizing youth with CFS or ME. Decisions need to be made about which case definitions to use if we are to have better prevalence data (Jason, Porter, & Rademaker, 2011). Some youth might meet more general clinical criteria, such as that proposed by the IOM (2015), whereas other youth might meet more restrictive criteria, which excludes those with other illnesses or conditions. Our study will advance the field as we improve efforts to identify youth with CFS and ME in the general population.

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No conflicts of interest.

Two Year Follow-Up of Impaired Range of Motion in Adolescent Chronic Fatigue Syndrome

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From the [1]Department of Pediatrics, Johns Hopkins University School of Medicine, Baltimore, MD, the [2]Department of Health Behavior, University of Alabama at Birmingham School of Public Health, Birmingham, AL, and [3]Rick Violand PT, LLC, Ellicott City, MD, USA

Background: We previously demonstrated that adolescents and young adults with chronic fatigue syndrome (CFS) have a significantly higher prevalence of impaired range of motion (ROM) of the limbs and spine than healthy controls matched by sex and degree of joint hypermobility. Little is known about the course of these ROM abnormalities over time.
Objective: To measure changes in ROM over 2 years in adolescents and young adults with CFS, and to determine whether improvements in ROM correlate with improved general function.
Methods: The Johns Hopkins Pediatric CFS Cohort Study followed 55 adolescents and young adults who met the Fukuda CFS definition for 2 years. All participants underwent a standardized examination of range of ankle dorsiflexion, passive straight leg raise, seated slump testing, upper limb neurodynamic testing, prone knee bend, and prone press-up. Abnormal ROM on each measure was defined before the study began (described in *J Pediatr 2014;165:360-6*). We calculated a ROM score that ranged from 0 (normal ROM throughout) to 11 (impaired ROM in all areas tested). All participants completed questionnaires measuring health-related quality of life, including the Peds QL. We performed bivariate correlation analyses for the change in the ROM score and the change in general HRQOL.
Results: Of the 55 subjects in the CFS Cohort Study, 2 who had improved within 6 months did not return for long-term follow-up. Of the remaining 53, the mean (SD) age 16.5 (2.1) years at enrollment; 93% were treated in physical therapy during the 2 years. The median ROM score was 5 at enrollment. By 24 months, the median ROM score was 2 ($P < 0.001$, Wilcoxon signed ranks test). Using a cut-point ROM score of ≤ 2 (the ROM score in healthy controls in this cohort study), 75% of CFS participants had a ROM score of 3 or higher at enrollment, compared to 26% at 24 months ($P < 0.0001$). In all, 43 had an improvement in ROM score over 2 years, and 10 were unimproved. There were no differences in age, sex, race, BMI, abrupt vs. gradual onset illness, HRQOL scores at baseline, or Beighton scores between the improved and unimproved groups. There was no significant correlation between change in the ROM score and change in the PedsQL total score ($r=0.21$; $P=0.14$). There was a weak correlation with the Peds QL physical function score ($r=0.30$; $P= 0.03$).
Conclusions: Adolescents and young adults with CFS and impaired range of motion at study enrollment notice significant improvement in ROM scores over 2 years in association with multimodal therapy. Improvement in impaired ROM was associated with some functional outcomes. The independent contributions of specific forms of physical therapy vs. general increases in activity to improvement in ROM scores warrants further study.

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No author has a conflict of interest. The study was funded by private philanthropy.

Allergic disorder phenotypes in ME/CFS and patterns of medical comorbidity and clinical dysfunction

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Background: Atopic disorders are more common in ME/CFS and have been associated with autonomic disturbances in some studies. Assessment of clinical characteristics and comorbidity among ME/CFS subjects with allergic diatheses may improve differential diagnosis and treatment selection.

Objective: To determine whether certain allergic disorders are more common in ME/CFS than in controls, and to compare clinical characteristics (severity and pain ratings; medical comorbidities) among ME/CFS subjects with and without certain allergic comorbidities.

Methods: Questionnaire data from the Chronic Fatigue Initiative (CFI) Cohort study (five US sites) were used to compare the frequency of allergic and other somatic conditions in ME/CFS (n=202 meeting Fukuda and/or Canadian criteria) and control subjects (n=202). Machine learning techniques (LASSO, Random Forest) were used to derive phenotypic subsets that differed between ME/CFS and control groups. SF-36 subdomain scores (Wilcoxon rank-sum tests) and prevalence of medical comorbidities (chi-squared tests) were compared between case groups meeting criteria for the two derived ME/CFS phenotypes. Orthostatic pulse changes from physical exams were also compared across phenotypic subsets. Adjustments were made for multiple comparisons.

Results: Machine learning approaches identified chronic sinusitis and hives as the allergic disorders that best discriminated cases from controls. ME/CFS subjects with sinusitis/hives (ME+S/H) had more severe pain (SF-36) and gastrointestinal disturbances, endocrine and inflammatory problems (DSQ) (all $p_{adjusted}$=0.029) than those without these allergic comorbidities. ME+S/H cases also had higher prevalence relative to ME subjects without sinusitis/hives of fibromyalgia (p=0.029); migraine (p <0.0001); tension headaches (p=0.0002), low back pain (p=0.002) and neck pain (p=0.003). Pain ratings were also higher in ME+S/H cases. Orthostatic pulse changes were equally common in ME/CFS with and without sinusitis/hives.

Discussion: A history of sinusitis and hives is predictive of an ME/CFS diagnosis and appears to define a novel phenotypic subset of ME/CFS with distinct patterns of comorbidity and exaggerated pain symptoms. Future studies will investigate whether S/H features are associated with altered immunity (Th2 dominance), including secretion of mast cell products that alter pain pathways. ME+S/H cases may represent a distinct subgroup with unique patterns of somatic comorbidity that may help predict response to selected therapeutic approaches.

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Financial conflicts of interest: None

Exploring the Role of Sex Hormones in Driving Symptom Severity in ME/CFS

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Background. Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) is a complex multi-factorial illness that involves immune and endocrine dysfunction. Women are disproportionally affected with ME/CFS and studies have demonstrated disruption in menstrual cycles and immune function.

Objectives. Our objective was to explore the role of sex hormones on symptom exacerbation in patients with ME/CFS.

Methods. Illness severity was characterized using standard self-assessment instruments including Multidimensional Fatigue Inventory (MFI). Blood samples were collected at rest from n=38 female ME/CFS

subjects, 18-63 years of age, and analyzed for concentrations of testosterone (15.4 ng/dL, SE 2.5), estradiol (100 pg/mL, SE 36) and progesterone (3.58 ng/mL, 0.69 SE) among other markers. Subjects were divided into four groups, based on age (less than and over 50 years) and progesterone levels with the luteal phase as progesterone > 1.1 ng/ml and follicular phase as < 1.1 ng/ml. Concentrations were log2 transformed and z-scaled. Standard t-tests were used to compare to hormone concentrations and ratios across groups. Spearman correlation corrected for body-mass index (BMI) was used to link progesterone and hormone ratios to general and physical fatigue within groups.

Results. There was a significant difference between age groups in estrogen levels (p=0.001; 0.006) regardless of overall progesterone levels being less than or greater than 1.1 ng/ml. Corresponding age related changes in progesterone to estrogen ratio did not achieve statistical significance (p=0.08; 0.05) in either group. In subjects aged ≤50 years, testosterone levels correlated negatively (*r* = -0.49, p=0.01) with general fatigue when progesterone <1.1 ng/mL but positively (*r* = 0.68, p=0.01) at higher progesterone levels. Similarly progesterone levels correlated negatively (*r* = 0.43, p=0.03) with general fatigue when <1.1 ng/mL but not significantly at higher levels in the younger ME/CFS group. Estradiol levels correlated positively with general fatigue but only in the older group at higher progesterone levels (*r* = 0.61, p=0.03). Correlation was improved by using a ratio with progesterone (E:P ratio) for general (*r* = 0.90, p<0.01) and physical fatigue (*r* = 0.84, p<0.01)

Conclusion. These result indicate that sex hormones, particularly the effects of testosterone and estradiol on fatigue severity in ME/CFS vary according progesterone levels when controlling for menstrual phase and menopausal status. Additional analysis of the joint effects of cytokines and sex hormones on symptom severity is ongoing.

Nurses' acute fatigue predicts sickness absence in the workplace: A 1-year retrospective cohort study

Sagherian K, Unick J, Zhu S, Geiger-Brown J

Background: Nurses' sickness absence (SA) creates an economic burden and harms the work productivity on hospital units. This occupational problem is often related to work-related fatigue in shift workers yet few studies have explored this relationship in nurses despite high fatigue levels.
Objective: The main purpose was to examine the relationship between fatigue at baseline and SA in 12-hour shift nurses in a pediatric hospital during 12 months of follow-up. A secondary purpose was to identify what other work and personal factors predict SA in this cohort.
Methods: The study used 1-year retrospective cohort design. Baseline data on 40 nurses from an intervention study were linked to SA data using hospital attendance records for the period 2012-13. This resulted in 6057 work shifts of which 5.2% were absence episodes. Fatigue was measured by the Occupational Fatigue Exhaustion Recovery scale. The questionnaire also included instruments assessing sleep, workload and personal characteristics. Using STATA14 software, generalized linear mixed models were used to test the association between fatigue, work and personal factors and SA, while accounting for the non-independency of repeated measures.
Results: Nurses were mostly white, single with a mean age of 30.90 ± 7.86 years. They had symptoms of insomnia (n=11, 27.5%) and sleep apnea (n=7, 17.5%). Nurses experienced low-to-moderate levels of chronic fatigue (41.67 ± 24.45) and intershift recovery (43.89 ± 21.15), and moderate-to-high levels of acute fatigue (66.11 ± 18.66). Higher acute fatigue was related to SA when personal and work factors were controlled. With 1 standard deviation increase in acute fatigue scores, nurses were 1.29 times more likely to be absent from work (odds ratio [OR]=1.29, 95%confidence interval [CI]=1.02-1.63, *p*=.036). Other factors such as perceived workload (OR=1.23, 95%CI=1.03-1.48, *p*=.024), intershift recovery (OR=1.32 95%CI=1.03, 1.69, *p*=.027), sleep apnea (OR = 2.05, 95%CI = 1.29-3.25,

p=.002) and marital status (OR=1.53 95%CI=1.01, 2.31, *p*=.045) significantly predicted SA too.
Conclusion: These findings suggest for nursing management to monitor for workplace fatigue and unit workloads, and nurses to be screened for sleep apnea and seek medical treatment in order to reduce the incidence of SA in the workplace.

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Examining the accuracy of a physical screening tool for Chronic Fatigue Syndrome/Myalgic Encephalomyelitis: A Blind Controlled Study

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Background: The screening technique is derived from novel physical findings over years of examining CFS/ME patients. Tender points in the chest and abdomen, palpable varicose lymphatic vessels, restricted and postural dysfunction of the thoracic spine, and a disturbed cranial rhythmic impulse have all been clinically observed.

Objectives. To explore the effectiveness of using 5 specific physical signs as an aid to diagnosing CFS/ME.

Methods. 52 CFS/ME patients diagnosed by consultants at NHS clinics and 42 healthy controls volunteered to take part and were screened for inclusion using the NICE guidelines and The ME - ICC.
A recently qualified osteopath with no clinical experience of CFS/ME and a physiotherapist, experienced in treating CFS/ME, separately examined each participant using the 5 physical signs. A physician experienced with CFS/ME also examined each participant using a standard clinical neurological and rheumatological examination whilst also observing general illness behaviour. The 3 practitioners received no information about symptoms, clinical history or prior diagnosis of participants. No conversation took place other than pertinent to the actual physical examination. Agreement on diagnosis between the osteopath and physiotherapist was analyzed using Cohen's Kappa (κ) and the accuracy of each practitioner compared with actual diagnosis was detected using McNemar's test, as well as calculating sensitivity and specificity.

Results. The osteopath and physiotherapist achieved a specificity of 0.86 and 0.83 and a sensitivity of 0.69 and 0.88, with overall accuracy of 77% and 86%, respectively, when using all 5 signs. This was compared with the physician's accuracy of 69%, which was highly affected by a sensitivity of only 0.44.
The accuracy of the osteopath and physiotherapist's diagnosis increased further to 81% and 88%, respectively, when using only signs of tender coeliac plexus and thoracic spine dysfunction. Also, agreement on overall diagnosis between the osteopath and physiotherapist increased from moderate when using 5 signs to substantial when using only 3 signs: thoracic spine dysfunction, coeliac plexus tenderness and chest tenderness $p < 0.001$.

Conclusion. This research provides highly significant evidence that novel physical signs improved the accuracy of screening for CFS/ME and so are effective as an aid to diagnosing the condition.

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Demographics of young people diagnosed with CFS in Victoria Australia

Background: The demographic characteristics of young people diagnosed and managed for Chronic Fatigue Syndrome (CFS) at the Royal Children's Hospital (RCH) are different from other hospital clientele. RCH is a secondary and tertiary referral centre for metropolitan Melbourne and the state of Victoria for a population of 5.8 million . Victoria is multicultural with 26% of citizens born overseas and an additional 30% have a parent born overseas. Hospital clinics reflect this demographic. 200 countries are represented and 260 languages spoken. More than 70 languages are spoken in the hospital.

Aim: To document the demographic features of the 1011 young people diagnosed at the Royal Children's Hospital Melbourne with CFS over a 20 year period.

Methods: The young people (age 6-18 years) had the diagnosis of CFS confirmed using the criteria of Holmes et al (1988) and Fukuda et al., (1994). The postcode, family background, parental occupation, recognized or diagnosed illness at onset, defined' (<1 month) or gradual onset (over several months), as well as investigations to exclude alternative conditions were documented.

Results: The M:F ratio was 1:3 and mean age of onset 14.6 years. The rural/urban mix was proportionate to the population however the ethnic mix was not representative of the population of the state nor of the clientele of the hospital. 80% had an Anglo-Celtic background (approximately 25% population), but predominantly Scottish/Irish descent, and another 11% northern European (Dutch, Scandinavian which is <0.5% population). No Middle Eastern or African patients were seen and 3 of 5 of Asian descent had Caucasian parentage as well. Socioeconomic status reflected the population.

Ninety percent reported a defined onset following an infection, most commonly EBV, but a variety of other infections were documented. Gradual onset was more commonly associated with orthostatic intolerance and hyperextensible joints. Occasionally CFS was associated with endocrine disorders (thyroid disease or diabetes), overtraining in athletes, or after neurological insult (1-2%). Depression and anxiety was reported at only marginally higher rate than the adolescent population.

Conclusion: This observation suggests a strong association between CFS developing following an infective process and ethnic origins in these young people.

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Lunch Panel

Special Interest Groups: International Research Networks
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European Network on Myalgic Encephalomyelitis/ Chronic Fatigue Syndrome (EUROMENE)"
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Background: Research on ME/CFS in Europe is characterised by the absence of a collaborative approach between research centres, while at the national level research and health services provision is usually concentrated in a few centres of competence.

Objectives; The main objective of the COST Action CA15111 "European Network on Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (EUROMENE)" is the establishment of a sustainable network of researchers in Europe working in diverse fields, to tackle the challenges arising from unknown aetiology, clinical variability, lack of diagnostic biomarkers, limited treatment options, and a high associated socio-economic burden. The initial task of the project is to harmonize the fragmented European research resources on ME/CFS by building a biobank platform with harmonized protocols and a bioinformatics repository.
The task objectives during the runtime of the Action are:
• Exchange of best practice for collecting population-based data on the prevalence and other epidemiological data of ME/CFS, to establish a synchronised European database;
• Promote co-operation among research groups for accessing potential ME/CFS biomarkers, by establishing special interest groups and harmonising infrastructure efforts;
• Determine unified ME/CFS case definition and diagnostic criteria for clinicians and researchers, to promote case finding, synchronisation of diagnostic criteria, prevention and treatment guidelines;
• Determine the social impact and assess economic consequences of ME/CFS.

Methods: The network will promote multidisciplinarity in ME/CFS research and foster of the full chain of translational research further capable to develop the much needed treatments and prevention strategies for improvement quality of life.
Results: 14 countries are participating in the network: Belarus, Belgium, Bulgaria, Denmark, France, Italy, Germany, Greece, Latvia, Norway, Rumania, Serbia, Spain, and the UK. Most of the involved groups have already developed long-term research on ME/CFS within their disciplines of interest, including epidemiology, biobanking, molecular biology, immunology, clinical research, diagnosis, treatment and research on social aspects in ME/CFS. The Action activities are organized in six working groups: on epidemiology; biomarkers; clinical research enablers and

diagnostic criteria; socio-economics; conferences, seminars, and training schools; dissemination and exploitation, patient involvement, and digitalisation.

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3. The authors have no conflicts of interest

The case for stratification in ME/CFS: Experience from the UK ME/CFS Biobank

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Background: ME/CFS is a heterogeneous multi-factorial disease with genetic and environmental contributions to its aetiology. The variability in clinical presentation and profile of biomarkers may reflect the predominance of different pathophysiological processes operating in different individuals and sub-groups. The treatment of cases as if they were part of a single homogeneous group has been a significant source of bias in research studies. Stratification of ME/CFS cases is essential to minimise errors, and for the better understanding of disease aetiology and pathophysiology; however, there is still no consensus on how sub-groups should be composed.
Objectives: To evaluate strategies of phenotyping and sub-grouping people with ME/CFS for research studies.
Methods: We use cases and controls who are part of the dataset created in support of the UK ME/CFS Biobank, to illustrate and compare sub-grouping options for recruitment and data analysis.
Results: A model for case stratification of ME/CFS is proposed, based on a multi-layered approach. Stratification initially based on clinical phenotyping has logistic advantages. It may take into account variables such as mode of onset and disease progress, clusters of symptoms, disease severity and others, with further incorporation of laboratory-based biomarkers, reflecting, for example, immune function, genetic susceptibility and expression, and evidence of infection. For that to be achieved successfully, we required standardisation of procedures for data and sample collection, sample processing and analysis, and precise case phenotyping
Conclusion: Stratification is essential to the further understanding of disease mechanisms operating in different sub-groups and improvement in diagnosis and treatment. The dataset used as part of the UK ME/CFS Biobank can be used as a model for standardised data collection for clinical phenotyping of PWME and comparison groups.

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Session 8: Research on Autonomic Functioning and Comorbidities

Session Chair: Peter Rowe, M.D., Johns Hopkins University School of Medicine

Postural Tachycardia in Chronic Fatigue Syndrome Induced by Exercise

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Background:
Chronic Fatigue Syndrome (CFS) and Gulf War Illness (GWI) have similar symptom profiles. Stress testing separated one third of the GWI group who developed postural tachycardia after exercise (START, Stress Test Activated Reversible Tachycardia; Δ heart rate [HR] >30). The remainder had no postural tachycardia (STOPP, Stress Test Originated Phantom Perception).[1] This suggests autonomic dysfunction in post exertional malaise.
Objectives:
Determine if CFS subjects develop postural tachycardia after exercise and the contributions of heart rate variability, sympathetic and parasympathetic dysfunction.
Methods:
HR, sympathetic (LFa, low frequency variability), and parasympathetic (RFa, respiration corrected high frequency variability) values were measured while recumbent (5 min) and standing (5 min). The incremental changes of ΔHR, ΔLFa, ΔRFa, ΔLFa/RFa were determined. Data were assessed for pre-exercise tests in 4 control & STOPP subjects, and 10 START subjects. 15 control & STOPP and 7 START subjects were assessed at 1h, 3h, and 24h after exercise.
Results:
This interim analysis showed 9/19 of the CFS participants met START criteria. Before exercise, there were no differences in HR, LFa, RFa, LFa/RFa, or the incremental changes (Δ) between the groups. After exercise, the control & STOPP group had equivalent ΔHR and ΔLFa. ΔRFa decreased significantly in both groups ($p < 0.05$ unpaired t-test). ΔLFa and ΔLFa/RFa increased significantly between recumbent and standing after exercise in the START group, but not the control & STOPP group ($p<0.05$ unpaired t-test).
Conclusion:
The significant increase in ΔLFa after exercise in the START group suggests their postural tachycardia was due to increased sympathetic activity. The observed postural tachycardia was dependent on exercise, which differentiates this finding from orthostatic intolerance identified by tilt table testing. Brain stem atrophy was reported in CFS and GWI START subgroups, which may contribute to this autonomic dysfunction.[2]

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Distribution of Dolorimetry in CFS, FM, GWI and Control Women

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Background: There is significant overlap of symptoms in CFS, FM, and GWI (Gulf War Illness). FM (fibromyalgia) may be distinguished by systemic hyperalgesia measured by tender point counts and dolorimetry. Hyperalgesia and tenderness are poorly described in GWI.

Objective: Determine the distribution of pressure-induced tenderness using dolorimetry in CFS, FM, GWI, and SC women. Determine if dolorimetry can discriminate between these groups.
Methods: CFS was defined using 1994 Fukuda criteria, FM by widespread pain and tender points (1990 ACR criteria), and GWI by Steele 2000 "Kansas" criteria. Dolorimetry was performed at 18 traditional tender points to measure the average pressure to cause pain. Two separate cohorts of women who participated in previous studies were examined. FM was not assessed in Cohort 2 because tender points were removed from the 2010 and 2011 ACR criteria.
Results: Cohort 1. FM (n=41) had a unimodal distribution and could be discriminated from SC (n=129) by a threshold of 4 kg (88% specificity, 94% sensitivity vs. controls). However, 32/41 FM met CFS criteria indicating significant symptomatic overlap. CFS women without FM (did not meet 1990 criteria) had a pain threshold of 6.5 kg (67% specificity and 66% sensitivity).
Cohort 2. As in Cohort 1, SC (n=308) had a wide distribution of pain thresholds (0.5 to 12.5 kg; mode 7 kg). CIF (n=83) had an equivalent distribution. CFS (n=125) had a narrower range of 1 to 7 kg. ROC analysis yielded a threshold of 6 kg to detect CFS (66% specificity, 63% sensitivity), while the 4 kg threshold gave specificity of 24% and sensitivity 88%. In contrast, GWI females (n=40) were very tender with a unimodal distribution and dolorimetry threshold of 4 kg (91% specificity and 88% sensitivity). GWI were distinct from CFS, SC and other groups.
Conclusions: There is considerable overlap between CFS and FM symptoms based on 2011 ACR criteria and because tender points and dolorimetry are no longer recommended for FM case designation. In contrast, GWI women can be positively identified by their history, symptoms that overlap with CFS and ME, and systemic hyperalgesia with the physical sign of tenderness to pressure.

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Truncal Ataxia is an Unrecognized Cause of Postural Intolerance in Patients with Myalgic Encephalomyelitis
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Objectives. Most patients with myalgic encephalomyelitis (ME) have orthostatic intolerance (OI) which is the primary factor restricting the daily functional capacity. OI is characterized by the inability to remain upright without severe signs and symptoms, such as hypotension, palpitation, pallor, fatigue and nausea. Most symptoms of OI have been surmised to be related to reduced cerebral blood flow and the compensatory sympathetic activation. Indeed, many patients have postural orthostatic tachycardia, orthostatic hypotension, neurally mediated hypotension and low cardiac output with a small left ventricle. With further progression of the disease, patients may have even sitting intolerance and finally become bedridden. Static balance is an essential element for the performance of postural stability. The possible role of disequilibrium in the genesis of both orthostatic and sitting intolerance was examined in the patients.
Methods. The study subjects comprising 35 patients with ME (8 men and 27 women, mean age: 36±10 years) underwent both the conventional 10-min standing and sitting tests separately and also neurological examinations including Romberg test.
Results. The patients were divided into 10 with a positive Romberg test (Group P) and 25 with a negative Romberg test (Group N). Postural sway was observed during the standing test in all (100%, $p<0.01$) of Group P in contrast to 5 (20%) of Group N. None of Group P was able to stand on one-leg or had normal tandem gait. All of Group P

complained of symptoms during both the standing and sitting tests in which many of them (40%) were not able to complete the 10-min standing, and some (20%) not even 10-min sitting. In contrast, all Group N patients were able to stand on one-leg and demonstrated smooth tandem gait. All of them were able to complete both tests. As compared with Group N (performance status scores: 3-6), Group P had significantly ($p<0.01$) higher performance status scores (5-8), suggesting severe restriction of the activities of daily living.
Conclusions: Patients with ME and a positive Romberg test complaints of not only OI but also sitting intolerance. Truncal ataxia or disequilibrium appears to play an important role in the genesis of the postural intolerance and can be considered a useful sign for advanced disease.

Session 9: Advances in Brain Research and Neurological Studies

Session Chair: Anthony L. Komaroff, M.D., *Professor of Medicine,* Harvard Medical School (retired)

Assessment of Neurobiological Dysfunction in Chronic Fatigue Syndrome

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BACKGROUND: Psychiatric disease comorbidity is common among many, but not all, patients with CFS. Identifying neurobiological dysfunction that can differentiate CFS with and without psychiatric symptoms could advance understanding of CFS.

OBJECTIVES: To derive measures of spinal fluid white cell count and protein levels, cerebral blood flow (CBF), brain ventricular lactate and cortical glutathione in CFS patients with and without current psychiatric diagnoses compared to healthy controls (HC).

METHODS: 44 consenting CFS and 17 HC subjects were enrolled in the study. Psychiatric diagnosis was established using the Structured Clinical Interview for DSM-4 (SCID); a battery of neuropsychological tests was also administered. Magnetic resonance imaging (MRI) techniques were used to measure CBF, ventricular lactate and cortical glutathione. Cell count and protein levels were determined in cerebrospinal fluid samples. P value for statistical significance was set at 0.05

RESULTS: None of the brain and CSF outcome measures differed between CFS patients with and without psychiatric diagnosis. On the other hand, CBF and glutathione were found to be significantly lower and ventricular lactate higher in the pooled sample of CFS patients compared to HC subjects, replicating our prior findings of these outcome measures. A similar group difference in spinal fluid was found with 9 of 35 patients having either high white cell count or elevated protein compared to none of 13 HC.

CONCLUSION: This study did not find differences in neurobiological abnormality between CFS patients with and without psychiatric diagnoses. However, significant differences in number of abnormal spinal fluids, ventricular lactate, cortical glutathione and CBF between the CFS and HC groups were found. Therefore, rather than focusing on psychiatric features, future efforts should instead focus on evaluating the objective brain and spinal fluid outcome measures that differed between HC and CFS as potential biomarkers of CFS.

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Disrupted Functional Connectivity in Gulf War Illness (GWI)
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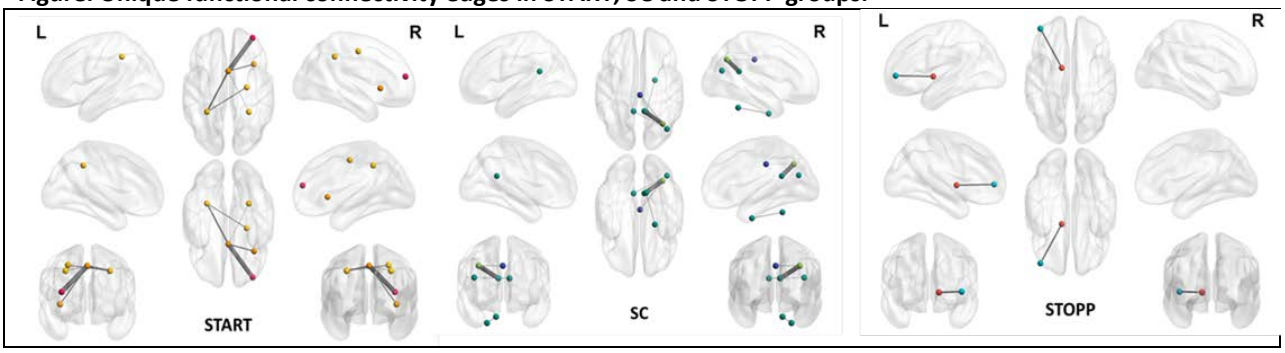
Background: Brain regions that are synchronously activated during a task can be considered nodes connected by edges. Functional connectivity describes the patterns of these links. Responses to exercise divided GWI subjects into START and STOPP phenotypes. START (Stress Test Activated Reversible Tachycardia) had brain stem atrophy (as seen in CFS), postural tachycardia following exercise, and disordered cortical activation during a cognitive task. STOPP (Stress Test Originated Phantom Perception) had increased activation of basal ganglia and anterior insula regions as cognitive compensation during a working memory task.
Objective: Assess functional connectivity in START, STOPP and sedentary controls (SC).
Methods: SC (n=8), START (n=10) and STOPP (n=18) subjects had blood oxygenation level dependent (BOLD) signals analyzed at rest and during a low cognitive load 0-back task (see a letter, push a button). Resting state signals were assessed by independent component analysis (ICA). 0-Back BOLD signals were assessed using cortical seed regions from the Shirer (2011) brain atlas. Pearson's correlation coefficients between activated regions (nodes) were z-transformed. Correlations (edges) that were significantly different from the null condition (FDR<0.02) and had Cohen's d>2.0 were identified.
Results: There were no significant differences between resting state ICA components. However, the 3 groups had distinctly different functional connectivity patterns during the 0-back task.
Figure. Unique functional connectivity edges in START, SC and STOPP groups.



