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

11th Biennial International Conference
Translating Science into Clinical Care

March 20-23, 2014
Parc 55 Wyndham Union Square Hotel
San Francisco, California, USA

Conference Syllabus

iacfsme.org
Welcome to the San Francisco 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 invited speakers are a particularly accomplished group. They include: Ian Lipkin, MD, the “master virus hunter” according to the New York Times; Abraham Verghese, MD, professor of medicine at Stanford University Medical School and best-selling author of Cutting for Stone; Noel Rose, MD, PhD, Director, Center for Autoimmune Disease Research at Johns Hopkins University School of Medicine; and Daniel Peterson, MD, distinguished CFS/ME clinician and researcher. Anthony Komaroff, MD will summarize the conference on Sunday with his superb ability to communicate research findings in an interesting and authoritative way.

Our innovative workshops include these first time presentations for our conference: Management of Pediatric ME/CFS; Treating the Severely Ill Patient with CFS/ME; Treatment of Orthostatic Intolerance; Immunology Primer for Clinicians; Translating Science into the Classroom; and Legal Issues and ME/CFS. We also have two highly rated return engagements: Behavioral Assessment and Treatment of CFS/ME and Management of Exercise Intolerance.

Our research talks represent a wide array of timely subjects including: the challenges of crafting a case definition; studies on pediatric CFS/ME; a new session on “provocation” studies in CFS/ME; and the neuroscience of fatigue. Our most popular clinical session: Diagnosing CFS/ME - Difficult Clinical Cases, chaired by Nancy Klimas, MD, has been expanded to 2 hours so that clinicians can have more Q and A time.

We also have a clinical session on the 2014 revised IACFS/ME Primer for Clinicians, which represents a one-year effort to provide the most accurate and up-to-date information for the health practitioner.

Our presenters reflect a truly international presence at conference, hailing from a dozen countries, including Australia, Canada, Italy, Japan, Latvia, Netherlands, New Zealand, Norway, Peoples’ Republic of China, Spain, Sweden, and the United Kingdom.

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 Friedberg, Ph.D.
President, IACFS/ME
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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 there under as they may now exist or as they may be hereafter amended.

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Recognition of IACFS/ME Lifetime Members

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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.

Stanford University
Pfizer, Inc.
CFIDS Association
Chronic Fatigue Initiative
Griffith University - Griffith Health Institute
K*PAX
New Reality
Routledge - Taylor & Francis
ME Research UK
Mycroft Softworks
Ola Loa
Workwell Foundation
# Conference Function and Room Locator

**Please Note:** All of these locations are on the 4th Floor

## Function

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<td>Mission Room - Workshop 5</td>
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<td></td>
<td>Hearst / Fillmore Room - Workshop 6</td>
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<td>Lombard Room - Workshop 6</td>
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<td>Poster Presentations - Networking Center</td>
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<td>Breaks, Refreshments - Networking Center</td>
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<tr>
<td>Patient Relaxation Room</td>
<td>Stockton Room</td>
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<td>City House Restaurant (in the hotel)</td>
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<td>Food Court and Restaurants (Shopping Complex,</td>
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<td>easy walking distance directly across from the</td>
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<td>hotel)</td>
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<td>Special Interest Meetings (Saturday - Bring your own lunch)</td>
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<td><em>Medical Education for CFS/ME</em></td>
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<td><em>Communicating CFS/ME: Can You Hear?</em></td>
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<td>Mission Room #3</td>
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<td>Cyril Magnin Foyer</td>
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</tr>
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<td>Restrooms</td>
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</tr>
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</table>
IACFS/ME AWARDS BANQUET

Saturday, March 22, 2014

Parc 55 Wyndham

RECEPTION
6:00 pm
Cyril Magnin Foyer

DINNER
7:00 pm
Cyril Magnin Ballroom

Banquet Ticket Required for Admission

AWARDS CEREMONY & KEYNOTE PRESENTATION

Governor Rudy Perpich Memorial Award
Nancy Klimas, M.D.

Nelson Gantz Clinician Award
Katherine S. Rowe, M.D., MPH

Junior Investigator Award
Madison Sunnquist, B.S.

Research Excellence Award
Peter Rowe, M.D.

Special Service Award
Pia and Richard Simpson

Banquet Keynote
CFS/ME and the IACFS: Past, Present and Future
Daniel Peterson, M.D.

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 sponsorship of the Foundation for Care Management (FCM) and the International Association for CFS/ME (IACFS/ME).

FCM is accredited by the ACCME to provide continuing medical education for physicians.

FCM designates this educational activity for a maximum of 25.5 AMA PRA Category 1 Credits™. Physicians should only claim credit commensurate with the extent of their participation in the activity.

The Foundation for Care Management is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education. Program #0347-9999-13-005-L01-P®.

*This CE activity is knowledge based.

The Foundation for Care Management is an approved provider of continuing nursing education by the Washington State Nurses Association Continuing Education Approval & Recognition Program (CEARP), an accredited approver by the American Nurses Credentialing Center’s Commission on Accreditation.

LEARNING OBJECTIVES  IACFS/ME  MARCH 2014

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

1. Recognize how medical investigators are researching CFS/ME for an epidemiological causation.
2. Identify how to appropriately order and interpret diagnostic immunological studies on patients presenting with the diagnosis of CFS/ME in order to facilitate such diagnosis; aid in determining prognosis and enable application of appropriate treatment for subsets of patients.
3. Recognize issues with patients and ERISA disability, particularly causation issues that may become relevant to the patient medical file.
4. Describe the importance of post-exercise impairment as a defining characteristic of CFS and learn about the paradigm of biomarkers developed to measure such impairment.
5. Recognize the use of “educational jargon” in public education in order to improve communication between physicians / healthcare professionals and schools regarding diagnosis and treatment of CFS in children.
6. Identify unique symptoms and complications with the severely ill CFS/ME and fibromyalgia patient and discuss management options available to clinicians.
7. Identify practical methods of behavioral assessment and individualized treatment strategies for patients with CFS/ME.
8. Identify the diagnostic criteria, pathophysiology and testing options for orthostatic intolerance in CFS/ME.
9. Identify the management of pediatric CFS/ME including using some of the current research and translating that into clinical treatment options for children.
10. Identify the current trend of using genomics in CFS/ME and how to manage the physician - patient relationship.
11. Describe the latest research in immunology including Allergy Related Immune Signatures, Plasma Cytokines and Controls before and after cardiopulmonary exercise, Natural Killer Cell Degranulation and Distribution and Genome-wide analysis of differential methylation associated with CFS/ME.
12. Describe the latest research in virology and CFS/ME including patients that have chronic pelvic pain, the occurrence of typical clinical symptoms and markers of human parvovirus B19, the pathogenesis of chronic enterovirus infection both in vivo and in vitro, and the findings from a cohort study and pathogen discovery in patients with CFS.
13. Identify treatment studies involving patients with CFS/ME such as treatment of orthostatic intolerance using Midodrine in patients with CFS, interventional effects of Baduanjin exercise on the fatigue state of patients, effects of isometric yoga on CFS, and a home based self-management for severe CFS/ME patients.
14. Participate in a discussion with CFS/ME clinicians on diagnosing difficult clinical cases.
15. Describe current research trends on CFS/ME case definitions and diagnostic criteria.
16. Identify current public health research studies involving CFS/ME such as a study of differential diagnoses from a community based sample, family aggregation studies, the ME/CFS biobank in the United Kingdom and the lay-scientific partnership that was developed, prevalence of health related characteristics of ME/CFS & FM and Environmental Sensitivities / Multiple Chemical Sensitivities, epidemiological studies involving the natural course of CFS/ME and what treatments alter the course of CFS.
17. Describe Provocation Studies in CFS/ME including diminished pulmonary ventilation and the effects of deconditioning and post exertional malaise, exercise testing including cardiopulmonary testing, and specific fitness profiles in CFS/ME.
18. Describe advances in pediatric ME/CFS research including studies on diagnosing and managing pediatric cases, impairment in motion, lab testing, milk protein hypersensitivity in pediatric cases, impact of adolescence in CFS/ME, sleep education and the effects of depression.
19. Describe advances in brain research and CFS/ME including alpha frequency and the relationship to CFS/ME, the neuroscience of fatigue in CFS/ME cases, and cognitive function.
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Kenneth Friedman, Ph.D.  No Significant Disclosure
Staci R. Stevens, M.A.  No Significant Disclosure
Rosamund Vallings, MNZM, MB BS  No Significant Disclosure
Lily Chu, M.D.  No Significant Disclosure
Dennis Mangan, Ph.D.  No Significant Disclosure

FACULTY ORAL PRESENTATIONS - DISCLOSURE

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:

Lucinda Bateman, M.D.  Pharma Sponsored Clinical Drug Trials: Pfizer, Eli Lilly, Hemispherx Biopharma.
John K. Chia, M.D.  Grants / Research Support: EV Med Research
Susan Cockshell  Grants / Research Support: Validity Indicator Profile provided at no cost by company for research study
Charles W. Lapp, M.D.  Consultant: Pfizer, Stock Shareholder: Hemispherx Biopharma, Speakers Bureau: Pfizer, Forest, Lilly Pharmaceuticals
Noel Rose, M.D., Ph.D.  Honorarium: Genzyme
Christopher R. Snell, Ph.D.  Consultant: Workwell Foundation
Abraham Verghese, MD, MFA, MACP, DSc(Hon)  Writer/Speaker: Random House, Leigh Speakers
Ruud C.W. Vermeulen, Ph.D.  Honorarium: Sigma Tau SPA, Consultant

The following faculty reported that they had no financial interest in any products or services to be discussed.