START activated salience network nodes (dorsal anterior cingulate cortex, right anterior insula) that are required for intense cognitive activities, plus frontal eye fields of the dorsal attention network to maintain focus on the visual cues. This level of activation was anticipated for high cognitive load tasks and indicates significant cognitive disability in START. SC activated ventral and dorsal default mode network nodes that indicate multisensory integration and "mind wandering" during this simple task. STOPP had only an edge between the left basal ganglia and left frontal pole.
Conclusions: The simple 0-back task was sufficient to identify significant differences in brain function between SC and the GWI phenotypes. These patterns offer models for potential pathological differences that may discriminate between CFS phenotypes.

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Functional Neural Consequences of Post-Exertion Malaise in Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS)

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Background: Post exertion malaise (PEM) is one of the most debilitating aspects of ME/CFS, yet the neurobiological consequences are largely unexplored. **Objective:** To determine the neural consequences of acute exercise using functional brain imaging. **Methods:** Fifteen female ME/CFS patients (Fukuda et al. 1994 and Carruthers et al. 2003) and 15 healthy female Controls completed 30 minutes of submaximal exercise (70% of peak heart rate) on a cycle ergometer. Symptom assessments (e.g. fatigue, pain, mood) and brain imaging data were collected one week prior to and 24 hours following exercise. Functional brain images were obtained during performance of: 1) a fatiguing cognitive task – the Paced Serial Auditory Addition Task (PASAT), 2) a non-fatiguing cognitive task – simple number recognition, and 3) a non-fatiguing motor task – finger tapping. Symptom and exercise data were analyzed using independent samples t-tests. Cognitive performance (PASAT) data were analyzed using mixed-model analysis of variance with repeated measures. Brain responses to fatiguing and non-fatiguing tasks were analyzed using linear mixed effects with cluster-wise (101-voxels) alpha of 0.05. **Results:** ME/CFS patients reported large symptom changes compared to Controls (effect size ≥0.8, $p<0.05$). ME/CFS and Controls had similar physiological responses to exercise ($p>0.05$). However, ME/CFS patients exercised at significantly lower Watts and reported greater exertion and leg muscle pain ($p<0.05$). For cognitive performance (PASAT), a significant Group by Time interaction ($p<0.05$), demonstrated pre- to post-exercise improvements for Controls and worsening for ME/CFS. Brain responses to finger tapping did not differ between groups at either time point. During number recognition, Controls exhibited greater brain activity ($p<0.05$) in the posterior cingulate cortex, but only for the pre-exercise scan. For the PASAT, there was a significant Group by Time interaction ($p<0.05$) with ME/CFS patients exhibiting increased brain activity from pre- to post-exercise compared to Controls bilaterally for inferior and superior parietal and cingulate cortices. Changes in brain activity were significantly related to symptoms for ME/CFS patients ($p<0.05$). **Conclusions:** Acute exercise exacerbated symptoms, impaired cognitive performance and affected brain function in ME/CFS patients. These converging results, linking symptom exacerbation with brain function, illustrate some of the potential detrimental effects of PEM for ME/CFS patients.

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Abstracts
General Session
Sunday, October 30, 2016

Session 10: Symptom Provocation Studies II

Session Chair: Betsy Keller, Ph.D.

Department of Exercise and Sport Sciences, Ithaca College

Blood lactate increases more rapidly after a previous exercise challenge in patients with chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME) than in healthy subjects

Lien K, Johansen B, Veierød MB, Haslestad AS, Melsom MN, Kardel KR, Iversen PO

Background: Previous findings from repeated cardiopulmonary exercise testing (CPET) suggest that exercise on day 1 negatively influences peak oxygen uptake (peak VO_2) on day 2 in patients with CFS/ME. Accumulation of lactate denotes a transition to anaerobic glycolysis, a limiting factor on maximal performance.

Objectives: The main aim was to examine the effect of an exercise challenge on peak VO_2 and lactate accumulation in CFS/ME patients performing CPET on two consecutive days.

Methods: Eighteen female patients (18-50 years) fulfilling the Canadian Consensus Criteria and the International Consensus Criteria for CFS/ME and 15 controls (healthy, sedentary women; 18-50 years) performed two CPET 24 hours apart. We measured oxygen uptake and collected arterial blood samples for lactate analysis at baseline and every 30th second during the tests. Two-sample and paired t-tests and mixed model analysis for repeated measurements were applied.

Results: Lactate levels per work rate were higher in patients than in controls on both test days ($p_{interaction}<0.001$). Furthermore, lactate accumulation on test 2 occurred earlier in the patients, and later in healthy subjects, compared to their respective lactate accumulation on test 1 ($p_{interaction}<0.001$). At test 1, mean (SD) peak VO_2 (ml/kg/min) was lower in patients than in the controls (24.2 (4.9) vs. 36.6 (6.2), $p<0.001$). Mean difference in test-retest peak VO_2 was -1.4 (1.1) among the patients ($p<0.001$), whereas no change was found in the controls (-0.9 (1.8) $p=0.07$). However, the mean test-retest difference in peak VO_2 did not differ between the groups ($p=0.33$).

Conclusion: CFS/ME patients have a higher lactate level than heathy subjects at baseline and per work rate on both tests. In addition, the first exercise test seems to induce an earlier lactate accumulation in patients, when retested the next day. This is not the case in healthy subjects. Furthermore, this study confirms that CFS/ME patients have a decreased physical capacity compared to healthy subjects, but the change in peak VO_2 after repeated CPET did not discriminate between patients and healthy controls.

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Conflict of interest: None

Subsets of ME/CFS patient responses to a 2-day CPET

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Background: Studies to assess the efficacy of a two-day cardiopulmonary exercise test (2-d CPET) protocol to identify post-exertion malaise (PEM) in ME/CFS first revealed that ME/CFS patients often fail to reproduce peak VO2 (VO2peak) during test 2 due to PEM provoked with test 1. Subsequent research indicated that a subset of patients failed to reproduce VO2 at ventilatory/anaerobic threshold (VAT), but did reproduce VO2peak, suggesting that responses to exertion may distinguish subsets of patients. Identifying subsets of ME/CFS patient responses to exertion would enable us to further explore other potential correlates, such as metabolic markers or bacterial microbiome of the gut.

Objectives: To classify the responses of ME/CFS patients to a 2-d CPET protocol to determine if ME/CFS patients demonstrate subsets of responses in addition to failure to reproduce VO2peak or VO2@VAT.

Methods: Responses to a 2-d CPET protocol were evaluated for 94 ME/CFS patients. Patient responses were evaluated based on failure to reproduce VO2peak or VO2@VAT, as well as failure to respond normally with regard to autonomic parameters (heart rate, blood pressure), ventilatory parameters, as well as cases that reproduced CPETs within normal variation.

Results: Of 97 cases, 34% comprised a subset of responders that failed to reproduce VO2peak, and 39% failed to reproduce VO2@VAT within normal variation. Additionally, subsets were also described by autonomic anomalies (43%), ventilatory anomalies (47%), and normal reproduction of CPETs (29%). Membership in more than one subset by several cases explained the sum total of all subsets greater than 100%.

Conclusion: Assessment of PEM using the 2-d CPET protocol should consider abnormal responses to exertion that extend beyond VO2peak or VO2@VAT and consider disruption of autonomic and ventilatory responses as indicators of inappropriate recovery, or PEM, following exertion. Additionally, patients diagnosed with ME/CFS who reproduce the 2-day CPET within normal parameters may describe a unique subset that requires further study. Preliminary data will be discussed which indicates that this subset may correspond with other prognostic indicators.

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Conflicts of Interest: none

Neuromuscular Strain Increases Symptom Intensity in Chronic Fatigue Syndrome

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Background: Myalgic encephalomyelitis/ chronic fatigue syndrome (ME/CFS) symptoms can be provoked by increased physical or cognitive activity, and by orthostatic stress. In preliminary work, we have also noted that ME/CFS symptoms can be provoked by application of longitudinal neural and soft tissue strain to the limbs and spine of affected individuals (Rowe PC et al., *Front Physiol 2013;4:115; J Pediatr 2014;165:360-6*).

Objectives: To investigate the role of neuromuscular strain in ME/CFS symptom provocation.
Methods: Sixty individuals with ME/CFS and 20 healthy controls were randomly assigned to either a 15 minute period of a true neuromuscular strain (a passive supine straight leg raise ([SLR] to mid-way between the onset of stretch and end-range for each participant) or a sham strain (5 degrees of supported SLR). Participants reported scores on a 0-10 scale for individual symptoms (fatigue, body pain, concentration difficulties, lightheadedness, and headache) at baseline, during the maneuver, and at 24 hours post-maneuver. Individual scores were summed to create a combined symptom score. To compare changes in individual symptom intensity scores we performed a two-factor (CFS vs control and type of strain) regression analysis adjusting for their baseline values.
Results: There were no differences in age, sex, race, or education between CFS participants and controls. Of the 60 with CFS, 85% were female; the mean (SD) age was 36.9 (10.4) yrs. After exposure to the passive SLR, those with ME/CFS had significantly higher individual and combined symptom intensity changes during and 24 hours after the maneuver compared to the healthy controls. Compared to individuals with ME/CFS in the sham SLR group, those with ME/CFS who underwent the true SLR strain reported significantly increased pain and concentration difficulties as well as combined symptom scores during the maneuver (all $P<0.05$). After 24 hours, the symptom-intensity differences were significantly greater for the ME/CFS SLR strain group for the individual symptom of lightheadedness ($P=0.001$) and for the combined symptom score ($P=0.005$). During the 15 minute maneuver, more in the CFS strain group than the CFS sham group had at least a 2-point increase in symptom intensity for at least 1 symptom (84% vs. 61%; $P=0.04$), at least 2 symptoms (63% vs. 36%; $P=0.04$), or at least 3 symptoms (47% vs 14%; $P=0.01$).
Conclusion: We conclude that a longitudinal strain applied to the nerves and perineural soft tissues of the lower limb is capable of increasing symptom intensity in individuals with ME/CFS for up to 24 hours. These findings confirm preliminary observations that increased mechanical sensitivity is a contributor to the provocation of symptoms in this disorder. Our findings have practical implications for the understanding of why exercise and certain activities of daily life might be capable of provoking CFS symptoms. Further studies are warranted to better understand the prevalence, risk factors, and impact of neuromuscular strain in CFS, and the optimal methods to restore more normal function to those with the illness.

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Polar Metabolites Distinguish ME/CFS Patients and Controls

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Background: Advances in mass spectrometry allow identification of hundreds of metabolites in circulation and quantification of the status of metabolic networks. A broad screening approach allows non-user biased discovery and offers a new gateway into knowledge of the effects of ME/CFS on the metabolism of the body, a chance for future targeted screenings as a mean of diagnosis, and potentially some clues about the underlying causes of the illness.
Objectives: To determine whether a pilot cohort of female ME/CFS patients and controls, and a pair of monozygotic male twins, differ in amounts of polar plasma metabolite amounts, and whether any such differences could be used to classify subjects as patients vs. healthy individuals.

Methods: Plasma samples from pilot cohort of 17 female ME/CFS patients (diagnosed by an expert physician), 15 healthy female, age-matched controls, and a pair of monozygotic twins discordant for ME/CFS were extracted for polar metabolites. The two monozygotic twins performed a two-day cardiopulmonary exercise test (CPET) that revealed that the ill twin was unable to reproduce his ventilatory/anaerobic threshold following induction of post-exertional symptom exacerbation by the first CPET.

Results: We identified and quantified 361 metabolites from plasma samples using reverse-phase chromatographic separation coupled to a high-resolution Orbitrap mass spectrometer with label-free quantitation, for a total of 11,913 data points. At both $P<0.05$ and a false discovery rate of $Q<0.15$, we found that 29 metabolites were lower in ME/CFS patients and only 4 were higher. Levels of plasma metabolites in both twins were affected by exercise, but to different extents. A notable number of metabolites that differ between patients and controls are involved in energy metabolism. A machine-learning approach allowed us to separate patients from healthy individuals.

Conclusion: Plasma metabolites differed between ME/CFS patients and controls at baseline, and before and after exercise by a pair of identical twins discordant for ME/CFS. Further investigation of the effects of exercise on plasma metabolites is warranted. The data indicate that it may be possible to develop an ME/CFS diagnostic test from blood metabolites, provided that results are replicated in a larger cohort at baseline.

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Conflicts of Interest: none

Session 11: Genetics Research

Chair: Jose Montoya, M.D.

Professor of Medicine, Stanford University Medical Center

Single Nucleotide Polymorphisms in Myalgic Encephalomyelitis: Possible Genetic Factors Influencing Pathophysiology

Benjamin Eike[1], Franco Garcia[1], Joseph Palmer[1], Kelly Gaunt[1,2], Sultan Majid[1], Melanie Perez[2] Dr. Irma Rey, M.D.[1,2]

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Background:

Over the last ten years, the amount of direct to consumer genetic testing has increased tremendously. This creates an excellent opportunity for ME researchers to use this data to look for genetic differences between the ME population and healthy individuals.

Objectives:

This study aims to find single nucleotide polymorphisms that differentiate the ME population from healthy individuals using patient provided genetic data.

Methods:

SNP data was collected from patients who have been diagnosed with Myalgic Encephalomyelitis (N=53) at physician clinics in Miami and Fort Lauderdale, Florida. SNP testing was performed by either 23andme or AncestryDNA using the Illumina DNA microarray platform. A total of 203 SNPs were assessed, and the prevalence

of specific genotypes within the patient population were compared to genotype data available through the NIH "1000 Genome Project" (EUR subset N=503, Genome assembly GRCh38.p5).

Results:

Of the 203 SNP compared, 3 SNPs of interest were identified. Raw genotypic p-values and Cramer's V calculations were performed for each SNP, resulting in the following: ($p \leq 5.3x10^{-3}$, X^2= 10.49, df=2, V=0.1376) for rs1142530, ($p \leq 0.0257$, X^2= 7.32, df=2, V=0.1159) for rs2332496, and ($p \leq 0.01$, X^2= 9.21, df=2, V=0.1311) for rs7258846. Raw allelic p values and Cramer's V calculations were performed for each SNP resulting in the following values: ($p \leq 2.7x10^{-3}$, X^2= 9.02, df=1, V=0.0934) for rs1142530, ($p \leq 0.0115$, X^2= 6.38, df=1, V=0.0799) for rs2332496, and ($p \leq 7.0x10^{-3}$, X^2= 7.27, df=1, V=0.0863) for rs7258846. All three SNPs reside within the NDUFS7 gene, a gene that codes for a subunit of NADH Dehydrogenase. NADH Dehydrogenase is an important complex within the mitochondrial electron transport chain and takes part in the production of ATP in aerobic respiration. Of the three SNPs, one (rs1142530) results in a missense variant within the coding region. The remaining two (rs7258846 & rs2332496) result in a non-coding transcript exon variant and an intron variant respectively.

Conclusion:

Review of the genetic data resulted in the three SNP variants of interest. Though these SNPs did not meet the criteria for a genome wide association study (raw p< 1.0x10-5), future studies with larger sample sizes should be performed to verify their significance.

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2. Unfunded

3. No conflicts of interest

Using Gene Expression Modules to Identify Gender Specific Treatments in Myalgic Encephalomyelisits/Chronic Fatigue Syndrome

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Objectives: Myalgic Encephalomyelisits/Chronic Fatigue Syndrome (ME/CFS) is a debilitating multi-symptom illness impacting up to 1 million Americans, with greater than 60% of the affected being women. However, while systemic and neuro-inflammation are known to be present in this illness, the pathogenesis and etiology of this complex condition is unknown, limiting the prospective treatments. Another barrier to treatment is the low prevalence rate in conjunction with the high cost of developing novel drugs treatment, discouraging innovation towards ME/CFS

treatment and diagnosis. Establishing genomic links, or identifying differentially expressed genes can serve to inform and encourage researchers towards improved diagnosis and treatment. Here, the researchers investigate this link by investigating gene expression datasets of ME/CFS patients to find unique expression patterns in ME/CFS that are related to the immune and inflammatory processes. Inflammatory and immune responses are of most interest as ME/CFS onset has been associated with infectious agents, and ME/CFS may be maintained by overextended immune and proinflammatory response.

Methods: Using gene expression data from 35 subjects with ME/CFS (23 women; 12 men) defined by the Fukuda definition and 22 healthy demographically comparable controls (16 women; 6 men) the activation of specific gene modules is estimated from the differential expression of each module' s constituent genes via nonparametric statistics. Gene modules are pre-defined based on cellular function and interactions as defined in the human protein-protein interaction network. Pathway annotation of differentially expressed gene modules was performed via over-representation analysis using the Consensus Pathway Database. Identified gene modules were then cross-referenced with drug atlas and pharmacogenomic databases to identify agents currently used successfully for treatment in other diseases.

Results: For both women and men preliminary results indicate that the top 1% of modules identified contain a greater than average reference to immune dysregulation accompanied by reference to the JAK-STAT pathway, hormone regulation and mitochondrial dysfunction (women: $p < .05$, FDR = .10, d = .46; men: $p > .05$, FDR = 0.10, d = .07).

Conclusions: Identification of these gene modules and relevant pathways associated with immune and inflammatory biology can lead to the identification of immune modulating based treatments strategies. Of the associated drugs identified, immunosuppressants, and hormone-based therapies were identified as potential candidates for treating ME/CFS symptoms.

Funding: Funding came from the US Department of Defense Congressionally Directed Medical Research Program (CDMRP) awards (http://cdmrp.army.mil/) GW093042 (Broderick - PI), the National Institutes of Health (NIH) (http://www.nih.gov) R01 award RES0008852 (Klimas - PI), and R01 award NS090200-01 (Fletcher - PI), as well as the U.S. Department of Veterans Affairs (Merit Award, N. Klimas, PI). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Epigenetic modifications and Glucocorticoid Sensitivity in Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS)

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Background: Differences in immune function have been reported in ME/CFS patients, including sensitivity to glucocorticoids. Several previous studies, including by our group, have indicated that epigenetic modifications to DNA (termed the 'DNA methylome') are associated with longterm changes in the function of endocrine systems that regulate the response to glucocorticoids. We previously published a DNA methylome study in a cohort of sudden onset ME/CFS patients, suggesting a potential role of epigenetic modifications in ME/CFS.

Objectives: To examine the DNA methylome in immune cells in ME/CFS, determine its association with the cellular response to glucocorticoids, and its interaction with clinical symptoms.

Methods: For this study, we obtained peripheral blood mononuclear cells (PBMCs) from 49 ME/CFS and 26 healthy females who did not consume medications with known immunological or epigenetic effects. Self-reported quality of life health scores were collected using the RAND-36 inventory. PBMCs were stimulated with phytohaemagglutinin, a T-cell mitogen, and cell proliferation was suppressed with dexamethasone, a synthetic glucocorticoid, to test glucocorticoid sensitivity. DNA was extracted and the DNA methylome examined using the Illumina HumanMethylation450 BeadChip array, corrected for batch, age, BMI, and cellular admixture. Differentially methylated loci with ≥ 5% mean difference were identified with a statistical cutoff $p \leq 0.05$ and explored with DNA pyrosequencing and permutation analysis.

Results: We observed 12,608 significant differentially methylated loci across the methylome. There was an increased mean sensitivity to dexamethasone in ME/CFS; however, two response subgroups emerged across ME/CFS patients. We identified 13 differentially methylated loci potentially related to glucocorticoid sensitivity, and found significant relationships between methylation, glucocorticoid sensitivity, and clinical symptoms associated with ME/CFS.

Conclusion: The results indicate that epigenetic modifications are a feature of ME/CFS, and suggest a potential role for epigenetic modifications in disease manifestation and glucocorticoid hypersensitivity in some ME/CFS patients. The different glucocorticoid response subgroups within the ME/CFS cohort highlight the need for subtyping in future studies. The differentially methylated loci could direct future ME/CFS research for potential clinical biomarkers to improve diagnosis, clinical subtyping, and our understanding of the biological basis of ME/CFS.

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The authors have no conflicts of interest to declare.

ME/CFS miRNA analysis, mRNA in-situ hybridization and STAT1 localization upon stress trigger.

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Objectives: Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) is a debilitating disorder that affects 42/10,000 people in the US. CFS/ME can't be attributed to a single cause and is often reported to occur after an infectious episode, indicating that viruses or a combination of pathogenic factors plus environment and genetic predisposition may interact to allow progression of the disease. Symptoms of CFS/ME coincide with characteristic reactivation of pathogenic viruses, as seen with Epstein-Barr virus. In recent years it has been shown that EBV encodes microRNAs (miRNAs), which negatively regulate gene expression through binding target mRNAs. Decreased levels of viral miRNA are indicative of viral reactivation/replication and also decreased cellular antiviral pathway activation. STAT1 pathway is at the first line of defense against viral infections and many viruses evade this signal transduction mechanism. ME/CFS patients show symptoms of viral reactivation upon stress trigger. Here we use stress triggers in vivo (exercise) and in vitro (DEX) in order to further study cellular mechanisms of ME/CFS.

Methods: Micro-RNA analysis: CFS/ME symptoms are triggered by physical exercise. PBMCs of 21 (13M and 8F) CFS/ME patients were collected before exercise challenge (t0), at peak effort (VO_2 max) (t1) and after 4 hours of rest (t2) following exercise and compared with carefully matched PBMCs of 23 (16M and 7F) HCs. Total RNA was isolated from all samples and analyzed by NanoString Technologies' nCounter system. In situ hybridization of mRNAs and IM: Approximately 5 M Cryopreserved PBMCs for each sample were thawed and grown on sectioned T/C cover slips using RMPI 1640 media supplemented with FBS, OKT3, IL-2 and antibiotics. Cells were stressed in vitro with DEX, then incubated for 4 h. In situ hybridization of total mRNA and IM of STAT1 followed. Samples are examined on a Zeiss LSM 880 confocal microscope.

Results: Micro-RNA analysis: We evaluated viral microRNAs at the respective time points (t0, t1 and t2). We found that analysis of one specific EBV miRNA, ebv-miR-BART21, calculated regardless of collection time or patient gender, shows that ME/CFS patients had an average fold change of -2.03, indicating that these cells express about half of the viral miRNA levels observed in healthy controls. In situ hybridization of mRNAs and IM: Preliminary results show that PBMCs from ME/CFS patients are smaller and have less cytoplasm volume than HCs. ME/CFS show higher levels of localized total mRNA. ME/CFS nuclei do not exhibit a classic plump shape observed in HCs. Instead, they are wrinkled, puckered and show and show large nucleoli. Expected translocation of STAT1 protein is observed upon DEX treatment in HCs, however, in ME/CFS, STAT1 gets accumulated at nucleoli centers.

Conclusion: Our preliminary NanoString studies suggest that CFS patients might express higher levels of EBV proteins, and are therefore more prone to viral reactivation from latency. Abnormal nuclear morphology of ME/CFS resembles accelerated aging disease. Nucleoli sequestering of STAT1 is indicative of viral reactivation. Further elucidation of such differential cellular/systemic responses using PBMCs will not only contribute to a possible identification and isolation of involved viruses, but also help to elucidate complex pathogenic viral mechanisms involving pathogen/host interactions. Furthermore, it will reveal key strategies for drug reassignment and therapeutic intervention.

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Genomics of Chronic Fatigue Syndrome Reveals Systemic Inflammatory Response

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Background: CFS patients often suffer of symptoms highly suggested of an inflammatory illness. Immune studies involving high throughput technology including gene expression studies are likely to elucidate the inflammatory nature of the disease. Understanding the biologic basis of disease in Chronic Fatigue Syndrome will be instrumental in development of future diagnostics and therapeutic.

Objectives: To determine whether a gene expression study could elucidate the nature of CFS

Methods: In this work, we conducted an age- and sex-matched case-control study with 200 CFS cases and 400 healthy controls. Each individual was phenotyped with multidimensional fatigue inventory (MFI-20). RNA was isolated from whole blood and subsequently analyzed using the Illumina HT-12 v4 BeadChip array.

Results: The results of gene expression analysis demonstrated a signature of gene expression changes very similar to that found in diseases such as systemic inflammatory response. Several of the expressed genes correlated with the severity of the illness.

Conclusion: This study is one of the largest gene expression studies conducted on CFS patients and provides support for an inflammatory- or immune-mediated basis of disease.

Session 12: Panel Discussion

"Nothing about us without us:" How community-engaged research can accelerate progress in the field of ME/CFS

Moderator: **Lily Chu, M.D., MSHS,** Co-Vice President, IACFS/ME; Collaborator, Stanford ME/CFS Initiative

Speaker: William Elwood, Ph.D., Expert, community-engaged research, US National Institutes of Health (NIH) Member, Trans-NIH Working Group for ME/CFS

Panelists
Jin-Mann Lin, Ph.D., Senior statistician/epidemiologist, US Centers for Disease Control and Prevention
Leonard Jason, Ph.D., Professor of community psychology, DePaul University (Chicago, Illinois)
Sonya Chowdhury, Chief Executive, Action for M.E.; Member, United Kingdom ME/CFS Research Collaborative
Jennifer Spotila, J.D., www.occupyme.net, former chairman of Solve ME/CFS Initiative

Session 13: Medical Education Proposals for ME/CFS

Panel Chair: Susan Levine, M.D., Visiting Fellow, Cornell University, Ithaca, NY

Fellowship program for CFS/ME research (I)
Mady Hornig, M.D., Columbia University Medical Center

Background: Only 6-20% of medical schools provide training on ME/CFS. Because care remains centralized in a handful of expert clinicians' private offices, exposure to ME/CFS is limited in traditional post-graduate training programs.

Purpose: Given estimates of up to 2,500,000 ME/CFS cases in the US, there is a critical need to improve awareness of accepted clinical criteria and the growing literature on biomarkers.

Proposal: Here we focus on a method that exposes fellows (post-graduate; mid-career) to an introductory research experience which focuses on epidemiological study design and biomarker identification in ME/CFS. All trainees will undergo a mentorship that leverages phenotypic and biomarker data from existing clinical and laboratory databases along with medical ethics training. A more extensive research experience will also be available.

Conclusion: This fellowship program will develop a new cohort of clinicians and clinician-scientists that is knowledgeable about the range of clinical and laboratory findings found in complex immune-mediated disorders such as ME/CFS.

A fellowship training program for ME/CFS (II)
Anthony Komaroff, M.D., Harvard Medical School (retired)

Fellowship opportunity in ME/CFS (III)
Daniel Peterson, M.D., Simmaron Research

Poster Presentation Abstracts

Poster 1

Application of lipidomics for identifying novel blood biomarkers of Gulf War Illness

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Background: Gulf War Illness (GWI) affects nearly 25% of the 700,000 veterans from the 1991 Gulf War (GW) and presents with a cluster of symptoms that include memory impairment, motor problems, fatigue and gastrointestinal problems. Due to the complexity of the clinical presentation and limited understanding of the pathophysiology of GWI, this illness remains difficult to diagnose. Furthermore, the current GWI diagnostic procedures rely heavily on self-reporting of exposures and symptoms.

Objective: The goal of this study is to apply lipidomics technology in order to identify novel blood biomarkers that can provide an objective diagnosis of GWI.

Methods: Plasma from age and gender matched veterans with GWI (n = 22) and GW era controls (n = 14) were used for these studies. Mitochondrial lipids, acylcarnitines, were analyzed using reverse phase liquid chromatography/mass spectrometry (LC/MS) with a high accuracy mass spectrometer. Plasma phospholipids (PL) were analyzed with normal phase LC/MS method. Total fatty acids using gas chromatography/mass spectrometry method.

Results: Our findings suggest that compared to control GW veterans, those with GWI have elevated levels of ether phosphatidylcholine (PC) and total lyso-PC (LPC) ($p < 0.05$). Several individual PL species that contained omega-3 and omega-6 fatty acids were also increased in veterans with GWI compared to controls ($p < 0.05$). While odd-chain acylcarnitine species were increased, long-chain and very long-chain acylcarnitine species were decreased in GWI compared to controls. Omega-3 and omega-6 fatty acids were differentially modulated in veterans with GWI compared to controls and a confounding affect of age on this relationship was also observed.

Conclusion: Our findings suggest that an evaluation of blood omega-3 and omega-6 lipids and mitochondria specific lipids may lead to the development of biomarkers for assisting clinicians with diagnosing GWI. Changes in these lipids could be due to the observed aberrant activation of the immune/inflammatory pathways and potential failure of mitochondria function, which warrant further investigation.

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Poster 2

Heart Rate Variability is associated with age and symptoms in Chronic Fatigue Syndrome/Myalgic Encephalomyelitis: A population-based cohort study

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BACKGROUND: The precise nature and extent of the involvement of the ANS in CFS/ME is yet to be determined. However, there is increasing evidence of autonomic dysfunction in a subset of CFS/ME patients. HRV analysis can be used to assess dysautonomia in CFS/ME, specifically in relation to sympathovagal imbalance.
OBJECTIVE: To examine dysautonomia using HRV analysis in a Spanish CFS/ME cohort.
PATIENTS & METHODS: Forty-five female CFS/ME subjects and 25 age- and sex-matched healthy controls underwent a 5-min HRV test at rest in the supine position (*FitLab®, www.healthsportlab.com*). The intervals between consecutive heartbeats (R-R) were continuously monitored over three 5-min periods. R-R intervals were analyzed by the time domain and vagal activity and sympathetic modulation by the frequency domain. All CFS/ME patients met the 1994 CDC/Fukuda case definition. Clinical data were collected from all participants through patient-reported outcome questionnaires including the Fatigue Impact Scale (FIS-40), the abbreviated Composite Autonomic Symptom Score (COMPASS-31), the Pittsburgh Sleep Quality Index (PSQI) and the Hospital Anxiety and Depression Scale (HADS).
RESULTS: As expected, CFS/ME patients had higher FIS-40, COMPASS-31, PSQI and HADS scores than healthy controls (all $p< 0.001$). CFS/ME subjects showed decreased R-R intervals. Measures of HRV in the time domain, standard deviation of R-R intervals (SDNN) and the root mean square successive differences (RMSSD) were significantly lower in CFS/ME than in healthy controls (all $p< 0.005$). Measures of HRV in the frequency domain and both low frequency (LF) and high frequency (HF) spectral powers were also significantly lower in CFS/ME subjects (all $p< 0.0001$). The data were also analyzed taking age as a covariate (ANCOVA). Age was significant in the analysis of SDNN, RMSSD, LF and HF, but it was not in the patient-reported symptom scores. All the significant differences between both groups remained significant in the ANCOVA analysis ($p< 0.001$). Moreover, statistically significant correlations between symptom outcomes and HRV analysis were also detected.
CONCLUSION: These findings indicate reduced cardiac vagal activity, and variations in age and symptoms, in at least a CFS/ME subset. Diminished HF reflects primarily parasympathetic influences and may indicate decreased HRV indices in this population. Thus, the autonomic response as assessed by HRV could serve both as a potential biomarker and as a surrogate endpoint in intervention studies for CFS/ME.

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Poster 3

Complete treatment using desmopressin of suspected central diabetes insipidus, postural orthostatic tachycardia, and/or Myalgic Encephalomyelitis/Chronic Fatigue Syndrome following a series of adverse immune events

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Background: Cases of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) and postural orthostatic tachycardia syndrome (POTS) can have varying etiologies, clinical presentations, and prognoses. While symptom management can lead to improvement, full recovery of pre-illness function is not common. Therefore, it is important to note subgroups of ME/CFS and POTS patients that do recover fully. Here we report a patient meeting ME/CFS and POTS criteria, plus symptoms of central diabetes insipidus (polydipsia and polyuria), who recovered completely after long-term oral desmopressin therapy. Her severe symptoms had developed suddenly following a series of possible viral infections.

Objectives: To present an example of full recovery of severe POTS and ME/CFS in a case characterized by central diabetes insipidus symptoms and a marked response to desmopressin treatment.

Treatment Methods: A trial of oral desmopressin (0.1-0.2 mg twice a day) was started two months after the onset of severe symptoms. Pacing of activity and management of sleep, pain, and anxiety were also included in the plan of treatment.

Results: The patient responded immediately and markedly to desmopressin, able to tolerate moderate paced exercise with an increased dose. Within a year of starting desmopressin, she recovered to almost 100% normal function. Over the course of another year, she tapered off desmopressin completely by decreasing the dose every three months. Since then, she has fully recovered pre-illness health and has no symptoms of POTS. She continues to take medication for sleep.

Conclusion: This case demonstrates the importance of identifying treatable hypothalamic dysfunction, such as central diabetes insipidus, that may be obscured by a severe symptom load meeting POTS and ME/CFS criteria in some patient subpopulations. Use of long-term oral desmopressin therapy, while still in need of large randomized controlled trial, could significantly restore health, function, and quality of life in such POTS cases. Early intervention may also be key.

Poster 4

Immunomodulatory effects of Low Dose Naltrexone (LDN) in patients with Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS)

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Background
Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) is a debilitating condition associated with immune activation with increased activated T cells, impaired NK cell cytotoxicity, and elevated circulating inflammatory cytokines. Low Dose Naltrexone **(**LDN) is currently used off-label to treat ME/CFS; LDN may reduce inflammatory markers, suggesting a possible mechanism of action.
Objective
To evaluate the immunomodulatory effects of LDN in patients with ME/CFS.
Methods
A retrospective chart review was performed at the Institute for Neuro Immune Medicine. Subjects were 18 years or older with a diagnosis of ME/CFS (Fukuda criteria, 1994). Patients who received LDN for at least 6 months were considered cases. Those who did not receive the medication were considered controls. We recorded

demographics, quality of life, pain levels, NK cell number and cytotoxic activity, T cell activation and cytokine panel, and EBV and HHV-6 viral titers before and after 6 months of LDN treatment. For controls these values were taken from initial visits and 6 months later. Statistical analysis included descriptive statistics and paired t tests.

Results

A total of 845 charts were reviewed from which 53 cases and 58 controls met inclusion criteria.
There was no statistical difference in the baseline cytokine levels and NK cell activity percentiles. After 6 months of LDN therapy, there was no significant difference in the levels of cytokines. However, we found the pro-inflammatory cytokines TNFα, TNFβ, IL1α, and IL17 decreased. After 6 months of LDN therapy, there was no significant difference in the levels of
NK cell activity percentiles. The most common side effect was sleep cycle alteration (58%).

Conclusion

Although the changes were not significant, our results demonstrate pro-inflammatory cytokines decreasing towards normal levels after 6 months of LDN treatment. We recognize that the results could have been affected by the concomitant use of other medications and small sample size. These results warrant a future prospective study of the use of LDN in ME/CFS patients to further investigate its immunomodulatory effects. This future study would remove confounding variables and could potentially lead to FDA approval of the use of LDN in ME/CFS.

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Poster 5

GROUP-BASED STRESS MANAGEMENT IN CHRONIC FATIGUE SYNDROME: COMPARING DIFFERENT DELIVERY VENUE EFFECTS ON STRESS, MOOD AND SYMPTOMS

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BACKGROUND. Our model of Chronic Fatigue Syndrome (CFS) holds that stress relates to physiological dysregulation and CFS symptom exacerbation. Cognitive behavioral stress management (CBSM) may offer benefit, yet CFS patients face practical barriers to receiving treatment, which may be reduced by technology-assisted delivery.
OBJECTIVES. We conducted 3 randomized controlled trials of approximately 3 months of weekly in-person (IP) group CBSM vs controls (trial 1), telephone-based group CBSM (T-CBSM) vs telephone health education controls (T-HE) (trial 2), and remote videophone/tablet-delivered CBSM (R-CBSM) vs remote health education controls (R-HE) (trial 3).
METHODS. We compare their relative ability to reduce stress (Perceived Stress Scale), distress (POMS) and fatigue symptoms in persons with CFS.
RESULTS. IP-CBSM significantly reduced in stress and symptoms over a 5-months follow-up (p's < .05) vs controls. While T- CBSM offered some benefits, direct comparisons revealed that IP-CBSM groups were more powerful (p's < .05). Trial 3 examined the effect of R-CBSM for vs R-HE. Preliminary analyses indicate that R-CBSM reduces fatigue over a 5-month follow-up vs no change in R-HE (p < .05). Non-inferiority analyses show patients assigned to either R-CBSM or IP-CBSM showed significant 5-month reductions in perceived stress, total mood disturbance, and fatigue (all *p*'s < .05), with no group x time effects for perceived stress, mood, or fatigue. **CONCLUSIONS**. Based on its equivalence to IP-CBSM, a videophone/tablet-delivered CBSM may strike a balance between the intensity of in-person sessions with the convenience of home delivery in the context of partner support.

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Poster 6

A Cross Sectional Study of the UK Myalgic Encephalomyelitis / Chronic Fatigue Syndrome and Multiple Sclerosis Biobank Cohort

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Background

The lack of well characterised, population based, longitudinal studies in Myalgic Encephalomyelitis / Chronic Fatigue Syndrome (ME/CFS) has been officially recognized in the UK, by the Medical Research Council. The UK ME/CFS Biobank was established as a disease-specific blood and clinical data repository of well characterized cases and controls, as an open resource for researchers world-wide.

Objectives

To describe and compare the prevalence of clinical features including patient demographics, symptoms, disease onset, and standardized clinical examination findings among the UK ME/CFS Biobank participants enrolled between September 2011 and April 2016.

Methods

Biobank participants recorded clinical data using standardized instruments and study-specific questionnaires, provided blood samples for biobank storage, and were assessed by a clinical researcher. Prevalence of clinical features and socio-demographic variables were compared between ME/CFS cases and control groups. The student's t-test or the non-parametric Wilcoxon-Mann-Whitney test were used for continuous variables. Categorical variables were compared using the chi-square and fisher's exact test.

Results

This cross sectional study examined 384 participants; 229 with ME/CFS, 47 with Multiple Sclerosis (MS), and 108 healthy participants, at the baseline time point. The average ME/CFS participant is female (77%), 42 years old, developed ME/CFS at age 30, has experienced symptoms for 12.6 years and meets CCC or CDC94 Criteria (100%). Onset is attributed to a variety of triggers, the majority of which are infectious (62.9%), the most common specified infection being glandular fever (n=38). ME/CFS participants on average experience greater levels of disability on all 8 component scores of the Short Form - 36v2^{TM}, a standardized survey measuring disability, when compared to MS participants and Healthy Controls ($p<0.05$).

Conclusion

The UK ME/CFS Biobank contains clinical data and blood derivatives for greater than 229 ME/CFS, 47 MS and 108 healthy participants, available as an open resource to researchers worldwide. On average, measures of fatigue and disease severity and disability are more severe in ME/CFS participants compared to MS and Healthy participants.

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3. The authors do not have any conflicts of interest.

Poster 7

Treatment of Postural Orthostatic Tachycardia Syndrome and Management of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome following West Nile Virus Infection

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Background: Postural orthostatic tachycardia syndrome (POTS) and myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) have been associated with a variety of viral triggers, but to the best of our knowledge, cases following West Nile virus infection are not yet reported in the literature. Here we present a case meeting criteria for POTS, ME/CFS (SEID) (2015 IOM case definition), and fibromyalgia, in which debilitating symptoms began with an acute viral illness with suspected encephalitis and repeat positive serum West Nile virus IgG.

Objectives: To present a case suggesting West Nile virus as another possible trigger of POTS and ME/CFS, and to highlight the importance of POTS treatment.

Treatment Methods: Multiple interventions were integrated in the patient's care, particularly targeting POTS symptoms. Behavioral interventions included compression clothing and increased fluid and sodium intake. Pharmaceutical interventions included desmopressin, midodrine, fludrocortisone, and propranolol.

Results: With pharmaceutical and behavioral interventions, the patient's POTS symptoms were significantly diminished, widespread pain was eliminated, and fitness and function were improved. In particular, compression clothing and desmopressin contributed significantly to his improvement. He continues to manage ME/CFS symptoms including fatigue, cognitive impairment, disordered sleep, and exercise intolerance, although long-lasting post-exertional malaise is less frequent and severe.

Conclusions: This case report highlights the importance of thorough medical history and examination. In particular, the evaluation and treatment for POTS in presentations of chronic fatigue can make a significant impact on patients' health. This case also contributes to the list of possible viral triggers of POTS and ME/CFS, as well as the possible enduring consequences of acute flavivirus infection. These findings are important from a public health

standpoint, since WNV has become the most common arboviral infection in the US, resulting in millions of clinical cases and establishment of cyclic outbreaks.

Poster 8

Population-Based CFS Prevalences Using Different Criteria and the *Styles* Questionnaire: The Oxford criteria grossly overestimate CFS/ME prevalence

James N. Baraniuk

Background: Progress in CFS/ME is hindered by differences in symptom severity between Oxford,[1] CDC,[2] Carruthers' Canadian Myalgia Encephalomyelitis (ME),[3] and other diagnostic criteria. The CFS Symptom Severity questionnaire (CFSQ) [4] that assesses Fukuda criteria [2] was included in the 2004 *Health Styles* survey.[5] Results are valid for the general U.S. population.
Objective: Compare diagnostic criteria based on severity scores from the *Styles* questionnaire.
Methods: Fatigue and 8 ancillary criteria were graded as none (score=0), trivial (1), mild (2), moderate (3) or severe (4).[4] Proxy scores were developed to estimate prevalences for published criteria. CDC criteria were compared using mild and moderate severity levels.[2] CFSQ fatigue and sum of 8 ancillary symptom severities charted the distributions of CFS, CFS Like With Insufficient Fatigue Syndrome (CFSLWIFS), Chronic Idiopathic Fatigue (CIF) and controls.[4] Fibromyalgia (FM 2011 criteria) [6] and exclusions (arthritis, high exercise) were assessed.[7,8] These proxies provided upper limits because physical examination, autonomic dysfunction, and other characteristics were not assessed. Data for 1,511 females were evaluated.
Results: CFS prevalences were 20.2% for Oxford, 9.7% Oxford with usual exclusions, 4.7% CDC using mild severities, 4.3% FM (2011), 3.3% CFSQ, 1.9% CDC with moderate severities, and 0.53% for ME. Frequencies of CFS, CFSLWIFS, CIF and controls were estimated.

Table. **Population-based prevalences for each criteria**.

Criteria	CFS	CFSLWIFS	CIF	HC	Standard CFS exclusions	N
Oxford	15.1% (46)	22.0% (67)	14.1% (43)	25.6% (78)	23.3% (71)	305
Oxford with exclusions	31.5% (46)	23.3% (34)	17.1% (25)	28.1% (41)	0% (0)	146
CDC mild severity	67.6% (48)	0% (0)	32.4% (23)	0% (0)	0% (0)	71
FM 2011	16.9% (11)	18.5% (12)	0% (0)	0% (0)	64.6% (0)	65
CDC moderate	89.3% (25)	0% (0)	10.7% (3)	0% (0)	0% (0)	28
ME	75.0% (6)	0% (0)	25.0% (2)	0% (0)	0% (0)	8

Conclusions: The Oxford criteria grossly overestimate CFS/ME prevalence and include unacceptable numbers of CFSLWIFS, CIF and control subjects. Study outcomes and treatment recommendations based on Oxford criteria cannot be generalized to CFS or ME. FM (2011) and CFS criteria overlap significantly.

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Poster 9

RNA-Seq Analysis of Gene Expression, Viral Pathogen, and B-cell/ T-cell Receptor Signatures in Complex Chronic Disease

Background. Chronic fatigue syndrome (CFS) remains poorly understood. Although infections have been speculated to trigger the syndrome, a specific infectious agent and underlying pathophysiological mechanism remain elusive. In a previous study, we described similar clinical phenotypes in both CFS patients and alternatively diagnosed chronic Lyme syndrome (ADCLS) patients – individuals diagnosed with Lyme disease by testing from private Lyme specialty laboratories but who test negative by US Centers for Disease Control and Prevention (CDC) 2-tiered serologic analysis.
Methods. Here we performed blinded RNA-seq analysis of whole blood collected from 25 adults diagnosed with CFS and 13 ADCLS patients, comparing these cases to 25 matched controls and 11 patients with well-controlled systemic lupus erythematosus (SLE). Samples were collected at subject enrollment and not during acute symptom flares. RNA-seq data were used to study host gene expression, B-cell/T-cell receptor profiles (BCR/TCR), and potential viral infections.
Results. No differentially expressed genes (DEGs) were found to be significant when comparing CFS or ADCLS cases to controls. Forty-two DEGs were found when comparing SLE cases to controls, consistent with activation of interferon signaling pathways associated with SLE disease. BCR/TCR repertoire analysis did not show significant differences between CFS and controls, or ADCLS and controls. Finally, viral sequences corresponding to anelloviruses, human pegivirus 1, herpesviruses, and papillomaviruses were detected in RNA-seq data, but proportions were similar (p=0.73) across all genus-level taxonomic categories.
Conclusions. Our observations do not support a theory of transcriptionally-mediated immune cell dysregulation in CFS and ADCLS, at least outside of periods of acute symptom flares.

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Poster 10

The prevalence of, and risk factors for severe neurocognitive symptoms in ME/CFS and MS

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Background: There are remarkable phenomenological and neuroimmune overlaps between both myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) and Multiple Sclerosis (MS). In both conditions, patients experience fatigue and cognitive dysfunction. Biochemical pathways have been implicated in the development of neurocognitive symptoms but little is known about differing risk factors or exposures, which may lead to severe neurocognitive symptoms.

Objectives: This study aims to gauge the extent of neurocognitive symptoms in both ME/CFS and MS patients (participating in the UK ME/CFS Biobank) and identify those at most risk of severe symptoms.

Methods: This was a cross-sectional study with 395 participants; 237 diagnosed with ME/CFS (according to either CDC-1994 or Canadian Consensus Criteria), 47 with MS and 111 healthy controls. Data were collected from participants via standardized written questionnaire at clinical visits. Neurocognitive symptoms included problems with short-term memory, attention, executive function, and sleep. ME/CFS and MS patients reported symptoms based on an ordinal severity scale. Multivariable logistic regression was carried out in the ME/CFS group to investigate socio-demographic factors associated with severe neurocognitive symptoms.

Results: All neurocognitive symptoms were most prevalent in the ME/CFS group, with trouble concentrating the most commonly reported symptom at 98.3%. Severe symptoms were also more commonly reported in the ME/CFS group, with 55% reporting severe unrefreshing sleep. Similarly, in the MS group the most commonly reported severe symptoms were sleep related. Logistic regression analysis revealed that ME/CFS patients aged over 50 were more than three times more likely to experience severe neurocognitive symptoms, compared with those less than 30 years (p=0.031). Current smoking increased the risk of severe neurocognitive symptoms by approximately three times (p=0.0030) and household incomes of less than £15,000 per year were at a 33% increased risk of experiencing severe symptoms compared to those earning more than this (p=0.017).

Conclusions: Neurocognitive symptoms are extremely common in ME/CFS patients, compared with both healthy controls and MS patients. Unrefreshing sleep was the most commonly reported severe symptom in both ME/CFS and MS groups, although was more prevalent in those with ME/CFS. In ME/CFS patients risk factors for severe neurocognitive symptoms were age (>50), smoking and low income.

No Conflicts of interest

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Poster 11

Avoiding the Crash: Designing Immunotherapies to Normalize Recovery from Exercise in ME/CFS

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Background. Post-exertional malaise (PEM) is a defining symptom of Myalgic Encephalomyelitis/ Chronic Fatigue Syndrome (ME/CFS) and consists of debilitating fatigue following even moderate exertion. The expression of inflammatory cytokines has been broadly linked to increased fatigue. Reduction in the severity and duration of PEM, possibly through normalization of immune response, would directly improve quality of life for ME/CFS sufferers.

Objectives. As metabolic and immune signaling networks are extensively intertwined, we hypothesize a course of well-coordinated interventions targeting specific immune signals may help restore capacity for normal recovery from physical exertion in ME/CFS.

Methods. In an ongoing study, blood samples were collected at 9 points during a maximal exercise challenge in n=4 female ME/CFS and n=5 matched healthy control subjects. At each time, blood samples were analyzed for the concentrations of 16 cytokines using a chemiluminescent assay. For each subject, the trajectory of individual cytokines were fit to standard rate equations describing immune response dynamics during exercise and recovery. Based on the latter simulations were conducted where the sequence, magnitude and timing of specific cytokine pulses were modulated. Treatment courses were constructed to minimize the maximum deviation of any individual cytokine from the corresponding healthy response trajectory while also penalizing candidate treatment courses for deviating from the cytokine coexpression pattern expected of a healthy immune response network.

Results. Computer simulations of immune network dynamics during exercise and subsequent recovery show that intervention courses targeting 2 cytokines far outperform single target regimens, reducing the overall average divergence of immune profiles during recovery by up to 50% compared to untreated. Of the 120 dual-cytokine candidate combinations the 16 top performers all include early IL-2 blockade. Combing this with subsequent IL-17 supplementation best supported normal inflammatory and anti-inflammatory cytokine expression in the wake of peak exertion.

Conclusion. Though additional subject profiles will be analyzed as they become available, these preliminary results suggest that immune response dynamics following exertion may be greatly normalized by early course IL-2 blockade and IL-17 stimulation either direct or indirect.

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*** The authors have no conflicts of interest to report.

Poster 12

RNA and microRNA profiles from peripheral blood in Myalgic Encephalomyelitis/Chronic Fatigue compared to healthy controls

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Background:
Chronic Fatigue Syndrome/Myalgic Encephalomyelitis (CFS/ME) is a pathology for which no molecular diagnostic test exists. The syndrome is currently diagnosed after 6 months of the subject experiencing an array of symptoms.

Objectives: Here, we sought to investigate gene expression changes in whole blood in CFS and matched controls to determine if gene expression biomarkers could be used as the basis of a diagnostic test.

Methods: We accrued a new cohort of 94 subjects, including 49 chronic Fatigue syndrome (CFS/ME) and 45 matched controls. Gene expression was assayed with RNA-Seq for messenger RNA as well as for microRNAs. Whole blood was collected in Paxgene tubes and banked. RNA was extracted in batches containing a matched number of CFS/ME and control samples. RNA was converted to cDNA libraries with the NuGen Ovation v2, which enables the amplification and sequencing of low abundance transcripts. Messenger sequencing was performed on

a HiSeq4000 instrument to yield an average of 53 million 100bp reads per sample. Reads were mapped to the human genome with GobyWeb and the STAR aligner. We analyzed data controlling for sex, age, body mass index and the season when blood was obtained, with Limma Voom and MetaR. We controlled for multiple testing with the Benjamini-Hochberg method.

Results: We observed no consistent gene expression changes in blood that could reliably distinguish CFS/ME patients from controls (FDR<20%). Several genes reported in previous studies were also tested in this cohort and failed to replicate.

Conclusion: Gene expression in whole blood was not found to be a reliable biomarker of CFS/ME. Differences with previous studies can be explained by the small size of some earlier cohorts, this study controlling for covariates previously shown to associate with gene expression changes, or the large variability in gene expression in blood caused by cellular heterogeneity in the human population. To address the last factor, we are conducting small and messenger RNA sequencing assays from RNA extracted from sorted B, T and NK cells.

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Poster 13

Chronic enterovirus (EV) infection in a patient with myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) – Clinical, Virologic and Pathological Analysis

John Chia, David Wang, Andrew Chia, Rabiha El-Habbal. EV Med Research. Lomita, CA,

Objectives: A 23 y/o Caucasian male developed prolonged, recurrent gastrointestinal symptoms, followed by onset of severe ME/CFS (CDC criteria, ICC). At initial evaluation, Echovirus 11 antibody titer was $\geq$1:640 (normal <1:10); IgG and IgM antibody for EBV and HHV6 were negative, CMV IgG was positive. He failed to respond to combination of alpha and gamma interferon; and debilitating symptoms of the stomach and central nervous system were minimally alleviated by SSRI, benzodiazepine and acid-suppressant. Repeated MRI scans of brain and spinal cords showed normal results. The patient committed suicide 6 years after the onset of symptoms. Brain was harvested and frozen within 24 hours of death for evaluation of chronic viral infection.

Method: Using EV- and dsRNA-specific monoclonal antibody (5D8/1 and J2 mAb), stomach and colon biopsies obtained 5 months after onset of illness were stained for viral capsid protein (VP1) and dsRNA by immunoperoxidase technique. Blood drawn in Paxgene tube 3 years after illness was screened for enterovirus RNA by RT-PCR. ~1 cm^3 sample was taken from the ponto-medullary junction (PM), medial temporal lobe (MT), frontal lobe (FL), occipital lobe (OL), cerebellum (CL) and midbrain/hypothalamus area (MB) of brain. The brain samples were homogenized in 10 ml of serum-free medium. Aliquots were processed for viral cultures. Trizol-LS reagent was used for RNA and protein extraction, as well as other lysis agents. Tris-Glycine and MES gels, wet and semi-dry transfer, then western blot was performed with Ibind (Life technology) using EV-, CMV- and HHV6-specific mAbs, patient's own serum and control serum samples. Viral culture was performed in WI-38 and BGMK-DAF cell lines. RT-PCR for conserved highly-conserved sequences of 5' end and 3D polymerase sequence were performed on extracted RNA.

Results: Stomach and colon biopsies stained positive for EV VP1 soon after initial infection documenting the initial viral infection; dsRNA was detected in the stomach biopsies. EV RNA was not detected in blood 3 years after illness. Initial culture of brain samples did not grow virus; 5' EV RNA sequence was not detected by RT-PCR. Using 5 D8/1 mAb, western blot revealed 37-42K and 46K protein bands in the brain samples, which corresponded to viral protein and creatine kinase b extracted from infected stomach biopsies, but not in brain biopsy samples taking

from patients with brain tuberculoma and lymphoma. 3D pol gene was amplified from the DNase-treated RNA extracted from PM, MT and FL. 5' RNA sequence was in one of the FL specimens.

Conclusion: The analysis of the second brain specimen taken from ME/CFS patient replicated the British findings published in 1994 (Ann. IM). The finding of viral protein and RNA in the brain specimens 6 years after documented acute enterovirus infection of the gastrointestinal tract is consistent with a chronic, persistent infection of the brain causing debilitating symptoms. EV is clearly one of the causes of ME/CFS, and antiviral therapy should be developed for chronic EV infection.

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Poster 14

Relationship between Sleep quality and Pain in female patients with Myalgic Encephalomyelitis (ME)/Chronic Fatigue Syndrome (CFS)

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Background: Reduced sleep quality is a common complaint among patients with ME/CFS that suffer from pain. Research aimed at delineating the predictors of poor sleep has produced results describing pain severity as one of the most frequently encountered predictors. It has been suggested that sleep disturbance in patients with pain may increase pain sensitivity and create a self-perpetuating cycle of sleep disruption and increased pain. **Objective:** To examine whether ME/CFS female patients suffering from pain differed from healthy control subjects who had no pain on subjective sleep quality measures. **Participants and Methods:** This retrospective longitudinal cohort study compared 80 females (40 ME/CFS diagnosed patients with pain to 40 healthy control subjects without pain on a measure of sleep quality. Cases and controls did not differ by age or sex. The study population had a mean age of 47 years **Results:** ME/CFS patients with pain (measured using Multidimensional Fatigue Inventory - MFI) had significantly higher scores than did healthy control subjects on the Pittsburgh Sleep Quality Index (PSQI) ($r=0.42$, $p<.05$). It was evident that pain intensity correlated significantly with poorer sleep quality. **Conclusions:** ME/CFS female patients with pain suffer from poor sleep quality compared to Healthy Control females without pain. However, in order to draw a causal relation that would be more substantial, further studies should be conducted in larger cohorts to validate these findings of sleep disturbance in ME/CFS patients with pain.

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Poster 15

The Use of the Respiratory Exchange Ratio in Assessing the Metabolic Efficiency of Patients with ME/CFS

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Introduction: Since patients diagnosed with ME/CFS have lower capacity for exercise, investigation into a possible difference in exercise efficiency is indicated. The Respiratory Exchange Ratio (RER) (VCO_2/VO_2) has long been linked to acute metabolic changes, especially during exercise testing. RER values at the lower end of the typical range (0.7-0.85) indicate prioritization of highly efficient aerobic metabolisms, while elevated values (≥1.0) indicate a less sustainable anaerobic state. If the anaerobic state is maintained for any significant amount of time, metabolic efficiency may greatly decrease. Thus the purpose of this investigation is to determine if CFS patients will reach the "metabolic threshold" of RER = 1.0 sooner than healthy controls, illustrating a lower metabolic tolerance for exercise.