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Fanny Collado, RN  
Research Nurse Coordinator, Health Science Specialist, Miami Veterans Affairs Healthcare System, Miami, FL

Roasanne Coutts, BHMS(c)(Hons)(SCU), PhD(SCU)  
Lecturer, Southern Cross University, Australia

Travis Craddock, Ph.D.  
Associate Director, Clinical System Biology Group, Institute for Neuro Immune Medicine, COM, Assistant Professor of Psychology and Computer Science, Center for Psychological Studies, Nova Southeastern University, Miami, FL

Ali Crichton, D Psych  
Ph.D. Candidate, University of Melbourne, Murdoch Children’s Research Institute  
Clinical Neuropsychologist, Victorian Paediatric Rehabilitation Services

Ernesto Martinez Duarte  
Research Associate, Nova Southeastern University, Miami, FL

Gilbert Eugene  
Research Assistant, Institute for Neuro Immune Medicine, COM, Nova Southeastern University

Mary A. Fletcher, Ph.D.  
University of Miami Miller School of Medicine  
Professor of Medicine, Microbiology/Immunology and Psychology

Fred Friedberg, Ph.D.  
President, IACFS/ME  
Research Associate Professor, Stony Brook University, Stony Brook, NY

Annike Fryxell Westerberg  
Registered Occupational Therapist, Karolinska Institute, Department of Rehabilitation Medicine, Danderyds Hospital AB, Stockholm, Sweden

Erin Garner  
Senior Occupational Therapist, The Royal Children’s Hospital, Melbourne

Mariela Guerrero Canto, M.D.  
Institute for Neuro Immune Medicine, Nova Southeastern University, Miami, FL

Ashok Gupta, MA(CANTAB), MSc  
Director, Gupta Amygdala Retraining, London, UK

Daniel L. Hall, M.S.  
Ph.D. Candidate, Clinical Health Psychology  
Department of Psychology, University of Miami, Miami, FL
Geoffrey Hallmann, B.Bus.(Hons)(UNE-NR), LLB (Hons)(Newcastle), DipLegPrac (Newcastle), DipFinPlan (Deakin)
PhD Candidate, Southern Cross University
School of Exercise Science & Sport Management

Maureen Hanson, Ph.D.
Liberty Hyde Bailey Professor, Department of Molecular Biology and Genetics, Cornell University, Ithaca, NY

Yvonne Hartman, B.Nurs, (Hons), Ph.D.
Lecturer, Southern Cross University, Australia

Jeanna M. Harvey
Medical Student, Department of Medicine, University of Miami, Research Associate, Miami Veterans Affairs Healthcare System, Miami, FL

Mady Horning, M.D.
Director of Translational Research, Center for Infection and Immunity and Associate Professor of Epidemiology at Columbia University Mailman School of Public Health, New York, NY

Gail Ironson, M.D., Ph.D.
University of Miami Department of Psychology and Psychiatry, Miami, FL

Leonard Jason, Ph.D.
Professor, Director of the Center for Community Research DePaul University, Chicago, IL

Youngshuk Jo
Student Research Associate, Department of Medicine, University of Miami, FL

Jon Kaiser, M.D.
Clinical Faculty, UCSF Medical School, Medical Director, K-Pax Pharmaceuticals, Inc.

Yosky Kataoka, M.D., Ph.D.
Team Leader, RIKEN Center for Life Science Technologies, Cellular Function Imaging Team, Kobe, Japan

Lawrence A. Klapow, Ph.D.
Researcher and Consultant on Parasites and Chronic Disease, Owner, Klapow BioScience

Sarah Knight, Ph.D.
Clinical Neuropsychologist, Clinical Science, Murdoch Childrens Research Institute, Research Fellow
Melbourne School of Psychological Science, Lecturer, Department of Paediatrics, The University of Melbourne

Konstance Knox, MSM, Ph.D.
Founder and CEO, Coppe Healthcare Solutions, Waukesha, WI

Hirohiko Kuratsune, MD, D.Med.Sci.
Professor, Faculty of Health Science for Welfare Kansai University of Welfare Sciences Japan

Eliana Mattos Lacerda, M.D., MSc, Ph.D.
Clinical Research Fellow, Faculty of Infectious & Tropical Diseases Clinical Research, Department - London School of Hygiene & Tropical Medicine, London, United Kingdom

Lynn Anne Lafferty, PharmD, N.D., CNC
Endowed Professor, Nova Southeastern University, Miami, FL

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

Ning Li, Chinese Medicine
Beijing University of Chinese Medicine, China

Jin-Mann S. Lin, Ph.D.
Health Statistician, Centers for Disease Control and Prevention, Atlanta, GA

Indre Bileviciute-Ljungar
Associate Professor, ME/CFS Rehabilitation, Karolinska Institutet, Danderys Hospital

Vincent Lombardi, Ph.D., Biochemistry and Molecular Biology
Assistant Professor, Department of Biochemistry and Molecular Biology, University of Nevada, School of Medicine, Director of Research, Whittemore Peterson Institute, Reno, NV

Per Magnus
Director, Division of Epidemiology, Norwegian Institute of Public Health
Adjunct Professor, Medical Faculty, University of Oslo, Norway

David Maughan, Ph.D.
Professor, Molecular Physiology & Biophysics, University of Vermont School of Medicine, Burlington, VT

Rachel McKean
Student Research Assistant, Department of Medicine, University of Miami, Miami, FL

Marvin Medow, Ph.D.
Professor of Pediatrics, New York Medical College, New York, NY

Kathryn Melamed, M.D.
Internal Medicine, Resident, Brigham and Women’s Hospital, Brookline, MA
Ruth Miller, Ph.D.
*Post-doctoral Research Fellow, School of Population and Public Health, Faculty of Medicine, University of British Columbia, Vancouver, BC, Canada*

Kei Mizuno, Ph.D.
*Special Postdoctoral Researcher, RIKEN Center for Life Science Technologies, Kobe, Japan*

Marianna Morris, Ph.D.
*Professor, Institute for Neuro Immune Medicine, COM, Nova Southeastern University, Miami, FL*

Ben Larson, Ph.D. Candidate
*Student, Physical Therapist, Thomas J. Long School of Pharmacy and Health Sciences, University of the Pacific*

Garth L. Nicolson, Ph.D.
*Professor Emeritus, Institute for Molecular Medicine and University of Texas at Houston*

Takakazu Oka, M.D., Ph.D.
*Associate Professor, Department of Psychosomatic Medicine, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan*

Gunnar Olsson
*Associate Professor and Director of Behavioral Medicine Pain Management, Karolinska University Hospital, Sweden*

Raymond N. Perrin, D.O., Ph.D.
*Honorary Senior Lecturer, Allied Health Professions Research Unit, University of Central Lancashire, UK, Research Director, FORME Trust, Clinic Director, The Perrin Clinic*

Irma Pinxsterhuis, OTR, MSc, PhD student
*Oslo University Hospital*

Irina Rosenfeld, MSN, ARNP, CCPR
*Nurse Practitioner, Institute for Neuro Immune Medicine, COM, Nova Southeastern University*

Katherine S. Rowe, MBBS, M.D., FRACP
*Pediatrician, Royal Children’s Hospital, Melbourne, Australia*

Peter C. Rowe, M.D.
*Professor of Pediatrics, John Hopkins University School of Medicine, Division of General Pediatrics and Adolescent Medicine, Baltimore, MD*

Jean-Michel Saury, Ph.D.
*Clinical Psychologist, ME/CFS Rehabilitation Unit, Rehabilitation Medicine University Clinic at Danderyd Hospital, Stockholm, Sweden*

Connie Sol, M.S.
*Clinical Exercise Physiologist, Neuro Immune Medicine, COM, Nova Southeastern University, Miami, FL*

Matthew Sorenson
*DePaul University*

David R. Strayer, M.D.
*Medical Director, Hemispherix Biopharma, Inc.*

Eve Stormorken, RN, CRNA, MNSc
*Ph.D. Candidate, University of Oslo, Faculty of Medicine, Institute of Health and Society, Department of Nursing Science, Oslo, Norway*

Elin B. Strand, Ph.D.
*Psychologist and Researcher, Oslo University Hospital, Oslo, Norway*

Madison Sunniquist, BS
*DePaul University, Chicago, IL*

Seiki Tajima, M.D.
*Chief Physician, Hyogo Children’s Sleep and Development Medical Research Center, Kobe, Japan*

Philippe Tournesac, M.D.
*Lill Trogstad, M.D., Ph.D.
Senior Researcher, Norwegian Institute of Public Health, Nydalen, Norway*

Rosemary A. Underhill, MB.BS, FRCS(E), MRCOG
*Physician Consultant, New Jersey CFS Association Epidemiological Research and Medical Writing on CFS*

Michael VanElzakker, M.A.
*Graduate Student, Tufts University Psychology, Massachusetts General Hospital Psychiatric Neuroscience, Medford, MA*

Saurabh Vashishtha, M.Sc
*Doctoral Candidate, Department of Medicine, University of Alberta, Canada*

Paula Waziry, Ph.D.
*Assistant Professor, Neuro Immune Medicine, COM, Nova Southeastern University, Miami, FL*

Jackie Yamada, BSc (Hons)
*Clinical Psychologist, Victorian Paediatric Rehabilitation Service, Royal Children’s Hospital, Melbourne, Australia*
AGENDA - THURSDAY, MARCH 20
IACFS/ME PROFESSIONAL WORKSHOPS

8:00 am - 8:15 am
Joint Session Welcome & Introduction
Fred Friedberg, Ph.D.
President, IACFS/ME
Research Associate Professor, Stony Brook University

8:15 am - 8:30 am
Joint Session Welcome from Stanford
Jose Montoya, M.D.
Professor of Medicine, Stanford University School of Medicine

8:30 am - 9:30 am (Last 15 Min: Q & A)
Small Game Hunting
Joint Session Special Guest Speaker: Ian Lipkin, M.D.
John Snow Professor of Epidemiology & Director, Center for Infection and Immunity, Columbia University