Methods: This study included 16 CFS Males, 13 GWI Males and their age-matched controls. Following a controlled breakfast, subjects performed a maximal effort exercise test on a recumbent bicycle. Resistance - initially set to 60 Watts - was increased by 30 Watts every 2 minutes, and speed was constant at 60 RPMs. Testing stopped when the subject could not maintain 60RPM or volitional fatigue was reported. Time to RER = 1.0 (tRER) was recorded when breath-by-breath RER was sustained above 1.0. Time to exhaustion (tE) was also recorded.

Results: Patients diagnosed with CFS reached tRER an average of 2 minutes, 12 seconds faster than healthy controls (2-tailed T-Test, $p<0.05$), but did not display a significantly different tE. This indicates that patients with CFS switched anaerobic metabolism sooner, and stayed in that state for a larger percentage of the test.

Conclusion: The fact that patients with CFS reached tRER sooner, and therefore at a lower intensity, than healthy controls but did not experience the same significant drop in tE indicates that CFS subjects spent less time working aerobically and significantly more time in an anaerobic state. This also might indicate an overall more difficult perception of exercise. This lack of metabolic efficiency and elevated perception of exercise could point to one of the possible causes of a lower exercise tolerance in the entire population.

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Poster 16

ME/CFS: Role of Volunteerism

Geoffrey Hallmann, **Dr Rosanne Coutts**, Dr Yvonne Hartmann
Southern Cross University

OBJECTIVES: To examine the role of volunteerism in the lives of persons with ME/CFS.

METHOD: The initial phase of the research involved a thorough review of the available literature to establish the interaction of those with ME/CFS with social institutions. A focus for this paper was made on the role volunteerism played in the lives of participants. In the data collection phase, a pilot study involving an investigation of the Australian perspective of the experience of ME/CFS was obtained. This was expanded in the main study and participants were provided the opportunity to reveal their stories. Participants were required to have a diagnosis of CFS, ME or ME/CFS from a medical practitioner and self-select themselves as compliant to the Fukuda CFS Criteria, Canadian ME/CFS Criteria and Ramsay ME Criteria.

A background questionnaire was provided to give an insight into the history of the participant, particularly interactions with social institutions and pathways to diagnosis. Social institutions are the complex social forms that are found within governments, family, universities, hospitals, incorporated entities, legal systems and other social structures and organisations. The interview drew upon the questionnaire for guidance, with the primary questions derived from information gained from the literature review. The interviews were transcribed, coded and the relationships and issues identified in order to guide the second phase of the research which was conducted further into the study.

The pilot study involved 3 participants, followed by a second, more comprehensive phase comprising 16 participants. Stories emerged from within those interviews with respect to interactions with society and these were broken down to reveal particular themes relevant to those experiences. In the context of this paper, the issues arising were examined from the gaze of the role of volunteerism in the lives of participants and their condition.

RESULTS: A total of 19 interviews were conducted. The average age was 41.95 across females (n=14) and male participants (n=5). The mean duration of the condition was 17.66 years, with 8.35 years from onset until diagnosis. Within the context of examination interaction with social institutions, volunteerism arose as a theme that played a significant role in the experience of ME/CFS. Volunteer roles included religious groups, ME/CFS support groups, and other roles. Volunteering provided a sense of usefulness, self-esteem and contribution, whilst also enabling skills to be utilised, albeit on an irregular, unpredictable and diminished basis. Some participants physically attended the premises of an organisation whilst others utilised an online environment to participate. Inconsistency was experienced and caused a sense of frustration and guilt, whilst some experienced adverse comments and treatment from other members when they failed to deliver on commitments.

CONCLUSION: Participants with ME/CFS reported that volunteering provided a generally positive experience in their lives. Whilst volunteering provided some sense of happiness, well-being, social involvement and achievement, there were some negative experiences associated with being unable to perform to the expectations of others and themselves, particularly when it came to reliability and performance of tasks. On occasions a lack of understanding of the condition led to adverse comments and treatment. These experiences and the conduct of activities at times impacted the participant's health adversely. Where participants were organisers of the volunteer group, participation of a non-ME/CFS person was of assistance to an effective operation, particularly where it was a family member.

Whilst volunteerism has at times been identified within the literature in the context of ME/CFS, there has been no thorough examination of the role of this activity, its experience or its impact upon the individual.

Poster 17

Psychosocial Perspectives on Chronic Fatigue Syndrome

Hayley Curran[1]

Background
Chronic Fatigue Syndrome is an illness with an unknown, contested and consequently controversial aetiology and as a result there is much pressure on those with CFS to conform to the sickness role, minimise the impact of stigma and protect their own selfhood.

Theoretical Perspectives
Four distinct categories of illness exist: acute, chronic non-stigmatising, chronic stigmatising and mental. CFS can fall under the category of a 'chronic stigmatising' illness which is classed as such because of:

- the difficulty others have in interpreting the symptoms,
- the degree to which the illness becomes a part of someone's identity,
- the severity and persistence of the social consequences of the illness.

Recent theories have suggested that there is a biological need for a society to be 'effective' and shun those who do not function to the same level. The stigma of being labelled 'different' can cause people to be placed in a 'liminal' state that separate them from others, can be linked with negative stereotypes and create status loss as well as direct and indirect discrimination.

Implications
To carry an accepted medical label our society requires a person with an illness to fulfil the sickness role by seeking treatment from a doctor. If a labelled person cannot fulfil a valid sickness role they are often stigmatised as a discredited person, one who is seeking attention and may not actually be ill. It is important, therefore, to maintain an on-going relationship with healthcare even without a 'cure' for CFS sufferers.

A person experiencing a potentially stigmatising illness fears the stereotypes and can feel devalued and so adopt coping strategies which often include secrecy and social withdrawal. When your illness is medically 'valid' like cancer your sickness label is more easily accepted by society; even a clear label can still make effective groups uneasy.

Life events, chronic life strains, self concepts, coping and social supports can come together to form a process of stress which when exacerbated can erode any positive self-esteem and even personhood to a point that one may no longer recognise who they are anymore

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Poster 18

Vitamin B12, hydrogen sulfide and mitochondrial bioenergetics: A possible role for B12 regulation of cytochrome C oxidase in CFS/ME

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Background
Mitochondrial dysfunction with impaired ATP production is emerging as a central focus in research directed at CFS/ME and fatiguing illnesses, but underlying mechanisms and causation remain poorly defined. Hydrogen sulfide (H_2S) is a key player in mitochondrial bioenergetics, sustaining ATP production under stress conditions, and we previously proposed that H_2S inhibition of cytochrome c oxidase (CCO) could contribute to CFS/ME. Here we consider the role of B-12 and its possible relationship to the activity of H_2S in that process.

Objectives
To clarify the mechanism(s) by which H_2S may contribute to CCO inhibition in CFS/ME

Methods
We examined the relevant literature in conjunction with our own measurements of vitamin B-12 (cobalamin; Cbl) and redox/methylation metabolite levels in post mortem brain tissue.

Results
Heme groups in CCO are subject to inactivation by H_2S as well as carbon monoxide, nitric oxide, nitrous oxide and cyanide (CN). In laboratory animals H_2S administration causes a profound decrease in metabolic rate, which may reflect CCO inhibition. H_2S is produced by two transsulfuration enzymes, cystathionine beta synthase (CBS) and cystathionase (CSE). In humans, brain CSE activity is very low at birth but appears to increase with aging, suggesting that increasing H_2S formation may function to restrict metabolic activity in an age-dependent manner. Environmental exposures, genetic vulnerabilities and/or infections that trigger CFS/ME may increase transsulfuration, resulting in H_2S formation, CCO inhibition and impaired energy production.

Numerous studies have described the ability of Cbls to reactivate CCO. Recent work has shown that the Cbl analog cobinamide works as a sulfide antidote through CCO reactivation and neutralization of sulfide-generated reactive oxygen species. Intracellular Cbl is provided in a glutathione (GSH)-dependent reaction and low GSH might

therefore limit Cbl availability for CCO reactivation. GSH levels are decreased in CFS/ME patients and augmentation of GSH provides benefit, while administration of Cbl also results in symptom improvement.

Conclusion
Based upon our collective observations we propose that inhibition of CCO by H_2S (and possibly other "gasotransmitters") plays an important role in CFS/ME and the clinical benefit of Cbl derivatives reflects, at least in part, reactivation of CCO.

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Poster 19

Evaluation of the prevalence of Gulf War Illness, Myalgic Encephalomyelitis/ Chronic Fatigue Syndrome, and Fibromyalgia in Gulf War veterans

Emily K. Donovan, BA
Rebecca Massey and Jarred Younger, PhD

Background: Twenty-six years after the 1990-1991 Persian Gulf War, we still have a poor understanding of the fatigue, pain, and other symptoms that affect approximately 250,000 veterans. Just as in Myalgic Encephalomyelitis/ Chronic Fatigue Syndrome (ME/CFS) and Fibromyalgia, the pathophysiological mechanism of Gulf War Illness (GWI) has not been identified, nor has an objective biological test been developed.
Objectives: To evaluate co-morbidity among three chronic illnesses with unclear etiologies.
Methods: 25 male Gulf War veterans in the pre-screening period of a clinical trial have been evaluated for GWI, ME/CFS, and Fibromyalgia using the Kansas inclusion criteria (Steele, 2000), the CDC case definition (1994), and the ACR Criteria (2010), respectively.
Results: Of the veterans evaluated, 68% (n=17) met inclusion criteria for GWI. Of those 17, 41.2% (n=7) also met criteria for both ME/CFS and Fibromyalgia, 23.5% (n=4) met criteria for GWI and Fibromyalgia only, 23.5% (n=4) met criteria for GWI and ME/CFS only, and 11.8% (n=2) met GWI criteria only. Of the veterans who did not meet inclusion for GWI (n=8), 25% (n=2) met criteria for both ME/CFS and Fibromyalgia, and 75% (n=6) did not meet any of the case definitions.
Conclusion: The findings show considerable overlap in symptomatology among GWI, ME/CFS, and Fibromyalgia. This overlap may indicate a common underlying pathophysiological mechanism. Scientific results from one of these diseases might therefore help advance our understanding of the others.

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3. The authors have no conflicts of interest.

Poster 20

Post-exertion malaise: Relationships of symptoms with Physical Activity and Sedentary Behavior in Myalgic Encephalomyelitis / Chronic Fatigue Syndrome (ME/CFS)

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Background: The research concerning the effect of acute exercise on subsequent physical activity (PA) and sedentary behaviors (SB) in ME/CFS is currently equivocal. Moreover, the relationship between symptoms of post-exertion malaise (PEM) and PA is largely unexplored. **Objective:** To measure PA and SB pre- and post- acute exercise and determine relationships with symptoms in ME/CFS. **Methods:** Fifteen female ME/CFS patients and 15 healthy female controls completed 30 minutes of submaximal exercise (70% of peak heart rate) on a cycle ergometer. PA and SB were measured objectively via accelerometry. Symptoms (e.g. fatigue, pain, physical function), PA and SB were assessed for 7 days pre- and post-exercise testing. Between-groups comparisons were determined using independent samples t-tests. Relationships were explored using Pearson correlations. **Results:** PA including light, moderate, and vigorous intensities and SB did not differ between ME/CFS and controls during the week preceding the exercise bout (p>0.05). There were no significant within-group changes for PA and SB for either ME/CFS or controls (p>0.05). However, during the week post-exercise, the ME/CFS group had significantly fewer minutes of moderate and vigorous PA compared to controls (p<0.05). Disease severity and physical function were positively associated with SB and negatively associated with PA pre- and post-exercise for ME/CFS (p<0.05). This was particularly true for self-reported muscle pain, which showed a moderate positive correlation with SB (r=0.59, p<0.05) and negative correlations with moderate (r=-0.63, p<0.05) and vigorous (r=-0.68, p<0.05) PA. ME/CFS patients had significant symptom exacerbation 24 hours post exercise (p<0.05) indicative of PEM, however this exacerbation of symptoms was not significantly associated with PA or SB during the week following exercise testing (p>0.05). **Conclusion:** Despite the presence of PEM, PA remained largely unaffected in ME/CFS; however, the relationships with illness severity were in the expected directions (i.e. the more severe the less active and more sedentary). Future studies that include detailed symptom assessment occurring concomitantly with PA measurement are warranted to better understand how PEM affects activity patterns in ME/CFS.

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Poster 21

An Observational Case Study of Chronic Fatigue Syndrome: Potential indicators of onset in a preschool child starting at birth through age 23

Patricia D. Fero

Background: Evidence collected for a more comprehensive look at symptoms and progression of the child's illness experience indicated that the mother's illness onset would warrant a second look at preschool indicators of chronic fatigue syndrome (CFS). Preschool onset has been mentioned by researchers, but there are no scientific studies or proposals that would suggest to a pediatrician that a child could have early onset CFS.

Methods: Detailed life span of medical records were collected and summarized. These records include primary care, comprehensive consultations with team specialists for testing and evaluation of children with physical, emotional, and psychosocial delays, neuropsychology, otolaryngology, orthopedics, school records, and journal records.

Results: This child is at risk for numerous physical and mental diseases. Premature birth complications include long - term in utero use of multiple antibiotics, terbutaline to stop labor, birth at less than 34 weeks, neonatal low blood sugar less than 50, and after birth treatment for streptococcus B. Medical records show 71 doctor visits prior to age five with heavy antibiotic use for upper respiratory infections, development of sleep disorder of unknown

origin, toxic exposure, parasitic infections, and head trauma. The possibility of genetic or in utero maternal transmission is apparent with the mother's diagnosis of chronic fatigue syndrome in 1987 and Myalgic Encephalomyelitis in 1994, eight years after the original viral onset in July 1980.

Conclusion: Preschool early onset risk factors in children have not been studied. To date, clinicians have little information that suggests the possibility of preschool children developing chronic fatigue syndrome. Small-scale maternal or genetic transmission research studies are underway, but replication of these studies and recommendations for at risk offspring are not forthcoming. In the interim, potential indicators discovered from this observational case study suggest that gathering complete medical histories from young children demonstrating symptoms, may lead to a better understanding of the course of the illness. Clinicians might be able to moderate the level of severity and improve the prognosis by providing medical, educational, and parental interventions and support.

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Poster 22

MODELING CAUSAL RELATIONSHIPS IN ME/CFS
ROBERT S. FREDERICKS

Background
ME/CFS associated with post exertional malaise demonstrating discordance in apparent oxygen consumption grants it categorization as a physical illness. Authentic metabolic mechanisms, when clarified, should reveal effective strategies for treatment. Anthropologic physicians engage case based investigation to discover authentic mechanisms, while epidemiologic physicians interrogate categories, authenticating their efficacy for appropriate care. The former develops mechanistic models that can accommodate all available data, while the latter values data applicable to analysis of categorical interventions. Authentic categories demonstrate continuous quality improvement with the anthropologic strategy refining epidemiologic observations. Anthropology, the study of humans, values narrative that captures the authentic intelligence of the patient and as a means to describe the organizing principles of biology that inform the mathematics of mechanistic models.
Objectives
Develop causal physiologic/metabolic models that direct appropriate personalized interventions, result in anthropologic refinement of the post exertional malaise category and clarify the foundation of metabolic disease in general.
Methods
Case based investigation incorporating challenge tests of oral calcium and immersion in water (gravity subtraction) exposing biology to be heterostatically organized, combined with a continuous quality improvement strategy to discover effective intervention and build mechanistic models.
Results
The cases inform a model that recognizes a fundamental behavioral decision, whether to hunt or to hide, is governed by internal and external cues regarding heat, sodium and phosphate consistent with discoveries in the basic sciences. The model serves to organize the vast amount of available data across disciplines and identifies interventions facilitating the patient's perception of integrity, a definition of health replacing normality, a surrogate measure often informing inauthentic categories.
Conclusions

The apparent efficacy of oxygen in post exertional malaise derives from its extraction from glucose (a concealed oxygen source) and impaired oxidative phosphorylation, a consequence of reduced 24, 25 hydroxy Vitamin D, a primitive hunt signal influenced by Vitamin B12.

Salt induced kinases, intracellular signals expressed with systemic volume loading, are modulated to influence hemodynamic adaptation, perception of fatigue, and salt craving/aversion.

Glucose toxicity, generating ROS, organizes physiology and metabolism that governs human health and body composition.

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Poster 23

Metagenomic Analysis of Peripheral Blood in Myalgic Encephalomyelitis/Chronic Fatigue Syndrome

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Keywords: Chronic Fatigue Syndrome, Myalgic Encephalomyelitis, Eukaryotic, Protozoan, Metagenomics, Sequencing

Background: The etiology of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) is unknown. It is estimated to potentially afflict hundreds of thousands, if not millions of Americans and is estimated to affect potentially 1% of the world population. Due to several features of ME/CFS we hypothesized a previously unrecognized vascular infection may be involved.
Methods: To address this possibility a blinded pilot study of 30 ME/CFS patients meeting the Fukuda criteria were compared to 48 normal controls. Population structure analysis by Next-Generation DNA sequencing detected and characterized the prokaryotic and eukaryotic microbes in the peripheral blood of ME/CFS patients.

Results: Protozoal and bacterial DNA sequence counts detected by Next-Generation DNA sequencing in normal controls was less than seen in ME/CFS patients; however, not reaching statistical significance. The observed microbiota does effectively differentiate between the experimental and control populations by multivariate analysis. Of the prokaryotic findings, the *Firmicutes* and *β-Proteobacteria* taxon were observed to positively correlate with the severity of the ME/CFS; however, they were not observed as a major driver of population separation. The percent of organisms belonging to the *Alveolata* super-phylum were not only a primary driver, but was statistically significant when comparing ME/CFS to normal controls.

Conclusion: Based on these correlations, we conclude that previously undetected eukaryotic microbes may play a role in the progression/initiation or may represent a potential biomarker for ME/CFS severity.

Poster 24

Symptomology in Patients Enrolled in Myalgic Encephalomyelitis/Chronic Fatigue Syndrome Genes Study
Kristina Gemayel [1] Kelly Gaunt [1], Ana Del Alamo[1], Melanie Perez[1], Irma Rey[1], Lubov Nathanson[1], Nancy Klimas[1,2], Maria Vera[1]
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Background: Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) is a complex illness characterized by severe disabling fatigue that is accompanied with symptoms of impaired concentration, short-term memory, disturbed sleep patterns, and flu-like symptoms. Previously most of the research in the ME/CFS field was not aimed at genomic studies, but there has recently been a push towards this direction. Coupling symptom

questionnaires with genomic data allows researchers to determine specific subpopulations of ME/CFS patients, allowing for further advancement in the field.

Objectives: In order to effectively characterize the symptomology in relation to the genomics of patients with ME/CFS, we are utilizing social medial platforms to recruit participants, and a secure online platform with questionnaires to obtain a detailed characterization of the ME/CFS population.

Methods: To circumvent the limitations of a large-scale study of this magnitude, a secure online platform, RedCap, is utilized to create a user-friendly environment for participants with ME/CFS to answer symptom questionnaires and upload genomic data. The survey is available to international parties, and qualifying parameters for participation in this study are based on the Canadian Consensus Criteria. Once an individual meets all participation criteria, they are granted access to a symptom questionnaire and a secure portal that allows the participant to upload their genomic data at their convenience.

Results: We have obtained over 300 completed symptom questionnaires, along with genomic information, from patients diagnosed with ME/CFS through our IRB approved study. Moving forward we intend to correlate the symptomology reported by ME/CFS participants to single nucleotide polymorphisms (SNP) patterns in order to facilitate subgrouping of this population. At the meeting we will present up to date data to test the subgrouping strategies of proven studies and look at initial correlates to SNP data.

Conclusion: It is the intent of this study to further characterize subpopulations of ME/CFS patients based both on their symptom trends in regards to their genomics. Utilizing a secure and readily accessible online platform facilitates recruitment, and enhances participation that is not restricted by geographical location.

Poster 25

Persistently elevated bone marrow somatic mutation as a biomarker of clinically relevant exposures in Gulf War Illness

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Background: Veterans who served in the Gulf war report debilitating health symptoms 2-3x more frequently than military personnel who were not deployed to the Gulf. These symptoms are multi-system and non-specific, involving fatigue, headache, memory issues, sleep disorders and musculoskeletal pain. Gulf war illness (GWI) is a life-altering disease presumably caused by exposures to radiation and/or chemicals. We hypothesize that our approach to environmentally-induced carcinogenesis, to measure the total cumulative effect of all genotoxic exposures, as modified by the genetic susceptibility of each exposed individual, can be translated successfully to a study of GWI. From our previous studies, it is clear that genotoxic exposures can induce both short-term and long-term effects, with the long-term effects associated with mutagenesis of the stem cell compartment. Stem cell mutagenicity, as demonstrated by persistent elevations in blood-based somatic mutation frequencies, would be expected to result in pleiotropic premature aging effects that could manifest as non-specific GWI.
Objectives: We are directly measuring somatic mutation frequencies in symptomatic and asymptomatic Gulf war veterans and controls to determine whether i) there is evidence of persistently elevated somatic mutation, and ii) it is indicative of disease or disease severity. In a subset of subjects with elevated somatic mutation we will also iii)

directly measure DNA repair capacity, to determine whether genetic predisposition is an important element in determining who will manifest clinically relevant symptoms.
Methods: Blood-based somatic mutation frequencies are measured at the glycophorin A locus, the genetic determinant for the MN blood group. DNA nucleotide excision repair is measured using the unscheduled DNA synthesis assay, which is used for clinical diagnosis of inherited diseases associated with this repair pathway.
Results: As the study has just begun, early data will be presented.
Conclusion: Identifying the characteristics of exposures capable of producing GWI would allow for targeted predictive screening of the current "at-risk" population. Such exposures could be avoided during future deployments (to the extent possible) to reduce the induction of new disease. Identifying the basis of genetic predisposition would also allow for the sequestering of "high-risk" personnel from exposures more likely to produce clinical disease in future deployments.

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No conflicts of interest declared.

Poster 26

Seeking a quantitative method to determine HHV-6 IgG antibody levels using qualitative ELISA

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Background: Myalgic Encephalomyelitis–Chronic Fatigue Syndrome (ME/CFS) is a debilitating illness of unknown etiology associated with neurological, immunological, and metabolic dysfunction. Previous studies have shown that ME/CFS patients tend to carry a higher degree of Human Herpesvirus-6 infection or reactivation and that patients with elevated viral titers reported more severe physical symptoms, supporting a role of HHV-6 in the symptomatology of ME/CFS. Meanwhile, ELISA assays to measure serum IgG remain qualitative, and at best only semi-quantitative. Here, we present a quantitative approach to measuring serum IgG antibody levels.
Objectives:

1. Develop a quantitative approach for measuring serum IgG levels using existing ELISA technology.
2. Evaluate serum HHV-6 IgG as a potential biomarker for symptom severity in ME/CFS.

Methods: Serum samples were obtained from ME/CFS and Healthy Control (HC) (n=121, 49) in a longitudinal biomarker discovery study and analyzed by ELISA in six serial dilutions. A linear regression model of antibody index measurements produced an intercept measure, reported in arbitrary units (AU) and validated by ANOVA. Linear classification analysis was conducted using repeated sub-sampling and bootstrapping to control for group size differences between cohorts. Inclusion criteria for ME/CFS were derived from the Canadian case definition reported in Carruthers et al.[1]
Results: This HHV-6 serum IgG intercept measure (HHV-6 AU) accurately distinguished between ($p<0.01$) and within ($p<0.01$) dilution groups. As a candidate biomarker for ME-CFS the HHV-6 AU slope and intercept used together increase classification sensitivity from 0.39 to 0.86 and improve negative predictive value 1.5 fold while maintaining the same positive predictive value in repeated sub-sampled estimates. We found a significant negative correlation ($r=-0.3069$) between HHV-6 AU intercept measure and SF-36 physical functioning sub-score ($p<0.02$).
Conclusion: This methodology allows for accurate stratification of patients by level of circulating serum IgG and provides an analytical approach for ELISA that increases specificity and comparability across titers with minimal additional cost. We have shown that HHV-6 AU is an accurate biomarker for symptom severity. We postulate that this measure can be used to guide the clinician in the management of ME/CFS patients, specifically in determining whether targeted antiviral therapies can be of benefit.
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Funding Source: 2R56AI065723-06A1 (PI MA Fletcher) Potential Conflicts of Interest: None

Poster 27

Amygdala Retraining Techniques for the Treatment of Fibromyalgia: A Randomized Controlled Trial

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Background: Fibromyalgia is a prevalent and disabling condition. Despite different pharmacological and psychological treatments being used, none of them have shown satisfactory results. Amygdala Retraining Techniques (ART) is a new third-generation therapy aimed at treating this disorder more effectively.

Objectives: The objective of this study is to assess the efficacy of this therapy for the treatment of fibromyalgia.

Methods: A randomized controlled trial was conducted, with a 6-month follow-up assessment. Patients were recruited from a primary care setting in the city of Zaragoza, Spain. Patients in the study had to fulfil the criteria for a confirmed diagnosis of Fibromyalgia, as defined by the American College of Rheumatology. They were formally diagnosed by a Rheumatologist. Sample size was calculated for a mean effect size of 0.5 for the main outcome, an alpha risk of 5%, and a power equal to 80% in a bilateral contrast. Patients were assigned to one of two arms: a) ART or b) Control treatment, which was relaxation therapy. Preliminary data on efficacy was assessed at baseline, and 6 months, using the following validated questionnaires: Fibromyalgia Impact Questionnaire (FIQ) (as main outcome), Global Clinical Impression, Five Factors Mindfulness Questionnaire (FFMQ), Self-compassion Scale (SCS), Acceptance & Action Questionnaire (AAQ2) and Hospital Anxiety Depression Scale (HADS). Analysis was carried out by intention-to-treat.

Results: Forty-one patients were randomized to both groups: 22 were randomized to ART and 19 to the control relaxation group. The sample was made up of middle-aged married women. At six-month assessment, FIQ scores were significantly lower in the ART group than in controls (effect size, ES=-0.98). Depression as measured by HADS was also significantly lower (ES=-0.47). Regarding other intermediate variables, ART significantly decreased experiential avoidance measured by AAQ2 (ES=-0.66)

Conclusion: The data is discussed in the light of previous studies on third-generation therapies. Preliminary data suggest that ART could be an effective treatment for fibromyalgia.

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The authors report no conflict of interest.

Poster 28

ME/CFS: Experiences of the Insurance Safety Net

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Southern Cross University

OBJECTIVES: To examine ME/CFS in the context of dealings with insurance companies.

METHOD: The initial phase of the research involved a thorough review of the available literature to establish the interaction of those with ME/CFS with social institutions. A focus for this paper was made on the access to and funding of insurance. In the data collection phase, a pilot study involving an investigation of the Australian perspective of the experience of ME/CFS was obtained. This was expanded in the main study and participants were provided the opportunity to reveal their stories. Participants were required to have a diagnosis of CFS, ME or ME/CFS from a medical practitioner and self-select themselves as compliant to the Fukuda CFS Criteria, Canadian ME/CFS Criteria and Ramsay ME Criteria.

The background questionnaire provided insight into the participant's history, particularly interactions with social institutions and pathways to diagnosis. Interview utilised this document for question guidance. The primary questions were informed by the literature review. Interviews were transcribed, coded and the relationships and issues identified in order to guide the second phase of the research which was conducted further into the study.

The pilot study involved 3 participants, followed by a second, more comprehensive phase comprising 16 participants. Stories emerged from within those interviews with respect to interactions with social institutions and these were broken down to reveal particular themes relevant to those experiences. In the context of this paper, certain issues were viewed from the gaze of access to the insurance safety net.

RESULTS: A total of 19 interviews were conducted. The average age of participants was 41.95 with all 14 females and 5 male participants. The mean duration of the condition was 17.66 years, with 8.35 years from onset until diagnosis. Most participants (n=13) identified having insurance ranging from Total and Permanent Disability (TPD), to Sickness and Accident income replacement (SA) and Workers Compensation (WC). 3 participants claimed SA. 2 participants claimed WC. 2 participants attempted to claim TPD.

CONCLUSION: Persons with ME/CFS who claimed personal insurance experienced significant issue obtaining benefits with insurers denying claims from the outset or removing claimants on the basis of technicalities or flawed IME reports. Claimants (n=3) avoided ME/CFS label in their claim, using instead depression and experienced less issues with ongoing claims being paid without interruption. Claims (n=4) with benefits paid for over 2 years (3 SA and 1 WC) were forced to legal action to obtain benefits. 3 of these claimants and 1 workers compensation opted to settle for a substantially reduced sum to remove the insurer from their life. 1 on SA achieved ongoing benefit. 3 participants with TPD failed to make claims due to a lack of knowledge of how to do so or a false belief that they had no claim. The participants who took legal action (n=3) received less monies than should have been paid by the insurer, due to legal costs. 2 participants failed to take legal action because they were too sick to do so. The younger participants (age > 30, n = 3) held no insurance at time of onset.

The narrative accompanying the management of claims was primarily negative, even where claims were accepted. The three claimants accepted as depression were not happy that the underlying ME/CFS was not used. Participants experiencing difficulties with payments reported distress, family upset, financial duress and exacerbation of symptoms. Those unable to obtain benefits expressed distress and financial duress, as well as frustration in being unable to claim or unable to achieve an outcome. Access to legal advice was an issue.

Whilst a small sample size, the results do raise significant questions as to why insurers haven't honoured ME/CFS claims, particularly when a diagnosis of ME/CFS exists, yet the claim was admitted on the basis of depression – which post-dated ME/CFS onset. Furthermore, there is a recurring anomaly of depression claims succeeding by not detailing or relying upon the ME/CFS condition as the basis of the claim.

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Poster 29

ME/CFS: Discrimination Within Social Institutions
Geoffrey Hallmann, Dr Rosanne Coutts, **Dr Yvonne Hartmann**
Southern Cross University

OBJECTIVES: To examine the nature and impact of discrimination experienced by persons with ME/CFS when engaged in interactions with social institutions.

METHOD: The initial phase of the research involved a thorough review of the available literature to establish the interaction of those with ME/CFS with social institutions. Social institutions are the complex social forms that are found within governments, family, universities, hospitals, incorporated entities, legal systems and other social structures and organisations. This paper focuses on the incidence, nature and effect of discriminatory behaviour that participants experience during interactions with social institutions..

In the data collection phase, a pilot study involving an investigation of the Australian perspective of the experience of ME/CFS was obtained. This was expanded in the main study and participants were provided the opportunity to reveal their stories. Participants were required to have a diagnosis of CFS, ME or ME/CFS from a medical practitioner and self-select themselves as compliant to the Fukuda CFS Criteria, Canadian ME/CFS Criteria and Ramsay ME Criteria.

A background questionnaire was provided to give an insight into the history of the participant, particularly interactions with social institutions and pathways to diagnosis. The interview drew upon the questionnaire for guidance, with the primary questions derived from information gained from the literature review. The interviews were transcribed, coded and the relationships and issues identified in order to guide the second phase of the research which was conducted further into the study.

The pilot study involved 3 participants, followed by a second, more comprehensive phase comprising 16 participants. Stories emerged from within those interviews with respect to interactions with society and these were broken down to reveal particular themes relevant to those experiences.

RESULTS: A total of 19 interviews were conducted. The average age of participants was 41.95 with all 14 females and 5 male participants. The mean duration of the condition was 17.66 years, with 8.35 years from onset until diagnosis. A number of issues arose, revealing an insight into the nature of the relationships that exist between persons with ME/CFS and various social institutions. Participants reported interactions that were both positive and negative. Such interactions were directly impacted by the diagnosis of ME/CFS. All participants had experienced some form of discrimination, with the majority being negative discrimination. Within these experiences, issues such as knowledge and understanding of the condition played a significant role in the discriminatory interaction. Misconceptions about the condition played a primary role. Abuse (verbal, physical and mental), withholding or withdrawal of goods and services, individual avoidance, social isolation, adverse employment decision, prescription of no or inappropriate treatment and the like were levelled against participants throughout their

experiences. The ability to take action against discrimination was limited because of the effects of the condition and/or a lack of knowledge or desire to go about it.

CONCLUSION: Participants with ME/CFS who engaged with social institutions were subject to various factors (such as abuse, attitudes, behaviours, comments, misinformation, misunderstandings, beliefs and policies) that directly or indirectly arise because of their diagnosis and the contested nature of the condition.

These factors play an important role in the form of discrimination that participants experienced across all social institutions. Positive discrimination was provided in the form of assistance, management, attitudes, comments and accommodations. Participants revealed circumstances in which discrimination was negative, including the refusal of assistance or accommodation, derogatory comments, malicious treatment and behaviours, inappropriate physical environments (due to noise, smells, access, furniture, line ups, public transport, etc.), inappropriate policies or procedures (eg onerous requirements, poor time frames, inability to be accessed remotely) or misinformed statements, treatment that was adverse (ie insufficient, inappropriate, adverse, deficient or damaging, and resulted consequences that were harmful to the physical, emotional or other interests of the participant). Of significance was the incidence of bullying behaviour that was associated with discrimination.

Those with more visible symptoms and presentation of ME/CFS (ie wheelchair and bed bound) received greater assistance at times, while those with more invisible symptoms and presentation found access to assistance a more difficult and at times impossible task.

Negative experiences had an adverse impact upon the person's condition as well as their emotional wellbeing On occasions the impact and effect was sufficient to constitute trauma. The ability to respond to discriminatory practices was limited by knowledge of process and procedure, the health constrictions that impact the ability to take action, the availability of advocates to assist in such action, and the knowledge of the condition of those taking the action or making decisions. On no occasion was a participant able to follow through on a formal anti-discrimination complaint.

Poster 30

ME/CFS Genes Study: Using Social Media as a Participant Recruitment Tool for a De-Identified Subject Population Genetic Database

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Background: This is a prospective multi-site ME/CFS study with the purpose to develop a de-identified subject population genetic database, using publicly available genetic testing sites, linked to symptom questionnaires, to utilize for future research discovery.

Objective: Our objectives are to systematically apply a set of instruments to assess the domains of ME/CFS and related syndromes, including severity of illness, function, comorbid and exclusionary conditions. We have implemented assessment tools using a computer/web-based format, collect de-identified genetic data from the ME/CFS population through the utilization of social media to maintain a database for future work in this area.

Methods: We are recruiting globally through the use of social media to obtain a geographically diverse subject population with sufficient sample size to drive polymorphism analysis (N >10,000). With the help of Dr. Nancy Klimas, a recruitment video has been posted on FaceBook, and we are partnering with various ME/CFS advocacy organizations such as Phoenix Rising and Open Medicine Institute.
Crowd-sourcing efforts have played a pivotal role in this project, because we have asked participants to donate their genomic data (eg. 23andme, and ancestry.com) to underwrite much of the cost of this study.

Results: Currently, we have created an online RedCap Platform with ME/CFS questionnaires, and obtained IRB approval for the first phase of our study. We have released the RedCap Questionnaire to the public, and have generated a sample size of 400+ participants, targeting 10,000. Additionally, we have obtained IRB approval to recontact participants for future studies and for the recruitment of Healthy Controls.

Conclusions: Utilizing social media as a platform to reach a large sample size of participants has alleviated some of burden associated with study recruitment. The combination of survey questionnaires, along with uploaded genetic data, will allow us to subgroup the population of participants based on symptoms and SNP patterns. The database can help with future funding and facilitate collaborative efforts among researchers in the ME/CFS field.

Poster 31

Precise Scientific Diagnoses of Myalgic Encephalomyelitis (ME), Based on SPECT Brain Mapping and Recovery of Enterovirus (EV)
Byron Hyde, M.D.

This definition of M.E. is distinct and exclusive of the various Chronic Fatigue Syndrome definitions. It is based upon over 30 years of patient investigation and M.E. literature. We propose M.E. and CFS be considered as separate entities.

Proposal: Myalgic Encephalomyelitis (M.E.), distinct from CFS is the result of an acute and chronic Enteroviral (EV) post-encephalitic injury, a close genomic cousin to the three recognized polioviruses. M.E. is diagnosed by (a) the clinical history and at least (b) two reproducible scientific tests, (i) proof of enteroviral infection & (ii) appropriate diagnostic brain SPECT mapping. These two tests are sufficient to make a diagnosis and to reduce diagnostic costs. Unlike the CDC definition, which requires a six-month wait to de ne disease, as in any true disease, both of these tests become positive within the rst week of illness. The (a) localization, (b) degree & (c) variability of SPECT brain injuries accord with the patient's clinical symptoms and disability. M.E. is a provable chronic encephalopathy.

Contributors: Sonia Neubauer Grunberg, Clinica Las Condes, Santiago, Chile, John Chia, EV Med Research LLC, California, USA, Lorenzo Memeo, & Gabriella Timpanaro, Med. Inst. Oncology, Italy, Byron Hyde, Nightingale Research Foundation, Ottawa, Canada

The following are the simple and accurate diagnostic criteria for disabling M.E. and can be utilized in arriving at both a clinical diagnosis and for all scientific research papers.

- The patient conforms to the clinical history of M.E. as described.

- Proof of E.V. infection at onset or from gastric or GIT biopsy in chronic patients.

3. HMPAO brain SPECT **(Single-Photon Emission Computed Tomography)** demonstrating significant hypo-perfusion (more than 2 standard deviations below normal mean) in at least the left temporal lobe and cingulate gyri.

4 Increased M.E. disability is associated with irregular brain hypoperfusion of both cerebral hemispheres. Motor difficulty is associated with hypoperfusion of motor cortex as seen in the following typical brain map of a chronic M.E. patient. M.E. patients with dysautonomia have significant insular lobe hypoperfusion.

5. Multiple tests can confirm M.E. disability (eg. Keller, B cardiopulmonary exercise test). These 2 tests confirm M.E. illness itself. Depending upon degree of E.V. brain area injury, dysautonomia, & ongoing muscle weakness can occur.

Poster 32

Structure-Based Repurposing of FDA-Approved Drugs to Identify Specific Small Molecule Inhibitors of TNF-alpha, IL-2, and the Glucocorticoid Receptor for Treatment of Gulf War Illness

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Background: Gulf War Illness (GWI) is a chronic multi-symptom illness with no current treatment that has debilitated nearly one-third of the 700,000 returning veterans of the 1991 Persian Gulf War. GWI is characterized by dysfunction in the body's regulation systems resulting in debilitating fatigue, severe musculoskeletal pain, cognitive and neurological problems. Previously, computational analysis by our group reported that GWI might be perpetuated at least in part by natural homeostatic regulation of the neuroendocrine-immune network. Subsequent analysis suggested a multi-tiered strategy specifically targeting Th1 immune activation followed by inhibition of the gluccocorticoid receptor (GCR) to reset homeostasis supporting extended remission, however, exact pharmacological avenues have not been explored. A major complicating factor in this predicted treatment regime is the reality that many pharmacological agents bind multiple protein targets and lack the require specificity.
Methods: To identify specific small molecule inhibitors of TNFa, IL-2, and GCR for treatment of GWI, we performed a computational simulation using a consensus-docking screen of FDA approved drugs using AutoDock 4 and Vina. We used multiple crystal structures for each target, including the androgen and estrogen receptors. Docking results were considered consistent if the poses between programs were within an RMSD cutoff of 2.0 Å, and the Vina algorithm was used to provide the binding energy for each protein ligand interaction. Pharmacologic agents

were deemed to be specific for a given target if their binding was at least one-third greater than all other off-target interactions.
Results: Preliminary results from our computational simulations indicate that of the 1824 FDA screened ligands, mifepristone consistently docked on GCR with little effect on the other proteins, indicating its use as a highly reliable selective antagonist. Additionally, a list of related antibiotic compounds (telithromycin, erythromycin, clarithromycin) docked consistently and specifically to TNFa, suggesting these are also highly selective binders. No specific binders were found for IL-2.
Conclusions: This methodology allowed us to take into consideration a large number of docking results that would normally be incomparable. Amalgamating numerous scoring schemes in order to determine binding affinities by consensus scoring reduces errors arising from one particular scoring function, to produce accurate results. The prediction of mifepristone as a specific GCR antagonist, and the erythromycin based antibiotics as specific binders of TNFa are both consistent with literature and are therefore promising pharmaceuticals to be used in our predicted multi-tiered intervention strategy for Gulf War Illness.
Sponsorship: Funding came from the US Department of Defense Congressionally Directed Medical Research Program (CDMRP) awards (http://cdmrp.army.mil/) GW093042 (Broderick - PI), and grant W81XWH-13-2-0085 (Morris - PI). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Poster 33

Exploring symptom subgroups in patients with ME/CFS

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Background: It is still not clear whether the diagnosis Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) represents one single disease entity, as diagnosis depends on clinical case definitions. The heterogeneity and variation of symptoms across individuals indicate possible differences in the relations between symptoms, and their impact on fatigue, mood, functioning and quality of life. To advance the knowledge of the relative importance of different symptoms, the investigation of relations between symptoms among patients with ME/CFS would be of great value.

Objectives
The present study examines the relations between symptoms in patients diagnosed with ME/CFS, to identify possible symptom subgroups and their relations to functioning and quality of life.

Methods
Data was collected from 106 adults as part of the standard assessment at a tertiary specialist clinic for ME/CFS. All included patients fulfilled the 1994 CDC and 2003 Canadian criteria for ME/CFS and were thus included in this study. All participants presented with longstanding unexplained fatigue, post-exertional malaise and symptom increase after activity as well as prolonged recovery period after mental, physical or emotional effort. Patients reported occurrence and severity of 14 different symptoms (Tender lymph nodes; Palpitations; Feverishness; Orthostatic dizziness; Irritable bowel; Sleep dysfunction; Numbness and paraesthesia; Joint pain; General pain; Body soreness; Difficulty concentrating; Memory problems; Chills and perspirations and; Headache). Symptoms were chosen based on the 2003 case definition (i.e. the Canadian criteria) and our clinical experience of the most commonly presented symptoms by patients. Data were analysed using principal component (PCA) and correlation analyses.

Results
The poster will present results from PCA as well as relationships between symptom subgroups and other clinical factors of importance. Principal component analyses suggested four clinically meaningful and statistically distinct subgroups of symptoms. Analyses of the relations between symptom subgroups and measures of fatigue, mood,

functioning and quality of life showed large differences in strength, indicative of differences in impact of symptom subgroups.

Conclusions
The results from this study further the understanding of symptom relations. The identification of symptom subgroups could be a first step towards a more systematic approach in investigating possible differences in aetiology between patients, as well as tailoring treatments depending on illness profile.

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Poster 34

Quantitative fMRI connectivity and activity changes in mental fatigue after mild Traumatic Brain Injury (mTBI)

Julin P, Nordin LE, Möller MC, Bartfai A, Hashim F, Li TQ

Background: Chronic fatigue is one of the most commonly reported and long-lasting post-concussion symptoms. Enhanced sensitivity to effort and limited endurance for sustained physical and mental activities are the main characteristics of central fatigue. The concept of fatigue appears deceptively simple, but researchers and clinicians do not as yet have a commonly accepted objective measure for it. We have recently found associations between mental fatigue and reduced brain connectivity in thalamic and frontal networks using a newly developed quantitative data-driven analysis ((QDA) method for resting state BOLD fMRI (1).

Objectives: In this study we have investigated the relationship between central fatigue and neural activity (quantitative regional cerebral blood flow) during the performance of a vigilance task

Methods: Ten mTBI patients with persistent cognitive dysfunctions and complaints of fatigue and ten matched normal controls were investigated by pseudo-continuous arterial spin labeling MRI measurements of cerebral blood flow during a 20-minutes performance vigilance test.

Results: The mTBI patients showed reduced vigilance performance and in addition to reduced brain connectivity at rest as previously shown (1) there were significant differences ($p<0.05$) in the patterns of neural activation between patients and controls in frontal brain areas.

Conclusions: Mental fatigue in mTBI patients seem related to both reduced brain connectivity and abnormal neuronal activation patterns in thalamic and frontal areas. Our findings indicate that quantitative fMRI measures of brain connectivity and activity can serve as markers of fatigue level in the neuronal attention system. We are now applying these methods to study neuronal dysfunction in patients with mental fatigue related to myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS).

Reference:

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Post mTBI fatigue is associated with abnormal brain functional connectivity
Sci Rep. 2016 Feb 16;6:21183. doi: 10.1038/srep21183.

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This work was founded through Karolinska Institute funds. Conflict of interest: none.

Poster 35

CFS Subject Perceptions About Emergency Department Encounters

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Background: There is little information about the experiences of CFS subjects who visit Emergency Departments (ED) for acute care of CFS – related symptoms.
Objective: Assess the quality of ED visit experiences by CFS subjects.
Methods: This on-line, cross-sectional, anonymous survey was created and disseminated using Google Forms [Rayhan, 2013]. Respondents rated overall ED experiences by ordinal 10-point scale anchored by 0="completely unsatisfied" and 10="completely satisfied." Other inquiries were anchored by 0="completely disagree" to 10="completely agree". Severities of fatigue and 8 ancillary criteria were scored as: 0 (no symptom), 1 (trivial), 2 (mild), 3 (moderate), and 4 (severe). Free text comments were codified to common themes. Respondents were grouped as those who did (EDyes) or did not (EDno) go to ED for treatment of CFS symptoms.
Results: EDyes were 59% of the 282 responses (87% female). Respondents met CFS criteria with scores of 3.5±0.2 for Fatigue, 3.3±0.5 for Exertional Exhaustion, 3.2±0.4 for Sleep, and 3.0±0.5 for Muscle Pain.
The most prevalent symptoms for ED visits were: dizziness/lightheaded (15%), general weakness (12%), diarrhea/constipation (9%), and fatigue (9%). The overall ED impression was 3.6±2.5 demonstrating general dissatisfaction. CFS subjects had an expectation that the ED should be able to treat their symptoms (7.2±3.0), but felt ED personnel were not knowledgeable about CFS (1.9±1.7). When asked,
"What would you do if you were better tomorrow?" 85% replied "I have a list of things to do."
"What happens if you walk a long distance?" 92% responded "My symptoms are worse."
"Do you tolerate alcohol?" 52% responded "I avoid alcohol because it makes my symptoms worse" and 24% "I rarely drink alcohol."
EDyes and EDno groups had equivalent responses except for ED visits. EDno respondents stated they did not go to the ED for CFS symptoms because "nothing could or would be done for them."
Conclusions: There was poor understanding of CFS by ED staff indicating an opportunity for education, perhaps using documents provided by CFS subjects. Severity Score and Attitude questions may help ED providers identify CFS. Treatment guidelines are required for self-help by CFS subjects and their primary care providers to avoid unnecessary or unproductive ED visits, and to guide ED physicians during visits for acute symptoms.

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No conflicts of interest.

Poster 36

High-order Diffusion Magnetic Resonance Imaging Identifies Different Levels of Glial Neuroinflammatory Response in a Rodent Model of Gulf-War Illness

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Background
Gulf War Illness (GWI) is a chronic disorder affecting 1990-1991 Gulf War veterans. These veterans were exposed to low-dose sarin nerve gas during their deployment that has been associated with compromised white matter integrity. An animal model of GWI was developed to assess glial activation and neuroinflammatory effects of these

exposures. GWI rats were administered corticosterone (CORT), a stress hormone, and diisopropyl fluorophosphate (DFP), a sarin surrogate. Prior results with this model showed increased neuroinflammatory cytokine signaling, altered myelination and poorer Morris water maze performance.

Objective
Our main objective was to determine if high-order diffusion MRI (hd-MRI) could be used to discriminate between different levels of glial neuroinflammatory response in a rodent model of GWI (O'Callaghan et al., 2015).

Methods
Twenty Sprague-Dawley rats were divided into 4 cohorts. Cohort 1 served as controls. Cohort 2 received CORT simulating deployment stress. Cohort 3 received the sarin-surrogate DFP and cohort 4 received both CORT and DFP. All rats were perfused 6 hours after treatment and the brains were fixed for imaging. The hd-MRI was designed to utilize more than 500 diffusion directions and different diffusion strength encodings up to 40,000s/mm^2. All images were post-processed to quantify the amount of diffusion in the brain tissue. Group comparisons were based on voxelwise statistics.

Results
Compared to cohort 1, cohorts 2-4 showed significant diffusion differences in the hippocampus, fornix and hypothalamus. Cohort 4 had more restricted patterns of diffusion in the hippocampus and hypothalamus. The largest and most wide-spread differences were between cohorts 3 & 1 in the thalamus, amygdala, piriform cortex and ventral tegmental area. Differences between cohorts 2 and 3 were in the anterior medial dorsal cortex, while differences between cohort 3 and 4 were in the medial ventral cortex and the amygdala.

Conclusion
Different levels of glia-associated responses were successfully identified from the hd-MRI applied post-mortem samples that also correlate with in-vitro models. Next we will explore the use of hd-MRI at later time points and with in-vivo models of GWI to see if we can gain further insights about the glial neuroimmune response over time and its resulting neurological effects.

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Conflicts of Interest: none

Poster 37

Disability in ME/CFS and MS: A comparative analysis of functional status and well-being in people with ME/CFS, MS, and healthy controls
Caroline Kingdon

Background

People with myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) continue to struggle to have their condition recognised as disabling in the face of public and professional prejudice and discrimination. Previous studies using the Medical Outcomes Survey Short Form-36 v2™(SF-36), a validated self-completed questionnaire commonly used to assess and monitor disease burden, have demonstrated the negative impact of ME/CFS on functional status and well-being when compared with reference populations. The SF-36 is used as a proxy for ascertaining the extent of a disability by measuring functional status and well-being in physical functioning and role, emotional functioning and role, and in overall physical and mental health using 36 generic and easily understood questions.

Methods

In this cross-sectional study with comparison groups, we compared actual SF-36 scores, collected as part of the UK ME/CFS Biobank project, of people with well-characterised ME/CFS (PWME), people with the neurological disease multiple sclerosis (PWMS) and healthy controls, Data from a separate study questionnaire provided information about employment, income and benefits. The study was largely population-based to maximise the reliability and validity of the findings.

Results

The SF-36 data from this study suggest that in almost all areas measured PWME experience greater disability than do people with MS or healthy controls. Particularly prominent and consistent in all examined age groups are lower scores for PWME in the Physical Component Summary, Role Physical, and Social Function domains. The analyses also suggest an association between PWME and lower income, consistent with a loss of functional status and well-being.

Conclusions

Disability was measurably greater in PWME than in PWMS or heathy controls in this study population using SF-36 scores as a proxy for impact of disability. Employment and income were negatively impacted and uptake of government benefit payments was increased amongst PWME. These findings should encourage public health authorities to advocate for PWME and to look at ways of improving access to employment to address the cost of the illness both to individuals and to society.

Poster 38

Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) patients' attitudes towards the use of web-based, self-report instruments for clinical evaluation

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Background:
The evaluation of patients with Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) relies on self-report instruments that assess the quality and intensity of their symptoms. The completion of paper instruments can be lengthy. Access to web-based, self-report instruments allows patients to fill them out at their own pace, decreasing the risk for cognitive fatigue during the clinical visit, as well as improving the data collection in the electronic medical record.
Objective:
To evaluate patients' attitudes towards a web-based instrument delivery system as well as their access to the Internet and possible concerns.
Methods: The study protocol was submitted and approved by our Institutional Review Board. Patients evaluated in our clinics received a voluntary and anonymous survey during their check-in process. The approximate completion time was 5 minutes for the 6-question survey. Patients only received the survey once, and data collection lasted four months.
Results:
Thirty people participated in our survey. The mean age of the participants was 49.9 years, 83% of them female, 67% white, and 33% with a graduate degree; 53% were married, and the mean number of children was 1. The most frequent employment status was disabled (43%).
Most of the participants owned at least 1 electronic device connected to the internet (97%), 80% felt comfortable filling out web instruments and 67% preferred filling out questionnaires through an online survey.
Finally, 70% of the survey participants thought that filling out questionnaires at home would have a positive impact on the quality of their clinic visit. It is important to mention that 7% of patients reported security/privacy concerns, 7% preferred paper forms and 7% will try it if the system is developed in a secure environment.
Conclusion:
Self-report web-based instruments are a viable alternative in the clinical evaluation of ME/CFS patients. Most of our participants had access to an electronic device connected to the internet, feel comfortable using these

instruments online, and think that this delivery system would positively impact the quality of their visits. Maintaining a secure online environment is essential, as well as providing alternatives for patients who are not computer-literate or do not have internet access.

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Conflicts of interest: None

Poster 39

A potential biomarker for fatigue: oxidative stress and anti-oxidative activity

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Background: We sought to determine whether oxidative stress and anti-oxidative activity could act as biomarkers that discriminate patients with chronic fatigue syndrome (CFS) from healthy volunteers at acute and sub-acute fatigue and resting conditions.
Methods: We calculated the oxidative stress index (OSI) from reactive oxygen metabolites-derived compounds (d-ROMs) and the biological antioxidant potential (BAP). We determined changes in d-ROMs, BAP, and OSI in acute and sub-acute fatigue in two healthy groups, and compared their values at rest between patients with CFS (diagnosed by Fukuda 1994 criteria) and another group of healthy controls.
Results: Following acute fatigue in healthy controls, d-ROMs and OSI increased, and BAP decreased. Although d-ROMs and OSI were significantly higher after sub-acute fatigue, BAP did not decrease. Resting condition yielded higher d-ROMs, higher OSI, and lower BAP in patients with CFS than in healthy volunteers, but lower d-ROMs and OSI when compared with sub-acute controls. BAP values did not significantly differ between patients with CFS and controls in the sub-acute condition. However, values were significantly higher than in the resting condition for controls.
Conclusions: Measures of oxidative stress (d-ROMS) and anti-oxidative activity (BAP) might be useful for discriminating acute, sub-acute, and resting fatigue in healthy people from patients with CFS, or for evaluating fatigue levels in healthy people.

Keywords: fatigue, oxidative stress, anti-oxidative activity

Poster 40

Understanding ME/CFS through the systemic actions of the bioenergetics mediator hydrogen sulfide

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Background:
Since writing my initial hypothesis on mitochondrial hypo-function and hydrogen sulfide (H_2S) in 2007, our recognition and understanding of H_2S's many biological actions in the human body, both beneficial and harmful, has increased exponentially. Emerging research has shown that this fundamental molecule is a central actor in

homeostasis whose collective actions in the body may help to explain the panoply of seemingly disparate findings in ME/CFS.

Objectives:
To provide a new perspective on ME/CFS by exploring the many links between key findings in ME/CFS and the actions of hydrogen sulfide gas throughout the body.

Methods:
This poster presentation will be based on a literature review and qualitative systematic evidence synthesis of specific key findings in CFS/ME and H_2S. Taking an integrated systems approach, the poster will provide an overview of relevant endogenous key functions such as the regulatory role of H_2S in the mitochondria, its role in hypoxia, vascular tone, signaling, muscle function, and inflammation. The results will be paired with key findings related to ME/CFS.

Results:
In the mitochondria, H_2S regulates the production of energy, DNA replication and mitochondrial transition pore opening. ATP-sensitive K^+ channels are mediated by H_2S, as is the mitochondrial carnitine/acylcarnitine carrier. Recent evidence suggests that H_2S plays a regulatory role in inflammation and vascular tone, modulates neurotransmission, induces angiogenesis, and detects cellular oxygen levels. H2S is related to mRNA increases in P2X4, TRPV1 and adrenergic receptors; CBS and CSE, two H_2S-producing enzymes, are critical for maintenance of glucocorticoid production in the adrenal cortex; H_2S confers resistance to hypoxia through its actions on the carotid body and vagus nerve; children with POTS have significantly increased levels of H_2S; and exhaled H_2S in breath has recently been proposed as a potential biomarker for SIBO in IBS. H_2S is also believed to play a role in mast cell activation, butyrate production, muscle dysfunction and disturbed sleep. All of the above have been implicated in ME/CFS.

Conclusions:
Recent specific empirical findings concerning H_2S track closely with those of CFS/ME and provide evidence for the "hibernation" hypothesis suggesting that dysregulation of this important gas could help to explain the panoply of symptoms seen in CFS/ME and co-morbid illnesses.
Focused research and testing of this hypothesis will lead to a broader and deeper understanding of the mechanisms underlying the symptoms of ME/CFS as well as the possibility of new treatments modalities.

Poster 41

A Case Study: Successful Treatment of ME/CFS Using Natural, Plant-based Antivirals
Toni E. Lesowitz, PhD

Objectives: This presentation describes my recovery from ME/CFS from which I had suffered for 29 years following acute onset of Epstein-Barr Virus (EBV) and additional infections in subsequent years. After unsuccessful treatment following a valacyclovir protocol, I made a complete recovery in 9 months using natural, plant-based methods.