Morning Session: 9:30 am - 12:30 pm

Workshop 1
Immunology Primer for Practitioners
Daniel Peterson, M.D.
Griffith University, Gold Coast, Australia, Owner, Sierra Internal Medicine, Incline Village, NV
Sonya Marshall-Gradisnik, BSc(Hons), Ph.D.
Professor of Immunology, Director, National Centre for Neuroimmunology & Emerging Diseases, Griffith University, Australia
Sharni Hardcastle, BBioMedSc (Hons)
Research Assistant and Practical Demonstrator, Ph.D. Candidate, Griffith University, Gold Coast, Australia
Nancy Klimas, M.D., Ph.D.
Professor of Medicine and Director, NSU COM Institute for Neuro-Immune Medicine Director, Miami VAMC Gulf War Illness and ME/CFS Research Program
Paula Waziry, Ph.D.
Assistant Professor, Neuro Immune Medicine, COM, Nova Southeastern University, Miami, Fl
Konsttance Knox, Ph.D.
Founder, CEO, Coppe Healthcare Solutions
David Baewer, M.D., Ph.D.
Medical Director, Coppe Healthcare Solutions
Isabel Barao-Silvestre, Ph.D.
Research Assistant Professor, University of Nevada, Reno, Simmaron Research Scientific
Gunnar Gottschalk, B.S.
Simmaron Research, Incline Village, NV
Troy Querec, Ph.D.
Associate Service Fellow, Centers for Disease Control and Prevention, Atlanta, GA
Dennis Mangan, Ph.D.
Director, Chalk Talk Science Educational Services, Santa Rosa, CA
Mary Ann Fletcher, Ph.D.
University of Miami Miller School of Medicine Professor of Medicine, Microbiology/Immunology and Psychology
Elizabeth Unger, M.D., Ph.D.
Chief, Chronic Viral Disease Branch, Division of High-Consequence Pathogens and Pathology, National Center for Emerging and Zoonotic Infectious Diseases. Centers for Disease Control and Prevention, Atlanta, GA

Workshop 2
Legal Issues and ME/CFS
Steven Krafchick, M.P.H., J.D.
Barbara Arnold, Esq
Workshop 3
Exercise Intolerance: Guide to Management and Treatment
Staci Stevens, M.A.
Vice President, IACFS/ME
Christopher Snell, Ph.D.
Professor, University of the Pacific
Mark VanNess, Ph.D.
Associate Professor, University of the Pacific
Todd Davenport, PT, DPT, OCS
Associate Professor, University of the Pacific

Workshop 4
Translating Science into the Classroom: A Workshop for Clinicians, Patients and Educators
Faith Newton, Ed.D.
Associate Professor of Education, Delaware State University

12:30 pm - 1:30 pm
Lunch Break / Visit Exhibits
Note: Lunch is Self Pay from hotel and local restaurants

Afternoon Session: 1:30 pm - 4:30 pm

Workshop 5
Invisible and ignored: Treating the Severely Ill Patients with CFS/ME and Fibromyalgia (FM)
Charles Lapp, M.D.
Medical Director, Hunter-Hopkins Center
Elin Strand, Ph.D.
Clinical Psychologist, Oslo University Hospital, ME/CFS Center, Oslo, Norway
Irma Pinxterhuis, OTR, MSc
Occupational Therapist, Oslo University Hospital, ME-CFS Unit, Oslo, Norway

Workshop 6
Behavioral Assessment and Treatment of ME/CFS and Fibromyalgia (FM)
Fred Friedberg, Ph.D.
President, IACFS/ME, Research Associate Professor, Stony Brook University
Leonard A. Jason, Ph.D.
Professor, DePaul University

Workshop 7
Diagnosing and Treating Orthostatic Intolerance in CFS/ME
Peter Rowe, M.D.
Professor of Pediatrics, John Hopkins University School of Medicine

Workshop 8
The Management of Pediatric ME/CFS: Translating Research into Clinical Practice
Sarah Knight, Ph.D.
Research Fellow, Clinical Sciences, Murdoch Children’s Research Institute
Lionel Lubitz, M.B.Ch.B.
Associate Professor, University of Melbourne
Kathy Rowe, MB.BS, MRACP, FRACP
Pediatrician, Royal Children’s Hospital, Melbourne

5:00 - 5:45 pm
The Physician-Patient Relationship in the Genomic Era
Joint Session Keynote Speaker: Abraham Verghese, M.D.
Professor of Medicine, Stanford University Medical School
Best-selling Author, Cutting for Stone
8:30 am - 8:45 am
Welcome and Introduction
Fred Friedberg, Ph.D.
President, IACFS/ME
Research Associate Professor, Stony Brook University
Editor, Fatigue: Biomedicine, Health and Behavior

8:45 am - 9:30 am (last 15 min. are Q and A)
Plenary Session: How Do We Recognize an Autoimmune Disease?
Noel R. Rose, M.D., Ph.D.
Director, Center for Autoimmune Disease Research, Johns Hopkins University School of Medicine

Paper Sessions: Following all the papers, the panel members will field questions written on cards by the audience and given to the chair as time permits.

9:30 am - 10:45 am
SESSION: THE LATEST RESEARCH IN IMMUNOLOGY
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

Allergy-Related Immune Signatures and Duration of Illness in CFS
Susan Levine, M.D.

Plasma Cytokines in ME/CFS Patients and Controls Before and After a Cardiopulmonary Exercise Test
Ludovic Giloteaux, Ph.D.

Natural Killer Cell Degranulation in Chronic Fatigue Syndrome/Myalgic Encephalomyelitis & Natural Killer Cell Subset Distribution of Lytic Proteins in Chronic Fatigue Syndrome/Myalgic Encephalomyelitis
Teilah K. Huth, BBioMedSc(Hons)

A Genome-wide Analysis of Differential Methylation Associated with Chronic Fatigue Syndrome
Mangalathu S. Rajeevan, Ph.D.

10:45 am - 11:15 am
Break / Visit Exhibits

11:15 am - 12:15 pm
SESSION: VIROLOGY RESEARCH
Session Chair: Jose Montoya, M.D.

Chronic Pelvic Pain (CPP) in Patients with Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) is Associated with Chronic Enterovirus Infection of Ovarian Tubes
John Chia, M.D.

Occurrence of Typical Clinical Symptoms and Markers of Human Parvovirus B19 Infection in Patients with Myalgic Encephalomyelitis/Chronic Fatigue Syndrome
Santa Rasa, MSc

Pathogenesis of chronic enterovirus infection in myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) - in vitro and in vivo studies of infected stomach tissues
John Chia, M.D.

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

12:15 pm - 1:15 pm
The Chronic Fatigue Initiative (CFI) - Findings from the CFI Cohort Study and Pathogen Discovery & Pathogenesis Project
Open to all attendees and includes a complimentary lunch
Scott Carlson, Mady Hornig, M.D., Nancy Klimas, M.D., and Gail Ironson, M.D., Ph.D., Dana March, M.D., Ph.D. and Anthony Komaroff, M.D.
Non-CME symposium sponsored by the Chronic Fatigue Initiative

1:45 pm - 3:00 pm
SESSION: TREATMENT STUDIES
Chair: Daniel Peterson, M.D.

Treatment of Orthostatic Intolerance (OI) Using Midodrine in Patients with Chronic Fatigue Syndrome (CFS); and Assessment Using Hours of Vertical Activity (HVA)
Nicole Baldwin

Intervention Effect of Baduanjin Exercise on the Fatigue State in People with Fatigue-predominant Sub-health - A Cohort Study
Wang Tian-fang, M.D.¹, Liao Yan¹, Zhang Cong¹, Zhang Yu¹, Xue Xiao-ling¹, Dai Jin-gang², Lin Yin³
¹ School of Preclinical Medicine, Beijing University of Chinese Medicine, Beijing 100029; ² China Academy of Chinese Medical Sciences

Effect of Isometric Yoga on Chronic Fatigue Syndrome: A Randomized Controlled Trial
Takahazu Oka, M.D., Ph.D., Tokunari Tanahashi, Takeharu Chijiwa, Nobuyuki Sudo
Graduate School of Medical Sciences, Kyushu University

Home-Based Self-Management for Severe CFS/ME: A Randomized Trial
Fred Friedberg, Ph.D.

3:00 pm - 3:30 pm
Break / Visit Exhibits

3:30 pm - 5:30 pm
SESSION: DIAGNOSING CFS/ME; DIFFICULT CLINICAL CASES
Session Chair: Nancy Klimas, M.D.
Immediate Past President, IACFS/ME
Charles Lapp, M.D.
Lucinda Bateman, M.D.
Rosamund Vallings, MNZM, MB.BS
Daniel Peterson, M.D.

5:30 pm - 6:15 pm
Visit Poster Presentations / Exhibits
6:00 pm - 7:00 pm
K-PAX Pharmaceuticals Social/Cocktail Hour
The Synergy Trial Update
Non-CME Function Open to All Attendees
Mission Room - 4th Floor
AGENDA – SATURDAY, MARCH 22