Methods: Since most ME/CFS cases present with an acute, infection-like onset (Kamaroff, 1988), much ME/CFS research has focused on detecting infections. In particular, much of that research has focused on EBV as a potential trigger (Fark, 1991; Hickie et al., 2006; Jason et al., 2014a). Additional research has explored the possibility of infection caused by enterovirus (Chia et al., 2010). Yet antiviral treatments using valacyclovir have produced mixed results (Lerner et al., 2010; Strauss et al., 1988) and can, furthermore, pose safety concerns when given in high doses. I experienced this firsthand during a 9-month course of valacyclovir (3000 mg, daily) during which time I experienced severe side effects and was ultimately hospitalized. Seeking a means to treat viruses naturally without the toxicity of antiviral drugs, I turned to plant-based methods. Plants have been used as medicine for at least 60,000 years (Nunn, 2002) and were widely used by many ancient societies. Thus, I decided to experiment on myself using highly concentrated doses of specific plants thought to have strong antiviral and antibacterial properties.

Findings: I made a complete and full recovery from ME/CFS and experienced no side effects from the treatment. Laboratory tests performed at the Institute for Neuro Immune Medicine at Nova Southeastern University confirmed that I was no longer actively infected with HHV-6, CMV, or enterovirus (Coxsackie A &B) previously found through lab tests and biopsy. After being bedridden off and on for nearly 30 years I resumed normal physical activity and my other symptoms were completely resolved (e.g., cognitive impairment, insomnia, gastrointestinal distress, etc.).

Conclusions: These findings are obviously neither statistically significant nor generalizable. I am currently attempting to replicate my findings with volunteers. However, the dramatic nature of my recovery suggests that this is a worthwhile area of exploration which I would like to share with the ME/CFS community.

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My work was self-funded and thus there are no potential conflicts of interest.

Poster 42

Post-exertion malaise: Variability of symptoms within and across two studies of chronic fatigue syndrome patients

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INTRODUCTION: Post-exertion malaise (PEM) has emerged as a cardinal feature of myalgic encephalomyelitis/chronic fatigue syndrome; however, consensus for (i) an operational definition of PEM and (ii) which symptoms best characterize PEM has not been established. Potential reasons for difficulty with defining and characterizing PEM include considerable between-study and within-patient group variability for types of symptoms (e.g., fatigue, mood, pain, somatic) that are exacerbated by physical exertion. Results from two prior studies from our laboratory are compared and discussed. **PURPOSE:** To emphasize within and between study variability among two investigations that measured mood, fatigue and pain symptoms before and after a single bout of exercise. **METHODS:** Hedges' *d* effect sizes (95% CI) were calculated to examine the magnitude of symptom change after exercise and coefficients of variation (%) were calculated to examine within-patient group variability at each measurement time-point. ME/CFS patients met the Centers for Disease Control and Prevention (CDC) case definition criteria in study 1 and both CDC and Canadian Consensus Criteria in study 2. **STUDY 1:** Symptoms were measured immediately before, and 48- and 72- hours post-exercise with the Multi-Dimensional Fatigue Inventory (MDFI), a Fatigue Visual Analogue Scale (VAS), the Profile of Mood States (POMS) and the McGill Pain Questionnaire (MPQ) (CFS = 13; Healthy Controls = 11). **STUDY 2:** Symptoms were measured immediately before and 24-hours post-exercise with the CDC Symptom Inventory, the POMS and the MPQ (CFS = 15, Healthy Controls = 15). **RESULTS STUDY 1:** Large and significant effect sizes for MDFI General [1.05 (-1.94, -0.16)], MDFI Reduced Motivation [-0.93 (-1.81, -0.05)], POMS Fatigue [-0.90 (-1.74, -0.06)], POMS Confusion [-0.93 (-1.78, -0.09)] and POMS Total Mood Disturbance [-0.90 (-1.75, -0.06)] were found at 72-hours post exercise. The mean (sd) coefficient of variation (%) for all 16 questionnaire sub-scales was 53.17 (35.84), 50.34 (34.34) and 50.30 (29.77) at pre-exercise, 48-hours post-exercise and 72-hours post-exercise, respectfully. **RESULTS STUDY 2:** A large and significant effect size was found for the MPQ Total score [-0.79 (-1.54, -0.05)]. The mean (sd) coefficient of variation (%) for all 19 questionnaire sub-scales was 114.18 (57.90) and 106.22 (57.86) at pre-exercise and 24-hours post-exercise, respectfully. **CONCLUSION:** In two studies employing acute exercise, we observed considerable variability in the type and magnitude of symptom exacerbation for ME/CFS patients. Although it is clear that PEM is central to this disease, defining the phenomenon remains a significant research challenge.

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Poster 43

Humoral immunity profiling of subjects with myalgic encephalomyelitis using a random peptide microarray differentiates cases from controls with high specificity and sensitivity

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Background

Myalgic encephalomyelitis (ME) is a complex and heterogeneous illness of unknown etiology. The search for biomarkers that can delineate cases from controls is one of the most active areas of ME research; however, little progress has been made in achieving this goal. In contrast to identifying biomarkers that are directly involved in the pathological process, an immunosignature identifies antibodies raised to proteins expressed during, and potentially involved in the pathological process. Although these proteins might be unknown, it is possible to identify antibodies that react to these proteins using random peptide arrays.

Purpose

The goal of this study was to: 1) identify random peptides that are uniquely immunoreactive to antibodies from ME cases when compared against controls, 2) use these antibodies to develop a diagnostic signature, and 3) identify the naturally occurring antigens to which these antibodies specifically react with *in vivo*.

Proposal

Sera samples from 23 ME cases and 23 controls from the U.S. and Europe were used to probe a custom 125,000 random 12-mer peptide microarray, developed by the Biodesign Institute at Arizona State University. After each array was probed, processed and imaged, the top 100 immunoreactive peptides that deleniate cases and controls were used to develop a diagnostic signature. Additionally, the respective peptides were used to conduct homology searches against viral, bacterial and human protein databases.

Conclusions

Our analysis identified a series of peptides that identified cases and controls with high specificity and sensitivity. Additionally, these peptides potentially represent viral and bacterial pathogens as well as human self-antigens. Additional studies using other disease cohorts are warranted in order to establish that the immunosignature can distinguish ME cases from other chronic and neuroimmune diseases that have overlapping symptomology.

Poster 44

Cardiac Function in a Murine Model of Gulf War Illness (GWI): Combination of Organophosphate (DFP) and Exercise Training

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ABSTRACT

Background: Gulf War Illness (GWI) is a debilitating disease characterized by a cadre of neural, immunological and autonomic symptoms. We had shown that exposures to sub-lethal doses of Sarin (GB) can lead to autonomic imbalances, chronic cardiomyopathy and central nervous system abnormalities. Diisopropyl fluorophosphate (DFP), a structural analogue of GB, can be used as surrogate agent in models of neurotoxicity and neuro-inflammation. There is limited evidence on the use of DFP in murine models of GWI for the study of long lasting cardiovascular-autonomic dysfunctions.Consideration should be given on the positive influence of exercise training (ET) in the prevention of cardiac dysfunction induced by exposure to organophosphates.**Objective**: The aim of this study was to determine the effect of the DFP exposure on the cardiovascular function of mice under long term exercise training. **Methods**: Male C57BL/6J mice were divided into two groups (n=8/group): Sedentary (S) and trained (T). ET was performed on an electronic wheel at low intensity for 1 hr a day, 5 days/wk. GWI was induced by corticosterone (CORT) administration during 7 days (200 mg/l in the drinking water) followed by the DFP exposure (1.5 mg/kg, s.c). Cardiac function and ECG were assessed by transthoracic echocardiography of the mice kept under isoflurane anesthesia (2 – 2.5% on 0.8 l/min of O_2). **Results**: The sedentary group significantly reduced cardiac output, end diastolic area, end systolic area, left ventricle mass and increased E/A ratio, ejection fraction and fraction shortening after exposure. Unlike the trained mice the sedentary group needed an adaptation period to keep a normal heart function while performing the dobutamine stress test; this was reflected on an increase in both, the isovolumic relaxation time and myocardial performance index. Furthermore, the trained mice showed a significantly higher increase of the heart rate after dobutamine administration when compared with the sedentary group. **Conclusion:** Combining the uses of DFP with physical exercise provide a feasible model for the study and definition of the outcomes of the autonomic failure observed in GWI. We demonstrated that exercise training prevent deterioration of vital cardiac parameters on mice exposed to DFP.

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Poster 45

Eukaryotes in the ME/CFS gut microbiome

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Background:
Many patients with ME/CFS suffer from gastrointestinal symptoms. Our lab has demonstrated a decrease in the diversity of prokaryotes present in ME/CFS patient gut microbiomes and increases in pro-inflammatory species. Additionally, we have shown increases in biomarkers that indicate an inflammatory state and possible leaky gut in patients. The human gut microbiome is also comprised of a small proportion of eukaryotic microorganisms that interact with prokaryotes and can be either commensal or pathogenic.

Objectives:
We characterized eukaryotic microorganisms present in the gut of ME/CFS patients and healthy individuals to determine whether they differ in composition and/or diversity.

Methods:
DNA was extracted from stool samples of 17 patients diagnosed with ME/CFS under the Fukuda criteria and 17 healthy individuals. The V9 region of the 18S rRNA gene was amplified according to the Earth Microbiome

protocol. Products were sequenced on the MiSeq platform. The QIIME pipeline was used to check sequence quality, pick open reference operational taxonomic units, and compare diversity and abundance of taxa. Taxonomy was assigned via BLAST against the SILVA 123 database.

Results:
ME/CFS patients and healthy individuals show comparable gut eukaryotic diversity, as measured by several indices of alpha and beta diversity. The majority of taxa identified were fungal, but also included Stramenopiles such as *Blastocystis*. Differences in abundances of specific taxa did not reach statistical significance. Patients and healthy individuals had similar relative abundance of fungi, but abundances of specific fungal phyla differed. Patients displayed increased Basidiomycota and decreased Ascomycota. As a result, the ratio of Basidiomycota to Ascomycota was increased in ME/CFS versus healthy individuals.

Conclusion:
ME/CFS patients exhibited a shift in the ratio of Basidiomycota to Ascomycota fungal phyla higher than that of healthy individuals. This ratio has previously been reported to increase during flares of Irritable Bowel Diseases, but return to healthy levels during remission, suggesting a correlation with inflammation. Overall, our results are consistent with an existing inflammatory state in ME/CFS.

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Poster 46

Detection of citrullinated protein antibody signature in ME/CFS

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Objectives. Chronic Fatigue Syndrome (CSF)/Myalgic Encephalomyelitis (ME) is a disease marked by post-exertion fatigue and delayed recovery. Recent studies suggest an auto-immune component to the disease that may promote intracellular metabolic dysfunction contributing to chronic fatigue. A potential mechanism involves citrullination (enzymatic conversion of arginine to citrulline) of intracellular proteins. This modification, in turn, may be targeted by the patient's immune system, akin to rheumatoid arthritis (RA). We tested the hypothesis that blood plasma from CFS/ME patients (n=105) contain a significantly higher titer of anti-citrullinated protein antibody (ACPA) compared to age-gender matched controls without CFS/ME (n=65).
Methods. Plasma samples from the Solve CFS Bio Bank were measured for IgG1 and IgG4 isotypes of anticyclic citrullinated peptide (ACCP) antibodies using an enzyme-linked, immunosorbent assay (ELISA). Group means were compared with ANOVA with age included as covariate. To eliminate the potentially confounding effects of age and gender, paired analyses using 39 age-gender matched strata were created (post-blind) for a conditional logistic regression (CLR) analysis.
Results. Unadjusted group mean ACPA titer levels (mean ± SE) for IgG1 were 12.0± 4.3 and 11.3±3.4; for IgG4, 8.7±2.0 and 6.8±1.6, for controls and patients, respectively. The CLR slope of IgG4 isotype titer comparing ME/CFS to controls revealed a significantly greater probability (p=0.02) that elevated IgG4 predicts a ME/CFS patient vs. a control subject, with an Odds Ratio of 1.113 per unit change in IgG4. For example, a sample with an IgG4 level of 10 indicates that the sample is 2.6 times more likely to be from a ME/CFS patient than from a control subject.
Conclusions. ME/CFS patients are significantly more likely to have elevated IgG4 ACPA titers compared to healthy controls. While limited sample size and high variability may have obscured differences in group means, CLR analysis supports our hypothesis that citrullination of a systemic protein is associated with ME/CFS in some patients. The presence of ACPA in controls suggests multiple factors may influence ACPA. Future studies may

benefit from use of CCP with citrulline-flanking amino acids matching protein(s) of interest to enhance the selectivity/sensitivity of the ACPA assay.

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Poster 47

A Metabolomic and Genetic Analysis of Post Exertional Fatigue in Patients with ME/CFS

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Post exertional fatigue (PEF) is significant limiting event noted in most patients with Chronic Fatigue Syndrome (MECFS). The aim of this study was to assess the metabolomic changes associated with reporting of PEF. Forty-seven MECFS patients and age/sex matched controls had: a clinical examination, completed questionnaires, standard serum biochemistry, glucose tolerance tests and serum, fecal and urine metabolomes in an observational study. Increases in PEF were associated with increases in reporting of febrile events (p<.008), diarrhea (p<.01), muscle weakness (p<.007) and avoiding physical activity (p<.006). Increased PEF also correlated with the adenosine breakdown product, hypoxanthine, in serum (p<.01) and increased levels of uracil (p<.001) in the fecal metabolome. The pattern of change suggesting a failure to transport the nucleotide from the gastrointestinal tract and reabsorb it in the kidney may indicate a potential nucleotide transport nucleotide anomaly in ME/CFS patients. In a separate study group (14 ME/CFS vs 24 Controls) we investigated the SNP mutations within the nucleosome transport genes SLC28A(1 to 4) and SLC29A(1&2). Increases in SLC29A1 rs9394992 (p<.02) and rs324148 (p<.001) were 6 fold more likely to be found in the ME/CFS group, with combined carriage of both mutations within the SLC29A1 gene being 5 fold more frequent in the ME/CFS patients (p<.001). Mutations in SLC28A1 were 7 to 11 fold more likely to be present in the controls: rs3743162 (p<.01); rs12910245 (p<.008); rs12916177 (p<.008). No mutation differences were detected for SLC29A2, SLC28A2, A3 or A4. A reduction of SLC29A1 RNA production (down to ~40% of normal) appears consistent with a reduction in the ability to transport nucleosides. These mutations may represent part for the basis for the development of post exertional fatigue within ME/CFS patients. Well-designed studies evaluating the association ME/CFS symptom expression are warranted.

Poster 48

Exercise-induced Changes in Salience Network Connectivity and Insula Activity During Interoceptive Awareness; An fMRI Case Study

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Background: Gulf War Illness (GWI) affects multiple regulatory systems, debilitating fatigue, cognitive impairment, pain and autonomic dysfunction. Acute exposure to Sarin have reduced gray matter volume in the right insular and temporal cortices compared with control (Yamasue et al., 2007). The insula plays a crucial role in the interception signals from our body (Crithcley et al., 2004); elevated activity is associated with memory impairment in GWI subjects following an exercise challenge (Rayhan et al., 2013). We hypothesized functional magnetic resonance imaging (fMRI) of the right anterior insula during an interoceptive awareness task and resting state fMRI of the salience network would change following an exercise challenge.
Methods: Patient was a 44-year-old female veteran experiencing: arthralgias, non-restorative sleep, and induced seizures. MRI Scan: GE®MR750 3.0T with a 32-channel head coil. After the resting state scan, the subject performed 3 interoceptive awareness tasks consisting of; attending to heart rate, attending to a tone, and attending to heart rate while ignoring a tone. Approximately 1.5 hours after baseline scan the participant completed an exercise challenge and returned for a second scan 5 hours after baseline.
Results: During an interoceptive awareness task shown to evoke activity in the anterior insula (Zaki et al., 2012), activity shifted from the right anterior insula (RAI) to bilateral interior frontal gyri after an exercise challenge. Resting state connectivity of the RAI was compared and prior to the exercise a robust connectivity was present between the RAI and the salience network, i.e., medial prefrontal cortex (MPFC) and anterior cingulate (ACC). Following exercise challenge the connectivity of the insula with the MPFC was reduced and a pattern of negative

connectivity was observed with the ACC and greater positive connectivity emerged with the left inferior frontal gyrus.
Conclusion: These findings suggest that exercise challenge diminishes interoceptive awareness in a female veteran with GWI as a function of reduced salience network connectivity via the RAI. After the challenge the patient showed greater engagement of cognitive centers to process internal bodily state. Impaired salience network functioning may explain some of the autonomic and visceral complaints as well as cognitive deficits post-exercise.

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Poster 49

B cell function in patients with Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS): Investigations of metabolic function during B cell maturation and differentiation
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Objectives: Fatigue in autoimmune rheumatic diseases is associated with cytokine production secondary to inflammation. The fatigue experienced by patients with ME/CFS differs in that there is no frank inflammation and it is induced by both physical and mental stressors. Due to the success of rituximab, removal of pathogenic B cells and their antibody products are proposed to play a role in ME/CFS. We have hypothesized that dysregulation of metabolic re-programming may disrupt appropriate B cell responses. In our initial extended B cell phenotype studies (Clin exp Immunol, 2016) we identified differences in ME/CFS patients from age-matched controls, notably increased expression, or possibly retention, of the adhesion molecule CD24 on naïve B cells and also changes in memory B cell populations. Here, *in vitro* studies were used to measure mitochondrial mass, proliferation and differentiation of B cells in response to cytokines, T-dependent (TD) and independent (TI) stimuli.
Methods: Eight ME/CFS patients (diagnosed by Canadian, CDC and Fukuda criteria) and 4 healthy controls (HC) were included. Flow cytometry was used to distinguish B cell subsets and examine proliferation (CFSE) and mitochondrial mass (MitotrackerRed; MTR). MTR accumulates in mitochondria in live cells, dependent upon intact cell membrane potential. B cell differentiation was measured through loss of soluble CD23 (sCD23) and maturation using IgM in culture supernatants.
Results: CD24 expression decreased with B cell differentiation after both TD and TI stimuli but not after exposure to the B cell cytokine, BAFF. This was in parallel with sCD23 production. At baseline there was lower mitochondrial mass in naïve compared to memory B cells, which after *in vitro* culture with TD or TI stimuli, increased compared to memory B cells, indicating increased energy requirement of naïve B cells which was not required for memory B cells. When PBMCs from HC were compared with ME/CFS patients there was a significantly higher mitochondrial mass in switched memory B cells (P=0.042) when cultured with BAFF. Upon stimulation, mitochondrial mass was similar in patients and controls. TI simulation resulted in the greatest proliferation and IgM production, but had a lower mitochondrial mass compared with TD stimulation.
Conclusion: These studies confirmed that, as *in vivo*, CD24 expression decreases with B cell differentiation. Our findings suggest that different metabolic pathways of energy requirement operate during B cell maturation. The particular pathway used reflected the route of activation/stimulation (TI or TD). We have also established an *in vitro* system to compare the metabolic function of B cells from ME/CFS patients with HC.

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Poster 50

Patient Satisfaction with Symptom Disclosure to Partners and Dyadic Consensus Relate to Better Cortisol Diurnal Regulation in Women with CFS/ME

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Background: Chronic Fatigue Syndrome (CFS/ME) may tax patients' intimate relationships, especially increasing partner caregiving burden due to disability and unemployment. Lack of dyadic satisfaction and couple-based coping strategies for communicating support needs may exacerbate patient symptoms via alterations in interpersonal stress. HPA axis dysfunction, as operationalized by diurnal cortisol slope, an index of stress, may be related to these interpersonal factors in this population.

Objectives: To estimate the indirect effects of dyadic adjustment on HPA axis functioning via patient satisfaction with disclosing their CFS/ME symptoms to partners.

Methods: Baseline data were drawn from CFS/ME women (N = 85), diagnosed by a physician using the CDC-Fukuda criteria, participating in a study testing the efficacy of a patient-partner dyadic group stress management intervention trial. The degree to which the members of each patient-partner dyad were compatible on lifestyle-related matters was measured by the dyadic consensus subscale of the Dyadic Adjustment Scale. Patients also reported their ability to express their symptoms to their partner and feel supported (Patient Symptom Disclosure Satisfaction, PSDS). Cortisol was measured by ELISA from saliva collected at four time-points for two days. Bootstrapping was used to estimate indirect effects by the PROCESS macro in SPSS. Age, education, and BMI were entered as covariates.

Results: Dyadic consensus related to diurnal cortisol slope indirectly through PSDS (b=-0.0016, se=0.0013; 95% Bootstrapped CI: -0.0052 to 0.0002), such that greater dyadic consensus was associated with better PSDS (b=0.2287, se=0.0806, p=0.0057), and PSDS was associated with a more negative diurnal cortisol slope (b=-0.0072, se=0.0040, p=0.0029). The total effect of dyadic consensus on diurnal cortisol slope via better PSDS was significant (b=0.0077, se=0.0029, p=0.0105) with the model accounting for 11.5% of the variance in cortisol slope, $F(4,80)=2.587$, p=0.0430, $R^2=0.1145$.

Conclusion: Results highlight that the overall quality of the couple's relationship, via more satisfying dyadic illness-related communications, may affect HPA axis functioning, which has been implicated in greater emotional distress and exacerbating CFS/ME-related symptomatology. Future research is needed to evaluate the bio-behavioral effects of interventions that target couple-based coping strategies in CFS/ME.

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Poster 51

Student and Faculty Knowledge and Perception about Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS)

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Background
Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) is a serious disease that significantly impairs physical/cognitive function and quality of life. Millions of people are affected but the majority have not been diagnosed. There might be a knowledge gap about ME/CFS in the medical community. Increasing awareness in this population may improve clinical care by enhancing diagnosis and access to treatment.
Objective
To assess the knowledge and perception about ME/CFS in medical students and Faculty of a South Florida University.
Methods
We designed an anonymous survey to assess the knowledge and perception about ME/CFS. The survey consisted of a case study, 17 questions assessing knowledge (maximum 100%), and 8 questions assessing perception about ME/CFS.
Upon approval from our Institutional Review Board, we distributed the survey through email.
Data on demographics and degree of training were collected. Statistical analysis included descriptive statistics and comparison of results using ANOVA.
Results
One hundred and five people replied the survey, 72% students and 25% Faculty (3% blank). The majority of students were in their second year (62%). The majority of Faculty held a PhD degree (37%), DO (15%), and MD (7%). Among respondents, mean knowledge score was 70%, very similar between students (69%) and Faculty (73%). The lowest scores corresponded to the sections on treatment (46%) and prognosis (45%). We found no significant difference between students (from first to fourth year of training) and Faculty (without difference according to their degree). The majority of respondents (78%) were interested in learning more about ME/CFS, 70% agreed that ME/CFS should be a part of the medical school curriculum, and 79% agreed more research on etiology/pathophysiology of ME/CFS is needed.
Conclusion
We found good knowledge of ME/CFS among responders, yet without a growing curve from medical students to Faculty, and a general knowledge gap in ME/CFS treatment and prognosis. Furthermore, the majority agreed more education in medical curriculum was needed, and expressed interest in learning more. Our findings suggest the need to incorporate ME/CFS in medical school curriculum.

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Poster 52

Plasma homocysteine levels and circulating microRNA profiles in patients with ME/CFS

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Background: Given the clinical heterogeneity of ME/CFS disease and gender differences, its etiology is not well understood while progression varies among individuals. There is relatively little known regarding validated biomarkers for ME/CFS.

Objectives: We investigated whether alterations exist in the plasmatic levels of specific biochemical factors and circulating microRNAs in ME/CFS patients.

Methods: A prospective study including French-Canadian patients (n=98, 79F+19M) who fulfilled the diagnostic for ME/CFS, according to the Canadian Consensus Criteria, were analyzed and compared to age- and gender-matched healthy controls (n=50, 20F+30M). Plasma levels of different biochemical markers were evaluated by ELISA methods. The circulating miRNA expression profile was analyzed by hybridization array using the Agilent expression array-Human miRNA 8 x 60k. Starting material was extracted from platelet-poor plasma obtained from a discovery panel, using the miRNeasy kit (Qiagen). This panel consisted of ME/CFS patients (n=11, 9F+2M) and healthy controls without familial antecedents of ME/CFS (n=7, 5F+2M). Agilent GeneSpring™ software was used to perform clustering analyses to identify microRNAs differentially expressed between ME/CFS and controls. An expression difference greater than or equal to 2-fold, with a false-discovery rate ≤ 0.005 was considered significant.

Results: Among the several biomarkers tested, the mean plasma homocysteine (HCY) levels were significantly increased in a subset of ME/CFS patients when compared to controls ($p < 0.05$; Student's t-test two-tails equal variants). The average values were 30±18 µmol/L and 7±3 µmol/L for high HCY ME/CFS (17F+5M) and low HCY ME/CFS (62F+14M) subgroup respectively (using a 16µmol/L cut-off), when compared to the matched healthy controls (10±8 µmol/L, 20F+30M). There was no age or gender difference in either ME/CFS subgroup. Interestingly, we identified distinct microRNA profiles associated with each ME/CFS subgroup, suggesting that changes observed in plasma HCY could be related to epigenetic effects.

Conclusions: Elevated levels of HCY have been previously reported in the cerebrospinal fluid of patients with fibromyalgia and ME/CFS (Regland et al. Scand J Rheumatol. 1997; 26 (4):301-7), and correlated with fatigability. Our preliminary data strongly suggests that microRNAs could play an important role in the elevation of circulating HCY levels in a subset of ME/CFS patients.

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Poster 53

Evaluation of cytokine activity in New Zealand patients with ME/CFS compared with controls and their responses to exercise

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Background

Post exercise malaise is a characteristic of ME/CFS compared with other fatigue illnesses. The molecular basis has not been well characterised, but can be documented using exercise physiology parameters during repeated incremental exercise tests. Comprehensive molecular analysis could complement these measurements in small patient cohorts to gain deeper insight into the malaise.

Objectives

My study aimed to measure plasma cytokines and how they change with exercise. This is part of a more comprehensive study that will analyse cytokines molecules before and after exercise. A Dunedin pilot study was evaluated as a predictor of ME/CFS patients in a Palmerston North cohort.

Methods

Independent pre-clinical cohorts of patients with ME/CFS and healthy matched controls were recruited in two different communities: 1. The "Dunedin Pilot study", with 10 ME/CFS who were diagnosed via the Canadian

Consensus Criteria 2004 and 10 controls, and 2. The Palmerston North "Exercise study", with 10 ME/CFS who were diagnosed via Fukuda (1994), Canadian (2004) and International (2011) criteria, 10 healthy controls and a small sub group of 5 Multiple sclerosis patients. Cardiovascular physiology parameters and blood samples were taken at three separate times (i) Prior to physical activity, (ii) immediately after and (iii) 24 h later after re-exercise. The Bio-Plex™ Human Cytokine 27-plex Assay (Bio Rad) was used for cytokine analyses, data were quantified using Linear models for independent data, mixed linear models for comparison of non-independent data. Paired *T* test were performed.

Results

Cytokines; IL-7 (P^*>0.004), IL-13 (P^*>7.41x10-^{5}), IP-10 (P^*>0.015) and VEGF (P^*<0.044) were significantly different between ME/CFS, MS patients and controls. With exercise, six cytokines were found to behave significantly differently in controls, but this was not found in ME/CFS or MS patients.

Conclusions

ME/CFS patients cytokines behaved differently from controls. On exercise ME/CFS patients did not show the expected changes found with initial group.

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Poster 54

Development of a recumbent isometric yoga program for patients with severe CFS/ME: A pilot study on feasibility and efficacy

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Background: Our previous randomized controlled trial demonstrated that isometric yoga in a sitting position reduces fatigue in patients with chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME) (Oka T et al., Biopsychosoc Med 2014). However, some patients experience difficulty sitting for long periods and practicing isometric yoga in a sitting position. So far, therapeutic interventions for patients with such severe conditions have not been established. Therefore, we developed a 20-min recumbent isometric yoga program for patients with severe CFS/ME to reduce fatigue. **Objectives:** The aim of this study was to assess the feasibility, safety, and usefulness of this program. **Methods:** This study included 14 adult patients with CFS/ME who met International Consensus Criteria 2011. Seven patients were reluctant to practice isometric yoga in a sitting position because of the severity of their fatigue (group 1). Another seven patients had previously practiced isometric yoga in a sitting position (group 2). Both groups practiced recumbent isometric yoga biweekly with a yoga instructor and in daily in-home sessions for 3 months. The short-term effects of isometric yoga on fatigue were assessed by the Profile of Mood Status (POMS), a self-rating questionnaire, immediately before and after the final session with the yoga instructor. The long-term effects of isometric yoga on fatigue were assessed by administration of the Chalder's Fatigue Scale (FS) questionnaire before and after the intervention period. Adverse events, satisfaction, and preference were also recorded. **Results:** All subjects completed the intervention. The mean POMS fatigue score was decreased significantly after practicing 20-min yoga program in both groups 1 and 2 (from 21.9 ± 7.7 to 13.8 ± 6.7, P<0.001, both groups). The Chalder's FS score was also decreased significantly after the 3-month intervention period in both groups (from 25.9 ± 6.1 to 19.2 ± 7.5, P=0.002, both groups). There were no serious adverse events. All subjects in group 2 reported that they preferred the recumbent isometric yoga program to the sitting program. **Conclusions:** Recumbent isometric yoga is both feasible and successful for relieving fatigue in patients with CFS/ME, even those who experience difficulty practicing isometric yoga in the sitting position.