8:30 am - 10:00 am
SESSION: CASE DEFINITIONS FOR RESEARCH AND PRACTICE
Chair: Kenneth Friedman, Ph.D.
Treasurer, IACFS/ME
Adjunct Instructor, Castleton State College
A Comparison of the Case Definitions
Leonard Jason, Ph.D.
Professor, DePaul University, Director of the Center for Community Research
Physical and social functioning in varying cases of Chronic Fatigue Syndrome/Myalgic Encephalomyelitis & immune and physical status in patients meeting new criteria for Chronic Fatigue Syndrome/Myalgic Encephalomyelitis
S. Johnston
Case Definitions: Diagnostic and Criterion Issues
Leonard A. Jason, Ph.D., DePaul University
Madison Sunnquist, B.S., DePaul University
10:00 am -10:30 am Break / Visit Exhibits
10:30 am - 12:00 pm
SESSION: PUBLIC HEALTH RESEARCH - PART I
Chair: Lily Chu, M.D.
CFS/ME and Fatiguing Illnesses: Differential Diagnoses from a Community-Based Sample
Nicoleta Carlo-Stella, M.D., Ph.D.
Expanding Access to Knowledgeable Healthcare for Neuro-endocrine-immune Diseases in Alabama - A Case Study
Tina M. Tidmore, Lori Chapo-Kroger, RN
Family Aggregation Studies in CFS
Jesus Castro, Ph.D.
The UK ME/CFS Biobank: 2 Years of Experience
Eliana M. Lacerda, M.D., MSc, Ph.D.
The Lay-Scientific Partnership That Shaped and Development of the UK ME/CFS Biobank
Eliana M. Lacerda, M.D., MSc, Ph.D.
12:00 pm - 1:15 pm Lunch Break / Visit Exhibits
12:00 pm - 1:00 pm
Special Interest Meetings:
Non CME Functions Open to All Attendees - participants are encouraged to bring a lunch and attend
- Medical Education for CFS/ME
  Susan Levine, M.D.
  Mission Room #2 - 4th Floor
- Cardiopulmonary Exercise Testing and Disability Evaluation
  Christopher Snell, Ph.D.
  Mission Room #3 - 4th Floor
- Communicating CFS/ME: Can You Hear?
  Dennis Mangan, Ph.D.
  Mission Room #1 - 4th Floor
1:15 pm - 2:30 pm
SESSION: PUBLIC HEALTH RESEARCH - PART II
Chair: Elizabeth Unger, M.D., Ph.D.
Chief, Chronic Viral Diseases Branch, Division of High-Consequence Pathogens and Pathology National Center for Emerging and Zoonotic Diseases, Centers for Disease Control and Prevention
Prevalence and Health-related Characteristics of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS), Fibromyalgia (FM) and Environmental Sensitivities/Multiple Chemical Sensitivity (ES/MCS):
Results from the Canadian Community Health Survey (CCHS) 20005, 2010 and 2012
Margaret Parlor
The Natural Course of Chronic Fatigue Syndrome: Evidence from a Multi-Site Clinical Epidemiology Study
Dana March, Ph.D.
What Treatments Alter the Course of Chronic Fatigue Syndrome? Evidence from a Multi-Site Clinical Epidemiology Study
Lucinda Bateman, M.D.
Chronic Fatigue Syndrome and Comorbid and Consequent Conditions: Evidence from a Multi-Site Clinical Epidemiology Study
Salima Darakjy, MPH, Ph.D. Candidate
2:30 pm - 2:45 pm
Break / Visit Exhibits
2:45 pm - 4:15 pm
SESSION: PROVOCATION STUDIES
Chair: Staci Stevens, M.A.
Vice President, IACFS/ME
Work Well Foundation, Founder
Superior Ability of a Two-Day CPET Protocol to Detect Functional Impairment in ME/CFS Compared to Either a Single CPET, A Submaximal Exercise Test, or a VO2 Prediction Equation
Betsy A. Keller
Diminished Pulmonary Ventilation in CFS Patients - Effects of Deconditioning and Post-Exertional Malaise
J. Mark VanNess, Ph.D.
Submaximal Exercise Testing Using Near Infrared Spectroscopy (NIRS) May Not Differentiate Those With Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) From Healthy Controls
D. M. Patrick, M.D.
Oxygen Extraction and Lactate Are Low during Cardiopulmonary Exercise Test in Patients with Chronic Fatigue Syndrome
R. C. W. Vermeulen, Ph.D.
Specific Fitness Profile to Effort in CFS
Jesus Castro, Ph.D.
4:15 pm - 5:15 pm
Visit Poster Presentations / Exhibits
5:15 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 & Banquet Keynote
CFS/ME and the IACFS/ME: Past, Present and Future
Daniel L. Peterson, M.D.
# AGENDA – SUNDAY, MARCH 23

## 11th International IACFS/ME Biennial Conference

### Translating Science into Clinical Care

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<tr>
<th>Time</th>
<th>Session</th>
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<tbody>
<tr>
<td>8:00 am - 9:15 am</td>
<td><strong>SESSION: ADVANCES IN PEDIATRIC ME/CFS RESEARCH - PART I</strong></td>
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<tr>
<td></td>
<td>Chair: Leonard A. Jason, Ph.D.</td>
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<tr>
<td></td>
<td>How is Pediatric Chronic Fatigue Syndrome/Myalgic Encephalomyelitis (CFS/ME) diagnosed and managed by Pediatricians? An Australian National Study Sarah Knight, Ph.D.</td>
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<td>Impaired Range of Motion in Adolescent Chronic Fatigue Syndrome</td>
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<td>Peter C. Rowe, M.D.</td>
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<td>Tracking Post-infectious Fatigue in Clinic using Routine Clinical Lab Tests</td>
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<td>Jeanna M. Harvey</td>
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<td>9:15 am - 10:30 am</td>
<td><strong>SESSION: ADVANCES IN PEDIATRIC ME/CFS RESEARCH - PART II</strong></td>
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<tr>
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<td>Chair: Rosamund Vallings, MNZM, MB.BS</td>
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<td>Impact of Adolescent Chronic Fatigue Syndrome</td>
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<td>Peter C. Rowe, M.D.</td>
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<td>What Do Young People Find Helpful in Managing Their Chronic Illness? Lessons From Chronic Fatigue Syndrome Katherine Rowe, MB.BS, M.D., FRACP</td>
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<td>Sleep Education During Elementary School Prevents School Non-Attendance in Junior High School Years Seiki Tajima, M.D.</td>
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<td>10:00 am - 10:15 am</td>
<td><strong>SESSION: BRAIN RESEARCH</strong></td>
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<td>Chair: Anthony L. Komaroff, M.D.</td>
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<td>Neuroscience of Fatigue and CFS/ME by Using PET Molecular Imaging and Functional Neuroimaging Yasuyoshi Watanabe, M.D., Ph.D.</td>
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<td>EEG Peak Alpha Frequency is Associated with Chronic Fatigue Syndrome: A Case-Control Observational Study Marcie Zinn, Ph.D.</td>
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<td>10:30 am - 10:45 am</td>
<td><strong>SESSION: IACFS/ME CLINICAL PRACTICE MANUAL: THE 2014 REVISED PRIMER</strong></td>
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<td>Guidelines Panel Chair: Fred Friedberg, Ph.D.</td>
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<td>Panel: Lucinda Bateman, M.D., Kenneth Friedman, Ph.D., Leonard Jason, Ph.D., Charles Lapp, M.D., Staci Stevens, M.A., Rosamund Vallings, MB.BS.</td>
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<td>10:45 am - 12:00 pm</td>
<td><strong>SESSION: IACFS/ME CLINICAL PRACTICE MANUAL: THE 2014 REVISED PRIMER</strong></td>
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<td>Lunch / Visit Exhibits</td>
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<tr>
<td>12:00 pm - 1:15 pm</td>
<td><strong>SESSION: IACFS/ME CLINICAL PRACTICE MANUAL: THE 2014 REVISED PRIMER</strong></td>
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<td>Networking Lunch - Offering an opportunity for clinicians to network and talk about assessment and treatment issues.</td>
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<td>1:15 pm - 2:15 pm</td>
<td><strong>SESSION: IACFS/ME CLINICAL PRACTICE MANUAL: THE 2014 REVISED PRIMER</strong></td>
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<td>Summary of the Conference</td>
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<tr>
<td>2:15 pm - 2:45 pm</td>
<td><strong>SESSION: IACFS/ME CLINICAL PRACTICE MANUAL: THE 2014 REVISED PRIMER</strong></td>
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<tr>
<td></td>
<td>Conference Concludes</td>
</tr>
</tbody>
</table>
Workshop 1  
**Immunology Primer for Practitioners**  
Daniel Peterson, M.D., Nancy Klimas, Ph.D., M.D., Elizabeth Unger, M.D., Ph.D., Gunnar Gottschalk, B.S., Sharni Hardcastle, Sonya Marshall-Gradisnik, Ph.D., Isabel Barao-Silvestre, Ph.D., Konstance Knox, Ph.D., David V. Baewer, M.D., Ph.D., Paula Waziry, Ph.D., Mary Ann Fletcher, Ph.D., Troy Querec, Ph.D.

Participants of this workshop will receive a brief overview of the immunology of Chronic Fatigue Syndrome including a review of the basic tenants of the innate and acquired immune system with special emphasis on cytotoxic T-cells, natural killer cells, B-cells, and an overview of cytokine formation and function. Recognized experts in these fields will additionally present the current status of research into the function and dysfunction of these elements of the immune system in CFS/ME and proceed with brief presentations of cutting edge research studies. Participants by the completion of the discussion session should be able to appropriately order and interpret diagnostic immunological studies on patients presenting with the diagnosis of CFS/ME. This will facilitate the diagnosis, aid in determining prognosis and enable application of appropriate treatment for subsets of patients.

Finally, a consensus panel will provide a discussion of cost effectiveness, commercial availability, and appropriateness of immunological testing in CFS/ME patients.

Workshop 2  
**Legal Issues and ME/CFS**  
Steven Krafchick, M.P.H., J.D., Barbara Arnold, Esq.

The workshop will help the participants understand the role of the physician or physician expert in handling requests for information regarding an ERISA or non-ERISA disability claim for one of your patients. You will learn the basic types of information you will be expected to provide and other types of information it would be useful for you to have to feel confident in supporting your patient’s claim for disability benefits. Often patient claims are terminated or denied because of a lack of understanding the treating physician has about the process or tricks the insurer or ERISA plan uses. Further you will learn how to address cold calls from insurers or their doctors or nurses to interview you about one of your patients. What you say or write can support or torpedo a disability claim.

Workshop 3  
**Exercise Intolerance: Guide to Management and Treatment**  
Staci R. Stevens, M.A., Christopher R. Snell, Ph.D., J. Mark VanNess, Ph.D., Todd E. Davenport, PT, DPT, OCS  

Post exertional malaise (PEM) is a defining characteristic of CFS and a difficult problem to manage for persons with CFS. Our research group has utilized a serial graded exercise test protocol while measuring work output and performing cardiopulmonary analysis to more clearly define PEM. Cardiopulmonary analysis helps to identify cardiac, pulmonary, metabolic and workload-related abnormalities that contribute to PEM. These measurements, made across two days, provide objective documentation for changes in pathology associated with the disease and may be useful for clinical trials examining treatments for this illness. We have proposed the paradigm as a biomarker for PEM in CFS as they appear to relate directly to aerobic system impairment, autonomic dysregulation, and immune dysfunction. This session will also provide a case study based approach to the use of a cardiopulmonary test-retest for identification and quantification of PEM, and provide a conceptual framework for rehabilitation using energy conservation education and analeptic exercise therapy.

Workshop 4  
**Translating Science into the Classroom: A Workshop for Clinicians, Patients and Educators**  
Faith Newton, Ed.D.

This workshop is intended to facilitate and improve communications between clinicians, educators, and parents when working to support children suffering from ME/CFS in their school environment. The workshop will include an introduction to the requirements that school administrators, psychologists, educational diagnosticians, and
teachers face in providing special services to these students, and how the language chosen by clinicians can be critical in determining whether or not a child will receive special services. The presentation will explain the "educational jargon" used in public education under IDEA that requires clinicians to justify those services. Parents and clinicians will be provided with information they can use with schools in situations wherein the existing staff may not have a firm grasp of either ME/CFS or the accommodations that make it possible for children suffering from this illness to succeed. The presentation will be equally valuable for parents who will learn the "educational jargon" to access services, and become more empowered when discussing their educational needs with the schools and physicians.

Workshop 5  
**Invisible and Ignored: Treating Severely Ill Patients with CFS/ME and FM**  
Charles Lapp, M.D., Irma Pinxsterhuis, OTR, MSc and Elin Boile Strand, Ph.D.

Up to 25% of persons with CFS/ME or FM may be housebound or bedfast, yet little is written about this severely ill but “invisible” population. Dr. Lapp will discuss the unique symptoms and complications seen in this group, and offer management strategies. Dr. Elin Strand and Irma Pinxsterhuis will also discuss their experience managing chronically and severely ill patients from the ME/CFS Unit at Oslo University Hospital, Norway.

Workshop 6  
**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 7  
**Diagnosing and Treating Orthostatic Intolerance in CFS/ME**  
Peter Rowe, M.D.

This workshop will review the diagnostic criteria, pathophysiology, and overlaps of NMH and POTS, describe the benefits and limitations of standing tests and tilt table tests for the diagnosis of OI in those with CFS/ME, discuss the non-pharmacological treatment of OI, and discuss the more common pharmacological agents used in managing OI syndromes in CFS/ME.

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

Workshop 8  
**The Management of Pediatric ME/CFS: Translating Research into Clinical Practice**  
Sarah Knight, Ph.D., Lionel Lubitz, M.B.Ch.B., Kathy Rowe, MB.BS

Managing ME/CFS in children and adolescents presents an ongoing challenge to clinicians. This workshop will integrate research and clinical perspectives on the management of pediatric ME/CFS. Particular attention will be paid to effective research translational methods and the practical aspects of ME/CFS management that are unique to the pediatric population.
SESSION: THE LATEST RESEARCH IN IMMUNOLOGY
Session Chair: Nancy Klimas, M.D.

Allergy-related immune signatures and duration of illness in CFS
Susan Levine,1 Xiaoyu Che,2 Andrew F. Schultz,2 W. Ian Lipkin,1 Nancy Klimas,1 Lucinda Bateman,4 Dan Peterson,3 Donna Felsenstein,6 Elizabeth Balbin,1,2,3 Aundrea Carter,1 Korinne Chu,1 Mary Ann Fletcher,1 Anthony Komaroff,1 Gail Ironson1 and Mady Horning1
1Private practice, NY, NY; 2Columbia U Mailman School of Public Health, NY, NY; 3Nova Southeastern U, Fort-Lauderdale-Davie, FL; 4Fatigue Clinic, Salt Lake City, UT; 5Simmaron Research Inst, Incline Village, NV; 6Harvard Med School, Boston, MA; 7U of Miami, Miami, FL; 8Miami VA, Miami, FL; 9U of North Carolina, Greensboro, NC; 10Physicians for Peace, Norfolk, VA

Objectives: Clinical features consistent with atopic and allergic disorders are reportedly more common among CFS patients. We sought to identify evidence for an enhanced allergic phenotype in CFS by comparing plasma levels of allergy-associated immune/inflammatory molecules in CFS patients with shorter vs. longer illness duration.

Methods: 293 CFS patients from two studies (NIH CFS and Chronic Fatigue Initiative studies) were pooled for analysis: 52 short duration (<3 years) and 241 longer duration subjects (>3 years). Plasma samples acquired at clinic visits were subjected to immune profiling analysis, and levels of allergy-related immune molecules were compared in short and long duration CFS.

Results: As compared with long duration CFS patients, patients with shorter illness duration had higher IL4 (p<0.001), IL13 (p<0.014), IL10 (p<0.001), IL6 (p<0.005), IL17A (p<0.001) and CCL5 (p<0.006). There was a trend toward lower eotaxin levels in the short duration subset (p=0.052). Short duration subjects also had elevations in other cytokines implicated in allergic responses, including IL1α, IL1β, IL1RA, IL6, MCP1, CXCL10, MIP1α, IL12p40 and TGFβ (all p<0.002), as compared with longer duration CFS subjects.

Conclusion: Elevated levels of allergy-associated cytokines and chemokines in CFS of <3 vs. >3 years’ duration has led us to postulate a role for these mediators in producing allergic-type clinical phenotypes. Previous studies examining allergic disorders (asthma, allergic rhinitis) - often implicated as comorbid conditions in CFS - support the presence of elevated plasma IL4, IL5 and IL17. Our finding of elevated levels of molecules involved in the allergic diathesis, including IL4 and IL17A as well as IL6, IL8, IL10, and eotaxin-recruiting chemokines such as CCL5, lends support to the hypothesis of a Th2 shift with a distinct immune signature in a subset of CFS. IL4 produced by basophils following encounters with allergens leads to T cell differentiation and IL17A production; IL17A in turn recruits eosinophils, mast cells, neutrophils and other cell types that then produce IL6 and IL8 in addition to other allergic mediators.

Elevated plasma eotaxin cationic protein has been reported in a group of CFS patients, but few other studies have investigated the role of allergic mediators. Our findings suggest pathways for possible therapeutic intervention and clinical trials. Leukotriene inhibitors used to treat asthma that reduce plasma IL-4 could potentially play a therapeutic role in certain CFS subsets. The unique immune signature found in our short duration subjects suggests at least one important pathophysiologic mechanism by which we can begin to understand the allergic CFS phenotype. The influence of eosinophil and basophil levels, age, level of disability, comorbidity, heritable conditions, ethnicity, sex and geographic site will be examined in addition to temporal and seasonal changes in the allergy-related cytokines/chemokines. Future studies should include determinations of levels of histamine, total and specific IgE, prostaglandin E2, tryptophan and serotonin, in addition to comparisons with healthy controls.

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Plasma cytokines in ME/CFS patients and controls before and after a cardiopulmonary exercise test
Ludovic Giotelou1, Betsy A. Keller2, and Maureen R. Hanson3
1Cornell University, Dept. of Molecular Biology and Genetics, Ithaca NY; 2Ithaca College, Dept. of Exercise and Sport Sciences, Ithaca NY

Objectives. Post-exertional malaise is a distinctive feature of ME/CFS. Patients often report an increase in ME/CFS symptoms following levels of activity that would not be challenging to healthy subjects. Unlike healthy subjects, ME/CFS subjects usually fail to reproduce maximum oxygen consumption (VO2max) and/or VO2 at ventilatory threshold (VT) in two successive cardiopulmonary exercise tests (CPETs). Because proinflammatory cytokines are known to cause sickness symptoms in other illnesses such as cancer, we investigated whether an alteration in particular plasma cytokine levels occurs in ME/CFS patients following the first of two CPETs.

Methods. 29 subjects diagnosed with ME/CFS according to the Fukuda criteria as well as 9 healthy controls performed CPETs on a cycle ergometer on two successive days. Expired gases were collected, analyzed using open circuit spirometry, and VT was identified from expired gas analysis using the V-Slope method. Blood was collected before the first and second CPET and plasma was separated and frozen on the day of collection. At rest before and after one CPET, we measured five pro-inflammatory cytokines (TNFa, IL-1a, IL-1b, IL-6, and IL-17), three Th1 cytokines (IFNy, IL-2 and IL-12), and chemokine IP-10 using xMap® technology (Millipore). Non-parametric Mann-Whitney U or Wilcoxon signed-rank tests were used to determine between and
within-group differences, respectively.

Results. VO\textsubscript{2}max and VT values were not significantly different between the first day and the second day in healthy controls. However, all the ME/CFS subjects exhibited abnormally low VO\textsubscript{2}max values during both CPETs and most exhibited reduced VO\textsubscript{2}max during the second day of testing in comparison to the first CPET. Pro-inflammatory IL-1\textalpha{} was detected in plasma of 10 CFS patients and two controls before exercise and after one CPET, but was undetectable in all other subjects. Before and after the first CPET, IL-2 levels were lower in CFS patients compared with the control group (1.70 ± 1.43 versus 2.69 ± 1.54 pg/ml, respectively; p<0.05) and decreased in both groups the day after completion of the CPET (1.44 ± 1.10 in ME/CFS subjects vs. 1.93 ± 1.44 pg/ml in controls; p=0.05) without reaching significance within groups. There were no other significant differences in the assayed cytokines between CFS patients and healthy controls before or after exercise. Overall, exercise did not induce any significant changes in the systemic cytokine levels that were evaluated except for chemokine IP-10, which significantly decreased after CPET in the patient group (385 ± 219 to 337 ± 150 pg/ml, p= 0.015).

Conclusion. IP-10 is secreted by several cell types in response to IFN\gamma{} and IL-2 has been shown to be a potent inducer of IFN\gamma{} gene expression in T cells. After acute high intensity exercise, IP-10 levels decreased in the ME/CFS subjects, indicating immune suppression. The difference in IL-2 levels between patients and healthy individuals reflects initial abnormalities in the ME/CFS population. Taken together, these data imply an abnormal immune response in ME/CFS patients. Further investigation, including analysis of levels of additional cytokines, will be required to understand how this dysregulation could explain the exacerbation of symptoms in ME/CFS patients following exercise.

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**Natural Killer Cell Degranulation and Lytic Proteins in Chronic Fatigue Syndrome/Myalgic Encephalomyelitis**

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\textsuperscript{3} Gold Coast Public Health Unit, Queensland Health, Queensland, Australia.