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3. The authors declare no competing interests.

Poster 55

Acceptance and Commitment Therapy for ME/CFS (Chronic Fatigue Syndrome) – an open case pilot study

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Background
Medical strategies alone appear insufficient to increase functioning and quality of life in ME/CFS. Cognitive behavioral therapy (CBT) is the only treatment approach with preliminary evidence of efficacy for improving functioning and quality of life. However, effect sizes are generally modest.
Behavior medicine treatment approaches based on Acceptance & Commitment Therapy (ACT) have gained increasing attention and research support within clinical trials for similar diagnoses (e.g. chronic pain, Fibromyalgia). Results from these areas illustrate the utility of this approach for individuals with somatic symptomatology. To date, the efficacy of ACT has not been evaluated for ME/CFS.

Purpose
The aims of this on-going pilot study are to explore the utility of ACT and to evaluate the feasibility of the treatment model for patients with ME/CFS.

Method
Treatment program: 13 weekly individual ACT sessions with a psychologist (10) and a physician (3) respectively. An open trial design is used, with assessments at pre-, mid- and post-treatment as well as at 3, 6 and 12 months follow-up.
Measures: History data, illness factors, psychological factors, functioning and quality of life.
Patients: Consecutively recruited via referrals to a specialist treatment centre *(n*=43).
Statistical analysis: Paired-samples t-test and Cohen's *d* for effect sizes. Multilevel analyses are planned to investigate treatment moderators and mediators.

Results
The poster will present results from approximately 30 patients. However, preliminary analyses indicate significant improvements seen from pre- to post-assessment in ME/CFS-related disability (t (21) = 3.524, p.=,002, *d* = 0.50), and a significant decrease in psychological inflexibility (t(21) = 5.377, p.=,000, *d* = 1.26).

Conclusion
Although preliminary, results indicate that an ACT-based behavioral medicine treatment approach may be effective in improving functioning for patients with ME/CFS.
Further analyses regarding preliminary efficacy, mediators and moderators, as well as feasibility will be carried out during autumn 2016.

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Novel isoform of Ribonuclease L

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Background: The innate immune system component: 2´-5´-oligoadenylate (2-5A)-dependent Ribonuclease L (RNase L), is a key enzyme in the interferon induced antiviral and anti-proliferate pathways. Deregulation of this pathway in chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME) patients leading to the production of a truncated overactive form of about 37 kDa has been reported. Fibromyalgia (FM) patients often present CFS/ME comorbidities; however, the presence of RNase L isoforms has not been evaluated in patients diagnosed with FM. In addition, the possibility of alternative RNase L isoforms product of alternative splicing events which could lead to defective immune-deficiencies is quite unexplored in the literature.
Objectives: To explore the presence of endogenous RNase L isoforms in PBMCs of participants by RT-PCR amplification and western blot analysis and determine the relative abundance of RNase L isoforms in a local cohort of FM patients presenting comorbid chronic fatigue as a potential criterion for FM patient subgrouping.
Methods: *Study population*- FM patients (ACR 1990 criteria) presenting persistent chronic fatigue [>6 month, multidimensional fatigue inventory (MFI)-assessed] (n=72) and a group of population-age-matched healthy controls (n=43). *PBMCs isolated by standard Ficoll-Paque Premium procedures*- were analyzed by western blot analysis and RT-PCR amplification using anti-human-RNase L antibodies (2E9.2G5, sc-23955 and E9, sc-74405, Santa Cruz Biotech), the later raised to C-t aas 442-741, or a custom-made antibody against a 17-aa KLH-synthetic peptide (MSKLRHRQIIFPTTQNQ) in the western analysis; and forward primers CATCTACCTGGGGTTCTATGAGAAGCAAG or GAAGCGTGTTTGGATGTGCACAGAG (exon2) together with reverse primer ACCAGCTCCATCACACTGAGGC (exon 7) or GGTCTGCCAATCTCTGACTGTCCAG (exon 6´) in the RT-PCR studies.
Results: The formerly described 37 kDa RNase L isoform was detected by western blot of either patient or control PBMC extracts. Significant 37/83 kDa isoform ratio differences were found between patient (n=63) and control groups (n=43) (p=0.04). However, large inter-individual variability and clustering of high ratio values in the patient group were observed, questioning its validity as a biomarker in our study group. Interestingly, a novel band of about 70 kDa was noticed in the patient group that could be originated by activation of an alternative cryptic site in intron 5, leading to a C-t truncated form as it seems to suggest the results of RT-PCR analysis of patient PBMC total RNA. Striking statistical significant differences ($p<0.0001$) between the patient (n=62) and control (n=41) groups were established. A custom-made antibody raised against the carboxy-terminal end of the hypothetical RNase L 70 kDa isoform has been successfully obtained as confirmed by western-blot analysis of HEK293 transfected with the human RNase L alternatively spliced cDNA construct obtained from FM patients.
Conclusions: Although significant differences between the 37/83 kDa ratio were obtained between the two groups, large inter-individual variability and clustering of high ratio values in the patient group lead us to propose the 37/83 kDa isoform ratio as a criterion for patient subgroup assessment rather than a disease biomarker. On another hand, a novel RNase L alternative transcript was identified by RT-PCR amplification of total RNA from FM patient PBMCs. Interestingly enough, western blot analysis of PBMC extracts showed the presence of a novel 70 kDa band which could derive from this alternative transcript mostly in the patient group ($p<0.0001$). Further analysis to unequivocally identify the detected 70 kDa band as an RNase L isoform and/or confirm its use as a molecular marker of the disease state in FM/CFS patients are warranted. We count with a custom-made antibody which might constitute a useful tool towards this end.

Poster 57

An evaluation of resilience interventions as a mechanism for burnout prevention in complex chronic disease health professionals

J. Pascoe

Background:
Though burnout is well-studied in health care literature, no previous research has assessed burnout levels of health professionals in the complex chronic diseases field. Generally, burnout rates in health professionals tend to be higher than in the general workforce with some studies reporting rates between 41%-76%. Thus interventions to prevent burnout in this population are increasingly important. Many mechanisms have been explored previously including psychosocial interventions, and solution-focused training. The present evaluation reports findings of a pilot intervention that uses a resilience framework to prevent burnout in Complex Chronic Diseases Program (CCDP) staff at the British Columbia Women's Hospital + Health Centre. CCDP staff work primarily with marginalized populations who often face mental health challenges that staff were not adequately equipped to handle. In response to high burnout, sick time and turnover rates, a resilience building program was implemented.

Objectives:
Higher resilience has not only been linked to better staff QOL, but also better patient care. This evaluation examines whether introducing resilience-based interventions is effective for preventing burnout, and reducing sick time and turnover.

Methods:
The program consists of four components: team education, care planning, daily huddles and rounds which target competence & confidence, self-awareness, communication, and positive outlook respectively. A utilization-focused outcomes evaluation was selected. All staff members (n=17) participated. Using a mixed methods approach, quantitative information was collected from staff records and the Maslach Burnout Inventory (MBI) while qualitative information was collected through a semi-structured interview. The MBI determined burnout scores, and the qualitative interview assessed perceived program utility. Analysis of sick time and turnover will be carried out on R software (Version 0.99.484) using data from the years prior to the intervention and one year after program implementation. Only posttest data is available for the MBI, however, by using a retrospective pretest design on qualitative interviews, pretest burnout information will be available. Qualitative analysis will be carried out using NVivo.

Results:
An evaluation of the interventions done indicate an increase in staff resiliency post-implementation. While all interventions implemented demonstrated an increase in resiliency, the addition of focused time on care planning and debriefing for complex cases showed the most benefit. Having structured time that is adaptable to the needs of the care team provides a safe environment to process their experience while ensuring that they are able to continue to provide care. Results also indicate the need to adapt interventions on an ongoing basis to ensure they continue to support clinicians in this area.

Conclusion:
Building staff resilience could result in improvements in burnout and ultimately patient care.

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3. None.

Poster 58

Psychosocial Impact of Memory Problems in patients with Chronic Fatigue Syndrome: The VideoHealth Study

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Background: Difficulty in cognitive functioning is a common problem reported by patients with Chronic Fatigue Syndrome (CFS), however evidence on how memory problems affect their mood and daily activities has not been consistently reviewed.
Objectives: Present preliminary data from the VideoHealth Study, a 4-year randomized technology-based intervention study for individuals with CFS and their partners.
Methods: A total of 156 CFS patients completed a baseline battery which included a demographics questionnaire, a shortened version of the Memory Functioning Questionnaire (MFQ), the Sickness Impact Profile (SIP) and the Center for Epidemiologic Studies Depression Scale (CES-D). Descriptive statistics were used to summarize responses to these measures. Based on MFQ responses, a Frequency of Forgetting Score (FFS) was calculated for each participant. Pearson's r was used to calculate the correlations between FFS and the participant's levels of social interaction, engagement in leisure activities, and symptoms of depression.
Results: The study sample was composed mainly of Caucasian (64%), women (87%), with a mean age of 48, who were unemployed (54%), with post-high school education (98%). Nearly 93% of the study sample reported experiencing memory problems, ranging from some minor problems to major problems. Most participants described difficulties in remembering things they had just read (79%) and events that occurred in the past (90%). The most frequent problem cited among participants was forgetting words (92%), followed by forgetting names (91%). Nearly 88% considered their memory problems to be serious and 96% reported using memory aids and/or mnemonics to help them remember information. Higher frequency of forgetting (a lower MFF score) was correlated with higher scores of social isolation ($r=-0.386$, $n= 152$, $p<0.001$) and reduction in engaging in leisure activities ($r=-0.247$, $n=152$, $p =0.002$). Analyses on the correlation between the FFS and symptoms of depression revealed a significant correlation between higher frequency of forgetting and higher scores on the CES-D questionnaire ($r=-0.495$, $n= 150$, $p<.001$).
Conclusion: A significant number of CFS patients reported having memory problems that interfere with their ability to engage in social activities and affect their mood. CFS patients with memory problems are particularly at risk of being

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Poster 59

ME/CFS Genes Study: Identifying SNPs frequencies in Genetic Data of De-Identified ME/CFS Patients.
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Background: ME/CFS is a debilitating disease with unknown causes. It is known that single nucleotide polymorphisms (SNPs) play an important role in gene expression changes that can manifest as phenotypic changes. Prior to this ongoing study, there existed no known databases of SNPs in patients diagnosed with ME/CFS.

Objective: Our objectives are to create a novel database of SNPs that are specific for ME/CFS patients, and to identify the relative frequency in our cohort of specific SNPs warranting further research.
Methods: A genetic database was created on-site through the use of a secure user-friendly online platform, REDCap©, for participants to upload their raw genetic data, acquired from 23andMe. The uploaded de-identified genetic data acquired from RedCap are modified to a suitable format for *Seattle Sequence Annotation 138.* The annotated data is then filtered to include only SNPs from protein coding regions (exons), microRNAs, and SNPs that are close to splice sites. Then, data was filtered to include only nonsense and non-synonymous SNPs. The frequencies of each SNP will then be calculated within our cohort, compared to public databases and those SNPs of differing prevalence will be noted for future analysis.

Results: Ongoing recruitment for submission of de-identified genetic data leads to a constantly increasing sample size for continual application of the aforementioned method. Additional investigation of the larger sample size will allow for validation of SNP trend significance relative to existing SNP data acquired from public databases of the general public.

Conclusion: The combination of survey questionnaires and SNPs identified will allow us to create subgroups of those diagnosed with ME/CFS to then look for further biomarkers of disease that may determine if a genetic component exists in patients.

Poster 60

Cerebrospinal Fluid MicroRNA (miRNA) in CFS and Gulf War Illness (GWI)
James N. Baraniuk, Narayan Shivapurkar

Background: miRNAs (~22 nucleotides) bind to mRNA and inhibit translation. Their roles are not defined in CFS or GWI.
Objective: Determine the spectrum of miRNAs in cerebrospinal fluid.
Methods: Cohort 1. Sedentary control (SC, n=23), CFS (n=41) and GWI (n=22) subjects had lumbar puncture (LP) at rest (without previous exercise). Cohort 2. Submaximal bicycle exercise distinguished GWI phenotypes with postural tachycardia after exercise (Stress Test Activated Reversible Tachycardia, START) or increased magnetic resonance imaging signal in anterior insula (Stress Test Originated Phantom Perception, STOPP). LP were performed in SC (n=7), START (n=7) and STOPP (n=16). Quantitative PCR was performed for 384 miRNAs using 0.5 ml aliquots. Six miRNAs present in all specimens were used as a normalizer for ΔΔCt quantification. PCR cycle counts (Ct) >35 were considered "undetectable."
Results: Cohort 1. There were no differences in miRNA expression between SC, CFS and GWI groups at rest. Cohort 2. Exercise induced significant differences in miRNA expression START had 16 miRNAs with higher levels than STOPP and/or SC (START>STOPP, START>SC, SC&START>STOPP conditions). The STOPP>START condition had 2 miRNAs. SC>START had 1 miRNA, and SC>STOPP had 3. Informatics analysis linked miRNA combinations to functional pathways and gene clusters that inferred augmented function of transforming growth factor beta (TGFB) in GWI, receptor tyrosine kinase and mitogen activated protein kinase (MAPK) in STOPP, and 14-3-3 proteins in START. Phosphatidylinositol enzymes and receptors were repressed in START. The inferred molecular pathologies of START and STOPP phenotypes were as different from each other as they were from controls.
Conclusions: This independent line of evidence supports on-going choroid plexus and brain neurotoxicity mechanisms in these GWI phenotypes. Exercise was an essential perturbation to reveal pathophysiological differences. Searches for biomarkers and mechanisms of disease are likely to be fruitless unless efforts are made to phenotype and classify GWI subsets using objective criteria instead of subjective clusters of symptoms. The same caveats apply to evaluation of CFS, where standardized triggers of dysfunction may be needed to reveal pathological changes and mechanisms of post-exertional exhaustion.

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Poster 61

Are symptoms of 'hypoglycemia' in Chronic Fatigue Syndrome (CFS) associated with hypoglycemia or orthostatic intolerance in young people?

Katherine Rowe, Rebecca Gebert, Susan Donath, Angas Hamer & Fergus Cameron

Background:
Symptoms of nausea, feeling faint, malaise and mild anxiety are common in young people with CFS and popularly attributed to 'hypoglycemia' resulting in various dietary interventions with little reported improvement.

Objectives:
To determine whether the symptoms are associated with measured hypoglycaemia using continuous tissue glucose monitoring or whether these symptoms are associated with documented orthostatic intolerance.

Methods:
Nine young people with CFS (mean age 20 years) and mean duration of 4.5 years with persistently troublesome symptoms were compared with 10 healthy adult controls without diabetes. Each subject agreed to 3 days Continuous Glucose Monitoring System (Medtronic CGMS). This is routinely used in adolescent diabetics to document food intake, tissue glucose levels and activity levels to monitor control.
Subsequently 8 of these had formal cardiac tilt table testing where heart rate and blood pressure are measured supine and during 70 degree head-up tilt for up to 10 minutes to assess the presence orthostatic intolerance (either postural orthostatic tachycardia (POTS) or neurocardiogenic hypotensive syndrome). If positive, appropriate medical management of increasing salt and fluids, gentle improvement of muscle tone and blood pressure support medications, was implemented.

Results:
The tissue glucose was calibrated with the blood glucose and all fell within acceptable normal range. There was statistical (but not clinical) significance in average tissue glucose in CFS subjects. 6% of time in controls and 16.8% in CFS was spent in the range <4mmol/L glucose (95% CI -23% to +2%, p=0.1) suggesting weak evidence for a difference given the variability and small sample size. The reported presence of symptoms throughout the day was not associated with significant reduction in tissue glucose levels.
Six had confirmed evidence for POTS, one for neurocardiogenic syndrome and one for a combination of both. All 8 reported improvement in all symptoms especially nausea, dizziness and malaise with active treatment of their orthostatic intolerance.

Conclusion:
This study could not confirm a link between putative symptoms of 'hypoglycemia' and documented hypoglycemia. This suggests that symptoms frequently attributed to 'hypoglycemia' may be due to orthostatic intolerance and further investigation and management of this condition provides more reported relief for these troublesome symptoms.

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Poster 62

Cervical spine stenosis as a cause of severe ME/CFS and orthostatic intolerance symptoms

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Background: Comparatively little has been published on the clinical features and management of severe forms of ME/CFS.

Objectives: To describe the presenting symptoms and neurological examination findings in three young adult women whose disabling ME/CFS symptoms and orthostatic intolerance improved after the recognition and surgical management of cervical spine stenosis (CSS).
Methods: This retrospective case series includes three consecutive individuals who (1) met the Fukuda and criteria for CFS, (2) had evidence of refractory orthostatic intolerance, (3) were unable to work or attend school, and (4) were minimally responsive to medical and psychiatric management. To investigate pathological reflex findings, all underwent MRI evaluations. CSS was considered present if the AP cervical spinal canal diameter (SCD) was less than 10 mm at any level. Overall function was assessed before and after cervical disc replacement surgery using (1) a clinician-assigned Karnofsky score (range 0 to 100) and (2) the SF-36 physical function (PF) subscale score (range 10-30). Higher scores indicate better function on both measures.
Results: Age at onset of symptoms was 12, 29, and 29 years. The onset of ME/CFS was acute in all three. Neurological exam findings included $\geq$ 3+ (brisk) deep tendon reflexes (DTR) in 2/3, positive Hoffman sign in 2/3, tremor in 2/3, and absent gag reflex in 1/3. Diagnosis was delayed for 6-9 years after the onset of symptoms. Brain MRIs were normal. The youngest patient had congenital CSS with a single level disc protrusion at C5-6 that caused further ventral cord compression and a SCD of 7 mm. Her mother also has cervical stenosis. A second patient had two disc protrusions at C5-6 and C6-7 with SCD of 7 and 9 mm, and myelomalacia (this patient has a sibling with Chiari I malformation). The third had acquired CSS due to a single level disc bulge at C5-6 (SCD = 8.5 mm). Improvements were evident within 2 months of single-level cervical disc replacement surgery (one patient also had fusion at an adjacent level). After 16-40 months of follow-up, all reported improved fatigue, cognitive dysfunction, PEM, lightheadedness, and anxiety. The pre- to post-op SF-36 PF scores improved from 13 to 30, 18 to 30, and 16 to 26, respectively, and the Karnofsky scores improved from 40 to 90, 40 to 90, and 50 to 100, respectively. Standing tests conducted at variable intervals from pre- to post-op showed a reduction in the maximal heart rate (HR) change during 5 minutes of standing from 64 to 22 bpm, 42 to 29 bpm, and 34 to 27 bpm, respectively.
Conclusion: This case series draws attention to the potential for CSS to contribute to ME/CFS and orthostatic symptoms, extending work by Heffez in fibromyalgia (*Eur Spine J 2004;13:516)*. Further work is needed to define indications for surgery. However, the improvements in HR and function following surgery emphasize the importance of detecting and treating CSS, especially in the subset of those with ME/CFS whose severe symptoms are refractory to other interventions.

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Poster 63

Exploring the role of environmental exposure in the causality of chronic illness and Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS)
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Introduction: The purpose of this presentation is to provide a different approach to the assessment of the patients with indeterminate chronic illnesses, including ME/CFS. Exposure to environmental pollutants can cause accumulation of toxic substances in the body and induce disease through several distinct mechanisms. A case study is used to describe the need for an environmental evaluation during the workup of complex multi-system disorders.
Case Presentation: A 66-year-old male presented to the clinic with chronic fatigue, muscle and joint pain, and severe post exertional malaise. The patient has difficulty falling and staying asleep as well as severe cognitive problems and orthostatic intolerance. The fatigue assessments scores placed his physical function levels well below the average as compared to the general population. Evaluation of his occupational history inferred possible

exposure to molds and heavy metals. 24-Hr urine test showed Arsenic 1329 ug/24 hr, Mercury 25 ug/24hr, and Aluminum 125 ug/24 hr. Urine test was positive for mycotoxin derivatives -Trichothecene group 0.24 ppb and Gliotoxin derivative 0.93 ppb by ELISA.
Management and Outcome: The patient began treatment focused strengthening of antioxidative capacity and removal of environmental pollutant. The patient reported improvement in his symptoms shortly after starting treatment particular elevation of cognitive symptoms.
Discussion: Among common extrinsic toxins are asbestos, benzenes, pesticides, persistent organic pollutants, molds and food additives. Intrinsic toxins are produced as a result of digestive process and are metabolites of food, intestinal dysbiosis, yeasts, fungi, parasites. The mold-related illnesses presented with multisystem symptomology that we frequently observe in the patients with CFS with chronic inflammatory processes and a greater intensity of neurological symptoms. Toxic load affects immunoglobulins ratios, creates immune dysregulation, and increases risk for autoimmunity.
Conclusions: The case study detailed in this presentation highlights potential dangers associated with exposure to mixed molds and heavy metals, leading to multiple problems involving the central nervous system and the immune system, and leading to the debilitating chronic disease.

Poster 64

Relationship between sleep quality and serum C-reactive protein (CRP) levels in Veterans who served in the Gulf War

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Background: Evidence relates disturbed sleep with an inflammatory response. Sleep disturbance is among the most common complaints of veterans who served in the 1991 Persian Gulf War. A large amount of research has examined cross-sectional and longitudinal relationships between sleep disturbance and inflammation. **Objective:** This study evaluated cross-sectional relationships between subjective sleep quality and C-reactive protein (CRP) in veterans who served in the Gulf War. **Participants and Methods:** We performed a cross-sectional type study that used 40 male Gulf War veterans from the Miami VA Hospital. The study population had a mean age of 41 years. Measures included the Pittsburgh Sleep Quality Index (PSQI) to assess subjective sleep quality, and serum levels of C-reactive protein as an indicator of inflammation. **Results:** There were 36 veterans who suffered from poor sleep quality (PSQI score of six or more). A substantial correlation was found between serum CRP level and the patients' sleep quality (p=<.05). Furthermore, a significant positive correlation existed between the different components of sleep quality measured by the PSQI and CRP (p=<.05). **Conclusions:** We conclude that there is a correlation between decreased sleep quality in Gulf War veterans and elevated CRP levels, which may have therapeutic implications. Future studies should longitudinally evaluate how these relationships may affect development of diseases associated with inflammation.
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Poster 65

Epigenetic approach to find novel biomarkers and mechanisms of CFS/ME

Sarria L., Rashid H., Collado F., Moturu A., Cash M., Galvez Cabezas K., Fletcher M.A., Klimas N.G., Nathanson L.

Background: Chronic Fatigue Syndrome/Myalgic Encephalomyelitis (CFS/ME) is a complex condition that is associated with a variety of symptoms including fatigue, memory problems, muscle and joint pain, gastrointestinal issues, neurological problems, hormonal imbalance and immune dysfunction. Currently, treatment relies solely on symptom management but does not address the underlying mechanisms of disease. Our previous research efforts have shown that the transcriptional regulation altered the phenotypic nature of CFS/ME. DNA methylation is one of the epigenetic mechanisms that regulates gene transcription without changes in the DNA sequence. It involves

the covalent binding of a methyl group to a Cytosine-5 at a C-phosphate-G (CpG) site. Negative associations between methylation and transcription are known to be enriched particularly in promoter regions.
Objectives: To provide insight into the biological mechanisms of CFS/ME, the main objective of this research is to identify novel mechanisms of transcriptional regulation. While previous research efforts in CFS/ME have focused on targets further down the pathways that have involved enzyme activation, our research efforts focus at the higher end of the signaling pathway.
Methods: We evaluated levels of DNA methylation in peripheral mononuclear blood cells isolated from 13 female CFS patients (CFS/ME diagnosis was based on the Fukuda and the Canadian criteria) and 12 female healthy controls using Illumina MethylationEPIC BeadChip arrays, controlling for the probes with the low detection, invariant probes and probes overlapping polymorphic sequences. DNA methylation analysis was performed using R software with RnBeads package. The mean difference in means across all sites in a region of the two groups, the mean of quotients in mean methylation and combined p-values calculated from all site p-values in the region were used to rank the degree of the differential methylation.
Results: We found an increased abundance of hypermethylated promoters of genes related to the immune functions, regulation of enzymatic activity, cellular bioenergetics, and signaling activity in the cells of CFS/ME patients. At the same time hypomethylated promoters belong to the genes that have activities associated with the cell cycle.
Conclusion: This data show the importance of the DNA methylation in the regulation of the changes in gene expression in CFS/ME.

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The authors declare no conflicts of interest.

Poster 66

Dysregulation of B lymphocytes with reduced diversity and increased clonality in chronic fatigue syndrome

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[**Objectives**] The dysregulation of the immune system in ME/CFS has been previously reported. B cell depletion therapy by anti-CD20 Abs ameliorated symptoms of two-thirds of patients in a phase 2 clinical study (Fluge O et al, PLOS one 2015). The aim of this study is to evaluate B cell subset and BCR repertoire abnormalities in ME/CFS patients.[**Methods**] 23 ME/CFS patients (age±SD=43±13 years old: Male/Female=4/19) fulfilled 2003 Canadian consensus criteria and 30 healthy controls were enrolled. 1) Peripheral blood mononuclear cells (PBMCs) were stained by mAbs to designate the B cell subsets defined as: B cells (CD3-CD14-CD19+); naïve B cells (CD19+CD27-); memory B cells (CD19+CD27+); transitional B cells (CD19+CD27-CD24+MTG+); activated naïve B cells (CD19+CD27-CD24-MTG+); plasmablasts (CD19+CD27+CD180-CD38high) (MTG: Mito Tracker Green FM). Surface molecules related to activation (HLA-DR and CD138), proliferation (Ki67) and costimulation (CD40, CD80 and CD86) were

evaluated by flow cytometry. 2) B cell receptor (BCR-IgG) repertoires from 20 ME/CFS patients (age±SD=38±14 years old: Male/Female=6/14) were analyzed with an unbiased repertoire analyses using next generation sequencing technology. The diversity and clonality of BCR repertoires of patients samples were compared with 10 healthy controls (age±SD=41±9 years old: Male/Female=4/6) by Shannon-Weaver index (SWI) and Kolmogov-Smirnov test. [**Results and Conslusion**] 1) Flow cytometer analysis demonstrated that the frequency of transitional B cells, which have been reported to have regulatory function, was significantly decreased in ME/CFS subjects ($p<0.01$). The analyses of various functional molecules of each subset showed that the frequency of CD80+ plasmablasts was significantly increased in patients ($p<0.05$). 2) BCR repertoire analyses of ME/CFS samples did not show significant change in SWI but 6 out of 20 samples (30%) showed significant higher clonality as shown by Kolmogov-Smirnov test (above the average+2SD of healthy controls). These results suggest, at least in some patients, a potential antigen-driven expansion of oligoclonal B cells in ME/CFS. To conclude, ME/CFS peripheral blood B cells are dysregulated with potentially reduced diversity and increased clonality.

Poster 67

Benefit of a high protein diet, conditioning exercise and nutraceutical supplements in chronic fatigue syndrome: a presumptive mitochondrial disorder

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Institutional Approval: Columbia University Medical Center Institutional Review Board

Background: Etiopathogenesis of chronic fatigue syndrome (CFS) is poorly understood, and no therapy has been particularly effective. A viral infection causes mitochondrial dysfunction and resultant symptoms, in genetically susceptible individuals.
Objective of this study was to determine whether therapy that has been therapeutically beneficial for mitochondrial diseases is also beneficial for CFS.
Methods: Twenty subjects were recruited for this feasibility case study, 12 of whom were eligible, having fulfilled the criteria for CFS diagnosis. Subjects received high protein diet, daily conditioning exercise, and nutraceutical therapy (DENT). Nutraceutical supplements were selected to enhance mitochondrial function and antioxidant action. Subjects received DENT for varying lengths of time, from 6 to 40 months.
Results: Subjects experienced a significant decrease in fatigue, as measured by the Modified Fatigue Severity Score (FSS-11), compared to their pre-DENT score, with a mean change of 34% (-26.1 points; 95% confidence interval, -35 to -17; $P< 0.05$), with marked functional improvement. Subjects were subsequently able to undertake normal, or near normal, physical and social activities, and were able to return to work or school. No side effects were observed.
Conclusions: By addressing CFS as a mitochondrial disorder, DENT presents an effective means of treating CFS.