Objectives: Reduced Natural Killer (NK) cell cytotoxic activity is a recurring finding in patients with Chronic Fatigue Syndrome/Myalgic Encephalomyelitis (CFS/ME). NK cell cytotoxic activity is important for removing virally infected or malignantly transformed cells and a critical component of NK cell cytotoxic activity is the release of the lytic proteins perforin, granzyme A and granzyme B by a process known as degranulation. This study measured NK cell perforin, granzyme A, granzyme B and degranulation in CFS/ME patients to determine whether lytic proteins or degranulation may contribute to the reduced NK cell cytotoxic activity in CFS/ME patients.

Methods: Peripheral blood mononuclear cells (PBMCs) were isolated from 30 CFS (mean age = 51.15±1.92 years) and 25 non-fatigued controls (mean age = 50.42±1.76 years). NK cell perforin, granzyme A and granzyme B levels were determined by intracellular staining and NK cells were stimulated to degranulate with K562 cells and phorbol 12-myristate 13-acetate/ionomycin (PHA/I) for 6 hours. NK cell degranulation was measured by surface expression of CD107a and NK (CD56\textsuperscript{+}CD3\textsuperscript{-}) cell levels of perforin, granzyme A, granzyme B and CD107a was determined with flow cytometric protocols.

Results: A significant increase (P<0.05) in NK cell expression of CD107a was observed in CFS/ME patients following stimulation with PHA/I and K562 cells. No significant differences in NK cell perforin and granzyme A were observed between the non-fatigued controls and CFS/ME patients. However, granzyme B in NK cells from CFS/ME patients was significantly reduced (P<0.05).

Conclusion: These results indicate that the aberrant function of NK cell lytic proteins and degranulation may contribute to the reduced NK cell cytotoxic activity reported in CFS/ME patients. Further investigations are required to determine if there is a correlation between dysfunctional NK cell degranulation and release of the lytic proteins required to induce target cell apoptosis.

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**A Genome-wide Analysis of Differential Methylation Associated with Chronic Fatigue Syndrome**

Mangalathu S. Rajeevan\textsuperscript{1}, Virginia Falkenberg, Irina Dimulescu, Elizabeth R. Unger, Centers for Disease Control and Prevention, Atlanta, GA

Background: The role of epigenetic changes in the pathogenesis of chronic fatigue syndrome (CFS) remains largely unexplored. Comparison of CFS to non-fatigued (NF) healthy controls alone is inadequate to confirm the specificity of CFS-associated abnormalities. Genome-wide analysis of differential DNA methylation between CFS and NF subjects is a first step in identifying candidate genes and pathways that may be implicated in the pathogenesis of CFS.
**Methods:** This study included 80 subjects (34 CFS and 46 NF) from the follow-up of the Georgia Surveillance study who participated in a 3 day study at the Emory General Clinic Research Center. CFS cases met the 1994 international research definition of CFS as evaluated by standardized questionnaires including the Multidimensional Fatigue Inventory, the SF-36® Health Survey, and the CDC Symptom Inventory. This case-control study was matched for age, sex and race. DNA from peripheral blood mononuclear cells was analyzed using the Illumina 27K methylation array following the manufacturer’s protocols. Quality control of the array data was conducted using HumanMeth27QCReport. Differentially methylated CpG sites were identified by linear regression (MethLab). DAVID v6.7 gene functional classification module and Ingenuity pathways were used for annotation. Gene expression in whole blood RNA was analyzed using Affymetrix Human Exon 1.0 ST array. Relative telomere length in DNA from whole blood was determined using real-time PCR with telomere specific primers and 36B4 as single copy reference gene.

**Results:** Methylation array data from 27 CFS and 41 NF subjects passed quality control. Differential methylation was identified at 1101 CpG sites (p <0.05) in 205 genes with pathway and functional annotation. The major pathways were apoptosis (76 genes), migration (54 genes) and immune function (34 genes). Among the 205 differentially methylated genes, only 17 showed differential expression (p<0.05) in whole blood and only one, TERT (telomerase reverse transcriptase), showed a significant correlation between expression and methylation (Spearman r = -0.3, p = 0.033). TERT methylation was lower in CFS compared to NF (p = 0.018), and in agreement with a general silencing effect of methylation on expression, TERT expression was significantly higher in CFS compared to NF subjects (p = 0.048). However, telomere length was significantly shorter in CFS compared to NF (p=0.009).

**Conclusions:** Differential methylation of genes in several pathways was identified in CFS, but only TERT was correlated with a corresponding change in gene expression. CFS subjects had decreased methylation and increased expression of TERT, yet had shorter telomere length. Because TERT has been associated with aging, and CFS shows some features of accelerated aging, further studies of pathways associated with aging could be explored in CFS.

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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 the Centers for Disease Control and Prevention.

**SESSION: VIROLOGY RESEARCH**

**Session Chair:** Jose Montoya, M.D.

**Chronic pelvic pain (CPP) in patients with myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) is associated with chronic enterovirus infection of ovarian tubes.**

**John Chia, David Wang, Rabiha El-habbal and Andrew Chia, EV Med Research, Lomita California**

**Background:** Similar to functional dyspepsia (FD) and irritable bowel syndrome (IBS), CPP is common in ME/CFS patients and often considered as a psychosomatic symptom. Pelvic pain would resolve in most patients after total abdominal or vaginal hysterectomy and bilateral salpingo-oophorectomy (TAVH/BSO), which suggested possible undefined etiology. We have previously demonstrated enteroviral protein in the stomachs, small intestines and colons of ME/CFS patients with FD and IBS. Enterovirus can cause infection of the male genital tract, and has been detected in the vaginal secretions of women. Viral protein was also found in the tubal tissue of a pre-coital female with tubo-ovarian abscess. We investigated the possibility of enterovirus infection of the ovaries/tubes as the cause of CPP.

**Methods:** 23 females fulfilling the CDC criteria for ME/CFS and criteria for chronic pelvic pain syndrome and had prior TAVH/BSO or unilateral salpingo-oophorectomy (USO) were enrolled in the study. Patients who had TAH/BSO or USO for uterine fibroids (5), endometrial or cervical carcinoma (4), involvement by adjacent intestinal diseases (3), large ovarian cyst (1) and cancer prevention (2) were chosen as control subjects. Using specific monoclonal antibody, 5D8/1 at 1:1000 dilution, Epithelium stained positive in 24/27 (89%) ovarian tube samples from ME/CFS patients and control subjects were stained for enterovirus capsid protein 1 (VP1) by immunoperoxidase technique. 3 mice with severe combined immunodeficiency (SCID) were injected with lysates of 2 cryopreserved, VP1+ ovarian tube samples. Polyclonal antibody gel electrophoresis and western blot were performed on lysates of selective samples, using 5D8/1 monoclonal antibody. Enterovirus VP1 was found in the ovarian tubes of most patients with ME/CFS and CPP but not in control subjects, and injection of tubal lysate caused infection in SCID mice. Improvement of unilateral pain following TAVH/BSO or USO correlated with finding viral protein in the ipsilateral tube in most of the patients. Chronic enterovirus infection of the ovarian tubes or chronic enteroviral salpingitis, is likely responsible for CPP, and these symptoms should not be referred to as psychosomatic complaints.

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Occurrence of typical clinical symptoms and markers of human parvovirus B19 infection in patients with myalgic encephalomyelitis/chronic fatigue syndrome

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Objective
Human parvovirus B19 (B19) has been implicated in the pathogenesis of myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS). B19 belongs to the Erythrovirus genus, Paroviridae family and Parovirinae subfamily. It is immunomodulating single-stranded DNA virus, which has tropism for erythroid precursor cells. Objective of this work was to estimate occurrence of typical ME/CFS clinical symptoms with presence of B19 infection markers in patients with ME/CFS.

Methods
One hundred and ninety patients (128 female and 62 male, mean age 38 years) with ME/CFS fulfilling CDC diagnostic criteria and 94 age and gender matched apparently healthy individuals were included in this study. Presence of B19 NS1 gene sequence was detected by nested polymerase chain reaction (nPCR).

Results
Using nPCR B19 genomic sequence was detected more frequently in ME/CFS patients’ DNA isolated from cell free blood plasma (41/190, 21.6%) (marker for active infection), than in DNA isolated from whole blood - 15/190 (7.9%), which was used as marker for persistent infection in latent phase (p=0.0002). Significantly higher frequency of B19 was found in patients with ME/CFS comparing to apparently healthy individuals (41/190 and 2/94, respectively, p=0.00001).

Severe chronic fatigue for at least six months was observed in all patients with ME/CFS. Post-exertional malaise had similar percentage in patients with B19 genomic sequence in cell free blood plasma DNA and whole blood DNA - 53.7% and 53.3%, respectively. Impaired memory and lymphadenopathy were ascertained more often in ME/CFS patients with active (70.7% and 51.2%, respectively), than with persistent B19 infection in latent phase (46.7% and 26.7%, respectively). Decreased concentration was observed in 56.1% of patients with active and in 53.3% of patients with persistent B19 infection in latent phase. Sleep disturbances had 65.9% and 60% of ME/CFS cases with active and persistent B19 infection in latent phase, respectively. In patients with active B19 infection subfebrility was detected significantly frequently than in patients with persistent B19 infection in latent phase (53.7% and 20%, respectively, p=0.0344). Headache of new type was observed in 51.2% and 46.7% of ME/CFS patients with active and persistent B19 infection in latent phase, respectively. However, muscle pain and multi-joint pain was detected in more patients with persistent B19 infection in latent phase (46.7% and 40%) than with active B19 infection (43.9% and 39%), respectively.

Conclusion
Association of active B19 infection with part of typical ME/CFS clinical symptoms shows possible B19 involvement in disease pathogenesis, however role of persistent infection cannot be excluded. Activation/reactivation of B19 may be as a risk factor for ME/CFS.

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Pathogenesis of chronic enterovirus infection in myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) - in vitro and in vivo studies of infected stomach tissues.

John Chia, Andrew Chia, David Wang, Rabîna El-Habbat. EV Med Research. Lomita, CA

Objectives: Chronic enterovirus infection has been implicated in the pathogenesis of ME/CFS. Previously, we demonstrated enteroviral protein (VP1), enteroviral RNA (EV RNA) and non-cytopathic viruses from the stomach biopsies of ME/CFS patients. The basis of viral persistence has not been clearly defined. Enterovirus can form double-stranded RNA (dsRNA) in tissue cultures and in muscles of infected mice and human. We evaluated stomach biopsies for the presence of dsRNA and possible infectivity in a mouse model.