Poster 68

Low Level Light Therapy Improves Sleep and Energy in Myalgic Encephalomyelitis/Chronic Fatigue Syndrome and Fibromyalgia

Eleanor Stein MD and Ryan Lukic BHSc

Background: There is a growing literature on the effectiveness of Low Level Light Therapy (LLLT) in a variety of pain, injury and degenerative conditions including Fibromyalgia. Clinical experience is that many patients sleep better the day or days after treatment over the spine or neck. LLLT exposes the body to red and infared light at frequencies absorbed by cytochrome C oxidase, the last enzyme in the respiratory electron transport chain of mitochondria. Cytochrome C oxidase establishes a transmembrane potential that the ATP synthase then uses to

synthesize ATP. The healing benefits of LLLT are thought to be related to this increase in cellular energy. There are no published studies on the impact of LLLT for sleep or energy.
Objective: To test whether LLLT at 660nm and 840 nm will result in better sleep at night and daytime energy in adults with ME/CFS and/or FM.
Method and Measures: So far 11 adults diagnosed with ME/CFS and/or FM have undergone a series of 10 LLLT treatments using a Bioflex® system as part of their clinical care. Each treatment consists of the application to the neck of LED light 660 nm, 3.6J/cm2 X 75 cm X 24 minutes + LED light 840 nm, 3.6J/cm2 X 75 cm X 24 minutes + Infrared laser 840 nm, 260J/cm2 X 6 minutes. Pre, post and 2 weeks post treatment evaluations consist of: sleep efficiency and steps/day using a Fitbit or similar tracker, Wood Mental Fatigue Scale, Pittsburg Sleep Questionnaire (PSQI) and Krupp Fatigue Severity Scale (FSS). Subjective symptom ratings were recorded at each session. The amount of light delivered was adjusted at each session based on the accumulated feedback for each participant.
Results: To date, 11 individuals have completed the protocol. There are statistically significant pre/post improvements noted on all of the WMFS, PSQI and FSS. In addition, pain including headache pain and generalized FM pain were improved. No differences were found on sleep efficiency or steps taken/day using the podometer/trackers. Most individuals reported no side effects. Some reported transient fatigue or being over-energized after treatment. 2 weeks after completing treatment, gains are decreased by remain significant for the PSQI and FSS.
Conclusions: There is preliminary evidence of benefit in sleep quality, fatigue, mental fatigue and pain in adults with ME/CFS and FM given 10 standardized LLLT treatments over 5 weeks. Side effects were few, not severe and transient. We are continuing to increase the sample size.
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Poster 69

Identification of a Subset of AMP-516 Patients with Twice the Response Rate with Regard to the Primary Endpoint, Exercise Treadmill Tolerance (ETT), Compared to the Entire CFS Population
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OBJECTIVES: Chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME) is a severely debilitating disease of unknown pathogenesis consisting of a variety of symptoms including severe fatigue. Initial analysis of rintatolimod (PolyI:PolyC_{12}U), a selective TLR3 agonist, in a Phase III, double-blind, randomized, placebo-controlled trial (AMP-516) demonstrated statistical significance ($p<0.05$) in the relief of fatigue as measured by exercise tolerance (ET). The primary endpoint has been reexamined post-hoc as a function of the duration of CFS symptoms prior to enrollment into the study.

METHODS: The ITT population (n=208) was separated into two subsets based primarily on baseline CFS symptom duration (2-8 years (n=75) and <2 years plus >8 years (n=133)). Responder analyses of the ITT population and both subsets were performed.

RESULTS: For the ITT population (n=208) a significantly greater percentage of rintatolimod patients (39%) vs. placebo patients (23%) improved ET duration ≥25% ($p=0.013$). For the subset of patients with baseline CFS symptom duration of 2-8 years, 51% vs. 18% of rintatolimod vs. placebo patients ($p=0.003$) improved exercise duration ≥25%. Thus, placebo adjusted improvement was 16% in the ITT population compared to 33% in the 2-8 year subset. In addition, a frequency distribution analysis of ≥25% improvement, <25% change and ≥25%

worsening in ETT from baseline at 40 weeks for the baseline 2-8 year cohort showed placebo adjusted net improvement to be 42% (p=0.011) vs. 18% (p=0.044) for the ITT population. The <2 year plus >8 year subset (n=133) failed to show any clinically significant ETT response to rintatolimod compared to placebo.

CONCLUSIONS: Responder analyses of rintatolimod vs. placebo patients improving ET duration from baseline by ≥25% shows over twice the % of patients with clinical enhancement in ET effect in the rintatolimod cohort compared to placebo for the 2-8 year subset vs. the ITT population. Rintatolimod was generally well-tolerated in this CFS/ME population.

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Poster 70

Brain Connectivity Patterns in Gulf-War Illness: Relationship with Cognitive and Immune Measurements

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Background
Identifying a reliable biomarker of Gulf-War Illness (GWI) has been a focus of the Boston Gulf War Illness Consortium (GWIC). Symptoms of GWI include fatigue, pain and cognitive problems. The GWIC is designed to compare these symptoms with proinflammatory cytokine and brain imaging biomarkers. Tools that assess the brain as a network have the potential to provide insight into how connectivity breaks down in response to chronic disease.

Objectives
We used a network based brain connectivity assessment framework (BCF) to determine if there is a unique brain connectional pattern specific to GWI. Further, we assessed the relationship between connectivity in white matter tracts to cognitive and immune measures in participants with GWI to determine how these measures impact connectivity.

Methods
To generate the connectivity patterns we used high angular resolution diffusion magnetic resonance imaging (HARDI) data from 18 veterans with GWI and 12 elderly control subjects. The GWI subjects also had cognitive and blood-immune markers. Regional brain connectivity was defined based on the existence and amount of white matter tracts between 68 cortical and subcortical regions. For the white matter connectivity assessments, BCF which is based on a machine learning algorithm was applied to define a subset of brain connections specific to GWI. Brain connections selected from the group assessments were then compared to cognitive and immune assessments in both univariate and multivariate general linear modeling schemes.

Results
Based on the BCF, 23 brain connections were defined as central features for GWI. Based on the leave-one-out cross validation, only one GWI participant was misclassified. Interleukin (IL) 5, IL-17, California verbal learning test II trial 1-5 was significantly explained by the right_Hippocampus–right_Thalamus and the right_Hippocampus–right_Temporal_pole connections. Also, IL-1a, IL10, TNF-RII and Conners CPT3_T_score were related to both the left_Pars_Operculus–left_trans_Temporal and right_Lingual–right_Temporal_pole connections.

Conclusion
The assessment of brain connectivity patterns may provide insight into network changes that have taken place in veterans with GWI. In this study we used connectivity patterns to identify GWI participants and found relationships with cognitive and immune measures. These preliminary findings will be expanded to our larger GWIC sample for further validation.

Acknowledgments: This work is supported by a CDMRP GWI consortium award (GW120037) to Dr. Kimberly Sullivan.

Conflicts of Interest: none

Poster 71

Comprehensive molecular analysis of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome in a pilot study
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Background

Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) is a prevalent but poorly understood illness with a complex range of symptoms, suggesting multiple body systems are affected. In New Zealand our relative isolation and modest population provides opportunity to sample a small group of well characterised cases for comprehensive molecular analyses.

Objectives

Our aim is to identify molecular biomarkers that could be developed for a simple clinical diagnostic test. We are studying an initial pilot group of ten ME/CFS patients, diagnosed by ME/CFS specialist GP Rosmund Vallings according to the 2011 Canadian Consensus Criteria, and ten matched healthy controls. We aim to analyse key molecules in plasma and blood cells, including cytokines, miRNA, transcriptome and proteome to provide a complete picture of the molecular changes characteristic of the disease-state.

Methods

Analysis of the circulating miRNAs in plasma samples used Taqman® miRNA Array cards, and data was evaluated using the BioC/R statistical package HTqPCR (high-throughput qPCR). Total RNA and small RNA (including miRNA) transcriptome libraries, derived from total RNA extracts of lymphocyte blood cells, were made and sequenced. Lymphocyte proteomes of the pilot study group, determined by mass spectrometry, will complete the studies.

Results

Analysis of the miRNA data by non-parametric Mann-Whitney U test has shown that three miRNAs; miR-142-5p (*P*-value = 0.02, fold-change = 1.3), miR-501 (*P*-value = 0.03, fold-change = 2.04) and miR-1825 (*P*-value = 0.01, fold-change = 1.5) are significantly changed between the two groups. The transcriptome sequencing data and proteome data are currently being analysed with advanced bioinformatic tools.

Conclusions
Our study will validate whether extensive molecular analysis can allow significant conclusions from individuals in a small study group and identify plausible diagnostic biomarkers. Furthermore, given the number of body systems

affected, significant results from these data sets can be correlated to identify affected biological pathways and give insight into the underlying disease process in ME/CFS.

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There are no potential conflicts of interest.

Poster 72

Neuroplastic Transformation of persistent pain in Myalgic Encephalomyelitis/ Chronic Fatigue Syndrome and Fibromyalgia

Karen Tanguay MD, Ryan Lukic BMSc and Eleanor Stein MD

Background: Both Myalgic Encephalomyelitis/ Chronic Fatigue Syndrome and Fibromyalgia (ME/CFS and FM) are defined by the presence of persistent pain. Existing cognitive treatments have the objective of learning to "live with the pain". Drug treatments are often poorly tolerated and/or ineffective over the long term. There is a need for new pain management approaches. Since persistent pain is primarily a disorder of neuroplasticity – the pain processing regions of the brain expand and become more active as pain persists - it follows that overriding this unconscious process with conscious interventions could reverse the neuroplastic changes and ameliorate persistent pain.

Objective: To evaluate the impact of a drug free approach teaching individuals how to use neuroplasticity to decrease and even eliminate persistent pain.

Method and Measures: Adults diagnosed with ME/CFS and/or FM met for 2 hours every other week in groups of 8 – 10 individuals for 8 sessions. Each session comprised reviewing one chapter in the manual "Neuroplastic Transformation" by Drs. Michael Moskowitz and Marla Golden (Moskowitz 2013) to ensure full understanding of the neuroscience rationale for the therapy. Participants were encouraged to practice the neuroplastic skills several times daily – every time they became aware of pain. Participants completed questionnaire ratings of pain (BPI, FIQ-R), functional capacity (SF-36, WHODAS) and psychiatric symptoms (GAD-7, PHQ-9, HADS) before and after the group as well as at 6 months post completion.

Results: To date, 18 individuals have participated in two groups. More are in process. Some participants declined to complete the questionnaires. Using paired T-tests for all subjects who completed both pre and post evaluations there was evidence of improvement on several scales of the SF-36 and BPI as well as total scores for the FIQ-R and GAD-7. There are no changes on the WHODAS or PHQ-9. Several participants reported increased fatigue with this intervention.

Conclusions: There is preliminary evidence of benefit from a neuroplasticity based group intervention for persistent pain in adults with ME/CFS and FM. We are continuing to increase the sample size.

References

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Poster 73

Assessment of Cellular Bioenergetics in Chronic Fatigue Syndrome

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Introduction: Abnormalities in bioenergetic function have been cited as one possible cause for chronic fatigue syndrome (CFS). One hypothesis to explain this suggests that CFS may be caused, at least in part, by an acquired mitochondrial dysfunction.
Extracellular flux analysers make real-time, *in vitro* assessment of cellular energy pathways possible. Using this technology, mitochondrial function can be measured in a variety of cell types in real-time thus increasing our understanding of the role of metabolism in CFS.

Objectives: This project aims to utilise extracellular flux detection technology in order to investigate the cellular bioenergetics of different cell types obtained from CFS patients and healthy controls.

Methods: Mitochondrial stress tests were conducted using skeletal muscle cells and peripheral blood mononuclear cells (PBMCs) derived from CFS patients and controls. During this test mitochondrial complexes are inhibited in turn to modulate respiration so mitochondrial function can be evaluated. The oxygen consumption rate of cells is measured which allows keys parameters of mitochondrial function to be measured and calculated in a single experiment, providing an overall assessment of mitochondrial function. Parameters measured are: basal respiration, maximal respiration and non-mitochondrial respiration. Proton leak, ATP-production and spare respiratory capacity are subsequently able to be calculated using the three measured parameters.

CFS patients whose samples were used in these studies were diagnosed using the Fukuda definition.

Results: Results using skeletal muscle cells obtained from CFS patients (n=3) and controls (n=5), indicate that there is no difference in the energy profiles of the skeletal muscle cells of CFS patients in any of the parameters investigated.

Mitochondrial stress test results using PBMCs show CFS PBMCs (n=7) to be significantly lower than control cells (n=10) in all parameters investigated ($p \leq 0.016$). Importantly, these results suggest that CFS PBMCs perform closer to their maximum under normal conditions. This means that when CFS PBMCs come under stress they are less able to increase their respiration rate to compensate for the increase in stress.

Conclusions: These findings provide an interesting starting point for investigations into cellular bioenergetics in CFS.

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This work was funded by the Medical Research Council and Newcastle University.

Poster 74

Increasing Resilience to Traumatic Stress: Understanding the Protective Role of Well-Being

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Background: The brain maintains physiological and behavioral homeostasis at least in part through a complicated network of feedback and feed forward mechanisms where neuro-chemicals and immune markers act as mediators. **Objectives:** We propose that this neurotransmission network is capable of supporting multiple regulatory regimes that in turn, give rise to self-sustaining psychological behaviors, both healthy and unhealthy. In addition, due to the overwhelming lack of physiological markers for the protective role of subjective well-being, we hope to find connections within the network that optimally support this protective role. **Methods:** To explore this hypothesis we describe a basic neurotransmission and immune system network as a discrete logic circuit. This circuit captures documented interactions within and between levels of biology as described by neurotransmitters and immune markers, and their influence on negative behavioral constructs such as depressive mood and anxiety and positive psychological constructs such well-being and hope. **Results:** The properties of this bio-behavioral circuitry were analyzed to find that two distinct stable regulatory regimes were supported. In addition to a normal healthy state, the circuit also supported a self-sustaining state of increased anxiety, led to by simulating the effects of a traumatic stress on the system. Once these two steady states were found, we hypothesized that there would be two well-being targets and two well-being feedback signals, and ran an optimization to find which neurotransmitter elements that, if connected to elevated well-being, minimized the system's ability to lapse into the anxious/depressive steady state. Our analysis found one combination of connections that best explain this protective role. **Conclusions:** This analysis suggests not only that high levels of well-being can serve as a protective factor against chronic anxiety following traumatic stress, but also that the regulation of bio-behavioral dynamics may be an important contributor to the mechanism of action through which positive psychological constructs, such as well-being, serve their protective function against negative affective states.

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Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Poster 75

Low dose naltrexone in a case with Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) and isolated liver enzyme elevation

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Objective:
To present the case of a ME/CFS patient with Gilbert's Syndrome who developed an isolated ALT elevation during treatment with low dose naltrexone (LDN).
Case description:
A 34-year-old woman who two years prior had a syncopal episode, secondary to a 3rd degree atrioventricular block. She received a double chamber pacemaker implantation, complicated with cardiac tamponade. After recovering from this hospitalization, she felt constantly fatigued and started presenting diffuse joint and muscle pain, post-exertional malaise, cognitive changes, orthostatic intolerance and unrefreshing sleep. An extensive evaluation only found Raynaud's Syndrome, with a negative workup for autoimmune and infectious conditions. Her past history included environmental allergies, mononucleosis in her teens, and Gilbert's Syndrome with normal liver function tests.
On laboratory evaluation: normal blood cell counts, liver, kidney, adrenal and thyroid function. Her immunologic tests showed: low natural killer cell number and activity, elevated tumor necrosis factor (TNF) alpha (19.2pg/mL), TNF receptors I (569pg/mL) and II (865pg/mL), and interleukin (IL) 1a (16.1 pg/mL).
She was diagnosed with ME/CFS (by Fukuda criteria), and was started on antioxidant supplements and LDN 0.1mg/day, with slow titration. She tolerated LDN up to 1.5mg/day, with improvement in pain levels and sleep quality. Then, LDN was titrated to 4mg/day, further improving symptoms and immunologic parameters: TNFa (11.2pg/mL), TNF-RI (392pg/mL), TNF RII (684pg/mL) and IL1a (10pg/mL).
After one year, she had an isolated ALT elevation (43, then 77IU/L). Other liver tests were normal. Medications were reviewed and adjusted, without improvement. Upon holding LDN, her ALT slowly normalized, but with a relapse in joint pain, stiffness, and poor sleep. Treatment with Ganoderma lucidum (reishi mushroom) improved her symptoms, and ALT remained normal.
Conclusion:
LDN is used in the management of pain and abnormal inflammatory response in ME/CFS. Naltrexone is metabolized by liver glucuronidation and patients with Gilbert Syndrome have an impairment in this detoxifying mechanism. Scarce reports describe ALT elevation on regular naltrexone dosage (50mg/day), but to our knowledge, this is the first reported case of isolated ALT elevation with LDN in a Gilbert's syndrome patient. Treatment was successful, but monitoring is warranted, and alternatives like Ganoderma lucidum may be required.

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Poster 76

A Wearable Ring Computer to Track Unrefreshing Sleep

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Background. The landmark report published by the Institute of Medicine (IOM) titled, "Beyond Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: Redefining an Illness" identified diagnostic criteria that capture the

disease's "***unique symptomatology***". The criteria include 1) functional impairment that persists for more than 6 months accompanied by debilitating fatigue; 2) post-exertional malaise; 3) unrefreshing sleep; 4) cognitive impairment and orthostatic intolerance. Sleep is essential to recovery and rejuvenation of every system in the body – immune, nervous, muscular, etc. During sleep the body builds up and replenishes the molecules essential for daily function. Unrefreshing sleep described as "*feeling as tired upon waking as before going to bed*" is pathognomonic of ME/CFS. Yet polysomnography studies have not determined the cause of unrefreshing sleep or how to objectively measure unrefreshing sleep in ME/CFS. This is due to several factors including small study size, patient heterogeneity and short duration of the polysomnography studies.

Objective. Our objective was to determine the feasibility of using a ring-sized sleep-assessment computer, called Ōuraring, together with Curious - a tracking and data aggregation platform – as tools to measure unrefreshing sleep in ME/CFS.

Methods. Ōuraring assesses sleep and daytime activity over the entire 24-hour circadian cycle. Measurements include resting heart rate, respiration, total sleep time, sleep efficiency, sleep disturbances, REM, deep sleep, sleep onset latency and circadian alignment. Daytime measures include exercise, steps, calories burned and time upright. This information is used in a algorithm to calculate a readiness score and a recovery index (how sleep and activity prepared you for the day).

Results/Conclusion. Ōuraring produces data comparable to polysomnography and uses artificial intelligence to learn about the individual and find patterns associated with unrefreshing sleep. Ōuraring is a fraction of the cost of polysomnography. It can be worn for weeks to generate continuous sleep and activity measures. We will present the results of this beta test including how Ōuraring works in ME/CFS patients, how it will be used as a tool to objectively measure unrefreshing sleep in research and as an outcome measure in clinical trials and how we intend to put the Ōuraring on hundreds of ME/CFS patients.

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Poster 77

10-minute NASA Lean Test as an important clinical tool in evaluating orthostatic intolerance

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Background: Fatigue, weakness, cognitive slowing, headache, dizziness, nausea, chest discomfort, and temperature intolerance are well documented symptoms in the ME/CFS patient population and contribute significantly to overall ill-health and well-being. Orthostatic intolerance (OI) has been shown to produce similar symptoms and is often comorbid with ME/CFS. Accessible and reliable clinical tools to effectively diagnose and treat orthostatic intolerance syndromes remain a necessity in the field.

Objectives: To evaluate the 10-minute NASA Lean Test[1] as a clinical tool for understanding systolic and/or diastolic blood pressure (SBP, DBP) and heart rate (HR) changes associated with orthostatic intolerance in patients meeting the diagnostic criteria for ME/CFS.

Methods: A search of our electronic clinic records using the terms "postviral fatigue syndrome" and "NASA Lean Test" identified 41 patients who were evaluated using the test. Data from the 41 tests were analyzed for maximal changes between supine and standing measurements for HR, SBP and DBP. Medications with the potential to affect BP or HR were also recorded.

Results: ME/CFS patients experienced an average supine-to-standing change in SBP of -5.3 mmHg, with 24.4% showing a decrease in SBP of ≥20 mmHg, and an average change in DBP of +12.0 mmHg, with 65.9% showing an increase in DBP of ≥10 mmHg and 14.9% showing a decrease in DBP of ≥10 mmHg. HR increased an average of 21.8 bpm from supine to standing, with 22.0% of patients meeting criteria for POTS [HR increase ≥30 bpm], and 58.5% of patients displaying a HR increase of ≥20 bpm. The majority of patients were taking one or more relevant medication and/or engaging in salt and fluid loading or wearing compression on the day of testing.

Conclusion: The 10-minute NASA Lean Test is an inexpensive, simple, and informative bedside test to assess OI. Although only 1/4 of patients met standard criteria for orthostatic hypotension [SBP decrease ≥20mmHg] and/or POTS, the vast majority of patients showed abnormal changes in BP and/or an abnormal increase in HR [≥20bpm]. We predict that testing done in the absence compensatory behavior and relevant medications will uncover even greater BP and HR irregularities.

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2.) No funding was provided for the study except the research intern stipend.
3.) The author declares no conflicts of interest.

[1] The NASA Lean Test is a bedside test that tracks HR and BP as a patient undergoes a 10-minute orthostatic challenge. We adopted the test for clinical assessment at the Bateman Horne Center in December 2015.

Poster 78

Widespread Pain and altered Renal Function in MECFS Patients

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Background: Widespread pain is noted in many patients with Chronic Fatigue Syndrome (MECFS), Fibromyalgia (FM) and Temporomandibular disorders (TMD). These conditions usually start as a localized condition and spread to a widespread pain condition with increasing illness duration. Purpose: To assess the changes in biochemistry associated with pain expression and alterations in renal function. Methods: Forty-seven MECFS patients and age/sex matched controls had: a clinical examination, completed questionnaires, standard serum biochemistry, glucose tolerance tests and serum and urine metabolomes in an observational study. Results: Increases in pain distribution were associated with reductions in serum essential amino acids, urea, serum sodium and increases in serum glucose and the 24-hour urine volume however the biochemistry was different for each pain area. Regression modelling revealed potential acetylation and methylation defects in the pain subjects. Conclusions: These findings confirm and extend our earlier findings. These changes appear consistent with repeated minor inflammatory mediated alterations in kidney function resulting in essential amino acid deprivation and inhibition of protein synthesis and genetic translation within tissues.

Poster 79

Right Arcuate Abnormality and Correlation with Serum Cytokines in CFS

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Background

Chronic fatigue syndrome (CFS) is a debilitating disorder characterized by 6 or more months of fatigue without any other medical condition. The high prevalence, profound disability, and poor prognosis motivates urgent scientific investigation. Brain imaging should provide insight into the disease, but volumetric and perfusion studies have demonstrated conflicting results. It is suspected that systemic inflammation underlies CFS and can be measured by serum cytokines. Brain microstructure may be affected by this putative inflammation, but DTI has not been thoroughly investigated in CFS. No study has performed a combined evaluation of MR imaging and serum

cytokines.

Objectives
(1) Detect microstructural abnormalities underlying CFS using diffusion tensor imaging (DTI), (2) assess if gray and/or white matter volumes are abnormal utilizing T1-weighted volumetric analysis, and (3) preliminarily correlate DTI findings with cytokine levels.

Methods
15 CFS patients and 14 controls provided informed consent in accordance with Stanford's IRB and HIPAA. Subjects underwent 3.0T volumetric T1-weighted imaging and two DTI acquisitions. Segmentations of supratentorial gray and white matter and cerebrospinal fluid were used to compare gray and white matter volume and cortical thickness. DTI was processed with automated fiber quantification (AFQ), which compares piecewise fractional anisotropy (FA) along 20 tracks. For 4 CFS patients, serum cytokines were available and were correlated with right anterior arcuate FA.

Results
In CFS, FA was increased in the right anterior arcuate fasciculus, and this increase correlated with disease severity. Bilateral supratentorial white matter volumes were reduced. Cortical thickness was increased in both right arcuate endpoints: the middle temporal and precentral gyri. A preliminary analysis correlating cytokines with DTI found an inverse correlation between right anterior arcuate FA and leptin levels.

Conclusion
CFS exhibits right hemispheric increased arcuate FA that may correlate with serum measures of inflammation. Right anterior arcuate FA may serve as a biomarker for CFS and warrants further investigation for correlation with neuroinflammation.

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3. Conflicts of Interest: None

Poster 80

Functional connectivity evaluated by resting state EEG is associated with dysfunction of the attention system of ME or CFS: An eLORETA study

Marcie Zinn, Ph.D.
Mark Zinn, M.M.
Leonard Jason, Ph.D.

Background

Recently, functional connectivity analyses of the cognitive impairment in ME or CFS have illustrated considerable deregulation in the brains of patients. Attention, which is often cited as one of the cognitive impairments experienced by the patients, is known to be inseparable from the other cognitive functions making it crucial for goal-directed behavior. We therefore hypothesized that the attention network may be deregulated in ME or CFS patients.

Objectives

To explore attention as a neurophysiological marker of ME or CFS, we explored the electroencephalography (EEG) of ME or CFS, and assessed functional connectivity using lagged phase synchronization with the Depaul Symptom Questionnaire (DSQ) to link patient symptoms to deregulation in the brain.

Methods

Ten patients diagnosed with ME or CFS and eleven healthy controls were enrolled in the study. 60-seconds of artifact free qEEG for each group were selected and compared using lagged phase synchronization, a nonlinear measure of functional connectivity that is independent of volume conduction. Seven frequency bands were assessed and compared to the DSQ.

Results

Results of an independent t-test found that patients with ME or CFS demonstrated significantly decreased connectivity in the delta and alpha-2 bands, as well as significantly increased connectivity in the beta-2 band ($t=1.495$, $p=0.021$, 2 tailed). A separate regression analysis using the DSQ attention item to predict functional connectivity found significantly increased activation in the attention network in all frequency bands, especially in the delta, alpha-2 and beta-3 bands ($r=0.281$, $p=0.042$, 1 tailed).

Conclusions

Our study indicated functional connectivity disruptions between the regions of the attention network, as measured by lagged phase synchronization and predicted by an attention item in the DSQ. Attention plays a crucial role in the representation and execution of action, making its study a necessary component in unraveling the cognitive impairment in ME or CFS. This research may represent a neurophysiological biomarker for ME or CFS.
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The authors confirm that this article content has no competing interest.
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Poster 81

Resting EEG functional connectome analysis reveals disease progression in Myalgic Encephalomyelitis
M. A. Zinn, M.L. Zinn, and L.A. Jason
Background
Cortical sources of electroencephalographic (EEG) rhythms are known to be abnormal in individuals with myalgic encephalomyelitis (ME). Since information processing in the brain involves interactions among spatially distributed brain regions, we hypothesized that EEG functional connectome analysis may indicate alterations in the network topology of patients.
Objectives

To explore neurophysiological connectome of ME, we investigated the EEG of patients using exact low resolution electromagnetic tomography (eLORETA) lagged phase synchronization, a measure of brain functional connectivity.

Methods

Five minutes of scalp-recorded resting EEG was collected from 10 patients with ME and compared to 11 healthy control individuals. Lagged phase synchronization between all nodes and across 7 discrete frequency bands was analyzed using eLORETA. Coordinates representing the center voxel for 42 separate Brodmann areas in each brain hemisphere were defined a priori and used as seed points in the analysis. Illness duration scores were taken from the DePaul Symptom Questionnaire.

Results

Independent t-tests confirmed that patients with ME had significantly decreased connectivity predominantly in the Alpha -2 band affecting the posterior occipital, parietal, and temporal lobes ($t = 5.42$, $p = 0.012$, FWE-corrected). Key hub nodes affected represent the most electrically active regions of the brain. However, a regression analysis showed globally increased connectivity in the alpha-2 band was predicted by illness duration, especially between nodes of left hemisphere ($r = 0.682$, $p = 0.013$, FWE-corrected).

Conclusion

Widespread functional dysregulation in the connectome is consistent with reports of neuronal degeneration in ME and may hold promise in understanding of disease progression. Global disruptions of alpha-2 sources in the topology of functional networks, if replicated, could potentially aid in staging of the illness. When integrated with clinical assessments EEG connectome analysis may have diagnostic value and assist with monitoring treatment responses.

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