Method: Using specific monoclonal antibodies, archived, paraffin-embedded stomach biopsies from ME/CFS patients and control subjects were stained for VP1 and dsRNA by immunoperoxidase technique. 24 mice with severe combined immunodeficiency (SCID mice) were injected with lysates of 24 cryopreserved, VP1+, dsRNA+ stomach biopsy samples; and control mice were injected with boiled VP1+, RNA+ samples (4), VP1+, RNA-negative samples (4) and culture medium (2). Mice were sacrificed 2-4 weeks after infection, and organs processed for viral cultures, EV RNA and viral protein staining.

Results: 259/314 (82%) and 198/314 (63%) of the stomach biopsies from ME/CFS patients whereas 9/47 (19%) and 5/47 (10%) of the control specimens stained positive for VP1 and dsRNA, respectively (p=0.001, χ² test). Pre-treatment with RNase III of selective samples diminished or abolished the dsRNA staining; higher concentrations of enzyme and longer incubation period were required for specimens from sicker patients. 21/23 (91%) of stomach biopsies previously tested positive for EV RNA by RT-PCR or had grown non-cytopathic virus stained positive for dsRNA. Of 24 mice injected with VP1+, RNA+ stomach biopsies, 2 died
in two weeks and 13/20 (66%) spleen specimens tested positive for VP1 whereas 1/10 control specimens tested positive for VP1 by immunoperoxidase staining (p<0.01, x² test). Of mice injected with RNA+ stomach lysate, 13/24 lung, 1/24 of heart and 0/24 of kidney specimens demonstrated VP1 staining, whereas all the control samples were negative. Tissue homogenates from first 10 mice given infected stomach lysates tested negative for EV RNA and had not grown virus in BGMK-DAF and WI-38 cells. Extract of paraffin-embedded tissues from 10 other infected mice tested negative for EV RNA.

Conclusion: DsRNA was frequently demonstrated in VP 1+ stomach biopsies taken from ME/CFS patients, and most EV RNA+ samples had detectable dsRNA by immunoperoxidase staining. DsRNA+ samples were infectious in SCID mice without forming true virions. Enteroviral dsRNA plays a central role in the pathogenesis of chronic EV infection and ME/CFS, and should be targeted for antiviral therapy.

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SESSION: TREATMENT STUDIES
Session Chair: Daniel Peterson, M.D.

Treatment of orthostatic intolerance (OI) using midodrine in patients with Chronic Fatigue Syndrome (CFS); and assessment using Hours of Vertical Activity (HVA).

Nicole Baldwin, St. Olaf College, Northfield, MN, and *Lucinda Bateman MD, Fatigue Consultation Clinic, Salt Lake City, UT. Funded by an OFFER research intern grant.

Objectives: To examine the effectiveness of midodrine as a treatment for OI in the clinic’s CFS/FM patients using HVA as a measure of functional improvement.

Methods: A retrospective chart review was conducted of CFS patients diagnosed with OI and offered a trial of midodrine for the treatment of OI symptoms. A word search for “midodrine” in clinic notes was conducted to identify patients offered midodrine from March 2011 to May 2013. Since March 2011 the clinic intake form has included a rating of HVA, the number of hours in a 24-hour time frame in which the patients have their feet on the floor (sitting or standing as opposed to supine or recumbent with feet up). Twenty-three patients were identified; 23 had been diagnosed with OI, 22 with CFS, 17 with comorbid fibromyalgia (FM), and 11 specifically with POTS (the postural orthostatic tachycardia sub-type of OI). These 23 patients were then divided into 3 groups according to their use of midodrine: 12 never actually started the midodrine, 5 took some midodrine but did not reach and continue the full dose, and 6 took midodrine at the full therapeutic dosage. Average HVA and numeric symptom scores (scale of 0-10 with 10 the worst) over defined intervals after midodrine was first offered were then calculated for each group. Standard symptom management treatments were continued for all patient groups.

Results: Patients taking midodrine, especially those on the full therapeutic dose, show a small sustained increase in HVA compared to baseline, while the others did not, even though receiving other standard interventions. Patients who reached the full dose had the lowest baseline HVA, while those who did not start midodrine had the highest HVA at baseline. Symptom scores were similar for all patient groups, although the patients showing variable compliance had the least improvement in all symptom scores.

Conclusions: Scheduled midodrine use can sustain a small but clinically meaningful increase in HVA in patients with CFS and OI. Midodrine is more effective when the full therapeutic dose is taken. Patients with low HVA at baseline may be more likely to reach and continue the full dose, and experience an increase in HVA. In addition, while other symptoms do not necessarily improve with the use of midodrine, the HVA measurement does reflect an increase in function for patients taking midodrine. Therefore, HVA may be a useful measure for objectively evaluating vertical activity tolerance and the effectiveness of midodrine.

Intervention Effect of Baduanjin on the Fatigue State in People with Fatigue-predominant Sub-health----A Cohort Study

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Objectives: To observe the intervention effect of Baduanjin (a set of qigong exercises that originated in China and are practiced throughout the world) on the fatigue state in people with fatigue-predominant sub-health.

Methods: The subjects that met the inclusion criteria were divided into Baduanjin cohort and control cohort according to whether they exercise Baduanjin or not. The subjects in the Baduanjin cohort had been exercising twice a day for six weeks. The fatigue state of all the subjects in both cohorts was evaluated with the fatigue Self-assessment Scale (FSAS) at baseline and the end of sixth week. And the changes of fatigue state were compared. The scale consists of the following factors of physical fatigue (PF), mental fatigue (MF), consequence of fatigue (CF), situationality of fatigue (SF), response of fatigue to sleep and rest (RFSR) and time mode of fatigue (TMF). In which the factor of TMF was not used in this study.

Results: Among 129 subjects included in the data analysis, there were 62 subjects in the Baduanjin cohort and 67 subjects in the control cohort. Compared with the baseline, the scores of all of the factors in the Baduanjin cohort are significantly declined (P<0.05) with the exception of the factor of SF and no marked changes (P>0.05) in the control cohort. Compared with the control cohort at the end of sixth week, the scores of all of the factors in the
Effect of isometric yoga on chronic fatigue syndrome: a randomized controlled trial

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Graduate School of Medical Sciences, Kyushu University

Objectives: Some patients with chronic fatigue syndrome (CFS) complain of persistent fatigue even after the conventional therapy, which includes pharmacotherapy and cognitive behavioral therapy. The aim of this study was to investigate the effect of isometric yoga on the conventional treatment-resistant CFS patients.

Methods: Twenty-four patients with CFS who hadn’t improved sufficiently even after the conventional therapy for at least 6 months were included in this trial. They were randomly divided into the two groups and were treated with either ordinary pharmacotherapy (control group, n=12) or ordinary pharmacotherapy plus isometric yoga (biweekly 20 min practice with a yoga instructor and daily home practice) (yoga group, n=12) for eight weeks. Adverse events, subjective symptoms, severity of fatigue and pain were evaluated before and after starting the yoga intervention. Severity of fatigue was evaluated by Chalder’s fatigue scale (FS) and F score of the Profile of Mood States (POMS).

Results: One subject with yoga group complained of dizziness only after the first practice of yoga. There was no one whose fatigue exacerbated by practicing isometric yoga. All subjects reported that their bodies became warmer and lighter after practicing yoga. At eight weeks after the intervention, Chalder’s fatigue scale (FS) and F score of the Profile of Mood States (POMS) significantly decreased compared to baseline.

Conclusion: The isometric yoga is safe and beneficial for relieving fatigue of conventional therapy-resistant CFS patients.

Home-Based Self-Management for Severe CFS/ME: A Randomized Trial

Fred Friedberg, Ph.D., Jenna L. Adamowicz, M.A., Viktoria Seva, M.A., Indre Caikauskaite, B.A.

Objective: This study is a randomized trial of a feasibility-tested fatigue self-management program. The objective was to test a home-based self-management protocol in people with severe CFS/ME. An effective home-based self-management plan has the potential to improve access to treatment for patients who may be unable to travel to regular appointments, to offer a substantially more time-effective and lower cost for higher credibility self-management protocol in people with CFS/ME, and to substantially reduce illness burden and improve quality of life for these debilitated patients.

The hypothesis was tested that two home-based self-management intervention conditions will be more efficacious than the wait list condition, yielding improvements in fatigue, functioning, and depression, and that outcomes between the two home self-management conditions will not be significantly different.

Methods: The efficacy of a home-based self-management intervention was tested in a target sample of 137 persons with severe CFS/ME (most were disabled and unemployed). Participants were randomly assigned to one of three study conditions: (1) wait list control (UC); (2) home self-management utilizing web diaries and activity monitors (FSM: ACT); or (3) home self-management utilizing paper diaries and step counters (FSM: CTR).

Results: At the one year follow-up, sample sizes were as follows: Home self-management utilizing web diaries and activity monitors (FSM: ACT) = 45; Home self-management utilizing paper diaries and step counters (FSM: CTR) = 44; and Wait list condition (UC) = 48. Preliminary analyses at the one year follow-up showed significant reductions (p<.05) in the combined self-management conditions on the effect of fatigue on functioning (Fatigue Severity Scale) and depression symptoms (Beck Depression Inventory). No significant changes were found on diary fatigue ratings, the SF-36PF, or the Beck Anxiety Inventory. Fatigue severity and depression outcomes were not significantly different between the two home self-management conditions.

Conclusion: A home self-management program for severe CFS/ME resulted in improvement in fatigue impact on functioning and depression. These findings indicate a role for home self-management activities in generating improved outcomes.

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A Comparison of the Case Definitions
Leonard Jason, Ph.D.
Professor, DePaul University, Director of the Center for Community Research

Current case definitions for Myalgic Encephalomyelitis (ME) and chronic fatigue syndrome (CFS) vary in the type and number of symptoms required. Case definitions that do not require cardinal symptoms of this illness might not accurately identify those with this illness. However, other case definitions that require seven or eight core symptoms could increase rates of psychiatric comorbidity. Current consensus-based case definitions may lack construct validity, resulting in inaccurate diagnoses of ME and CFS. We review current case definitions as well as promising methods for identifying these features which include statistical approaches such as factor analysis and data mining.

Immunological, physical and social functioning in varying cases of Chronic Fatigue Syndrome/Myalgic Encephalomyelitis

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Objectives: The purpose of this study is to determine whether immunological, physical and social functioning varies in Chronic Fatigue Syndrome/Myalgic Encephalomyelitis (CFS/ME) patients that meet different diagnostic criteria for the illness, and healthy controls.

Methods: A total of 35 patients diagnosed with CFS/ME and 22 healthy controls from the South East Queensland region of Australia provided a blood sample for standard screening of illness and immunological analysis. Participants also completed a diagnostic questionnaire, the Short-Form General Health Survey (SF-36), and the World Health Organization Disability Adjustment Schedule 2.0 (WHO DAS 2.0).

Results: Eighteen patients were classified as 1994 Centers for Disease Control (1994 CDC) cases, and 17 were classified as International Consensus Criteria (ICC) cases. No differences were found between the two groups for standard blood tests. Natural Killer (NK) cell activity was consistently and significant decreased, while regulatory T cells (Tregs) were significantly increased in both CFS/ME subgroups, in comparison to healthy controls. Salient differences between 1994 CDC and ICC groups were also detected in human neutrophil antigens and expression of NK cell receptors. ICC patients however, were found to report significantly lower SF-36 scores for physical functioning, physical role, bodily pain, and social functioning. These findings were also supported by the WHO DAS 2.0 scores with ICC patients reporting greater impairment across all measures.

Conclusion: These preliminary findings suggest that the ICC case definition identifies a subgroup found within 1994 CDC patients, with more severe impairment to their physical and social functioning. Further, the ICC may be more effective at detecting salient differences in the immune system found in CFS/ME. Further investigation is required into the clinical presentation of these patients to determine whether more profound and specific relationships can be found. The presence of immune abnormalities combined with clear clinical measures could potentially serve as an important diagnostic tool for the illness.

Keywords: Chronic Fatigue Syndrome; Diagnostic criteria; Myalgic Encephalomyelitis; Health Related Quality of Life.

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Case Definitions: Diagnostic and Criterion Issues
Leonard A. Jason (Ph.D., DePaul University), Madison Sunquist (B.S., DePaul University)

Objectives: Considerable debate surrounds the search for the defining features of chronic fatigue syndrome (CFS), Myalgic Encephalomyelitis (ME), and Myalgic Encephalomyelitis/chronic fatigue syndrome (ME/CFS). Current case
definitions were created through clinical consensus, but empirical methods may better identify the core domains of the illness. This presentation will describe recommendations for empirically defining essential features.

**Methods:** Data will be presented regarding the prevalence of chronic fatigue in the general population, defined as having six or more months of chronic fatigue. Of these individuals, we will also provide estimates of the percentage of those with medical or psychiatric reasons for their fatigue. Of those that remain, we will examine the limitations and challenges of current case definitions to define this group.

**Results:** It is interesting to note that Fibromyalgia and Multiple Chemical Sensitivities have approximately the same prevalence rates as chronic fatigue. Of the patients with chronic fatigue, medical (e.g., cancer, heart disease, etc.) or psychiatric explanations were found in all but 0.5-1.0% of individuals. These remaining individuals represent the group that current case definitions attempt to define. Current case definitions for this group will be compared and contrasted. We will use data mining strategies to show that requiring fewer targeted and fundamental symptoms results in better sensitivity, specificity and accuracy in the selection of cases, while those that require many symptoms increase rates of psychiatric comorbidity within samples.

**Conclusion:** Current consensus-based case definitions may lack construct validity, resulting in inaccurate diagnoses. Furthermore, the requirement of a large number of symptoms may inadvertently increase psychiatric comorbidity. In order to progress the search for biological markers and effective treatments, essential features of this illness might be empirically identified so that individuals included in samples have the same underlying illness. Advanced statistical techniques such as data mining are promising methods for identifying these features.

**Relation to Conference Theme, “Translating Science into Clinical Care”:**
In order to further the search for biological markers and beneficial treatments, both essential for effective clinical care, case criteria must be reliable and valid.

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**SESSION: PUBLIC HEALTH RESEARCH - PART I**

**Session Chair:** Lily Chu, M.D.

**CFS/ME and fatiguing illnesses: differential diagnoses from a community-based sample.**
_Nicoletta Carlo-Stella MD, PhD, free professional, Pavia, Italy_

**Introduction:** ME/CFS when diagnosed in a clinical setting is considered to be an exclusionary diagnosis, and scientific literature frequently cites the diseases characterised by fatigue, which should be taken into account when considering a diagnosis of CFS/ME. However data on the frequency of making an alternative diagnosis in patients with fatigue are scarce.

**Materials and Methods:** 89 consecutive self-referred patients complaining of PENE (post-exertional neuroimmune exhaustion) (1) were seen in a private practice specializing in CFS/ME from 2007 to 2012. A thorough work-up including history, clinical examination, lab testing and imaging, when necessary were undertaken.

**Results:** 31.4% of the patients were male; 68.6% were female. The ages ranged from 20 to 60 years of age. A diagnosis of CFS/ME was confirmed in 36 patients (40%); however rheumatological diseases (43%), endocrine disorders (5.6%), psychiatric diseases (5.6%), gastrointestinal diseases (4.5%), haematological cancer (2.2%) and urological bladder cancer (1.1%) accounted for the remaining 60% of diagnoses of patients complaining of fatigue.

**Conclusions:** notwithstanding the fact that these patients were mostly self-referred and moreover through information gathered through the internet and social networks, 40% of them were correctly diagnosed as having CFS/ME. However 60% of the patients were not. This is in accordance with a recent paper on conducting a pilot registry in Bibb County, Ga (2). Thus caution is warranted before making a final diagnosis of CFS/ME.

**References**


Expanding Access to Knowledgeable Healthcare for Neuro-endocrine-immune Diseases in Alabama - A Case Study

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Objective: Complex chronic diseases of the neurological, endocrine, and immune systems include myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS), fibromyalgia, and chronic Lyme disease. Early diagnosis and treatment are important for optimum outcomes. We sought to accomplish this goal through increasing medical professional knowledge of and establishing a specialty center for these diseases in central Alabama.

Methods: In the summer of 2012, we discovered a politician has a personal interest in one of these diseases. He arranged for us to meet the CEO of a 4-hospital system in central Alabama. We requested they sponsor continuing medical education courses in tick-borne infections, fibromyalgia, and ME/CFS. We conducted a patient survey showing evidence of this unmet medical need in Alabama.

Results: In 2013, St. Vincent’s Healthcare System sponsored a 1-hour ME/CFS CME course for its affiliated physicians. Sixty-nine medical professionals attended. The attendees received a copy of the International Association of CFS/ME Physician Primer. St. Vincent’s scheduled a 1-hour fibromyalgia CME course for January 14, 2014. They plan to have a future CME course on tick-borne illnesses. A physician with an interest in being a part-time medical director of a center for these diseases was found through the CME course. She studied about the diseases and, with organization assistance of the costs, she attended the 2013 International Lyme and Associated Diseases medical conference. She later declined to continue pursuit of being the medical director for a neuro-endocrine-immune center because she did not want to give up her primary care practice or hire another doctor to care for her current patients. Hospital administrators researched the financial viability of a clinic in a hospital setting, but could not take any more actions without having a clinician interested in the diseases and being the clinic director. The hospital system’s administrators’ priorities shifted to finding more primary care physicians to meet the demand brought by the Affordable Care Act. Also, four Alabama clinicians and two Alabama researchers have agreed to receive information of neuro-endocrine-immune disease research.

Conclusion: Physicians avoid patients with neuro-endocrine-immune diseases because they lack the knowledge to effectively treat them and the disease complexity takes long clinical visits for which insurance providers do not adequately reimburse, especially in a primary care practice and for which there is little income through procedures or therapies (as in radiation or chemotherapy in a cancer center). Administrators must first have a clinician wanting to care for these patients before a center can be created, and a business model for a financially viable clinic must be formed. Thus, increasing knowledge and interest in local physicians who already have interest in related conditions, attracting a physician in a residency program or a medical school student are possible first steps in creating a center for these diseases in areas where there is no expert.

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Family Aggregation Studies In CFS

Alegre J, Castro-Marrero J, Ribases M, Aliste L, Saez N, Calvo N, Marquino A, Fernandez de Sevilla T and Fibromyalgia and CFS Spanish Genetic and Clinical Data Bank (FSGCDB Group) and Foundation FF.

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CFS is a multisystemic disorder with immunogenetic background, as well as several triggers and a number of alterations in the response proteomics, immune dysfunction, which result in the disabling of the complex symptomatology in chronic fatigue. In the literature, several authors mention that a high percentage of family history of autoimmune diseases and rheumatologic conditions.

Objectives: To know the family history and familial aggregation in a series of Spanish CFS patients.

Patients And Methods: A prospective study included patients who fulfilled the diagnostic criteria for CFS and first-degree relatives, initially involved in the DNA Bank Genome Spain Foundation and later in Genetics Group (Psychiatry Research Lab, Vall d'Hebron University Hospital, Barcelona, Spain). First-degree relatives, they performed a medical history, physical examination and review of complementary, for the screening of fatigue.

Results: 1140 patients diagnosed with CFS included in the DNA Bank, (114 men/1026 female). 13 % had a family history of CFS, 12% fibromyalgia, 8% immune diseases, 7% rheumatic diseases, 10% thyroid disease and with at least one of the specified family history in 36%. 468 healthy controls individuals were included as first-degree relatives. The 39% of first degree relatives could not be considered as healthy controls, being affected by CFS, chronic
fatigue associated with fibromyalgia and/or immunological diseases vs. rheumatology conditions. 167 households were found not healthy controls, 25 with 5 or more members’ affections, 15 with 4 members, 46 with 3 members and 81 with 2 members. CONCLUSIONS: 1140 CFS patients are included in the DNA Bank of FMS and CFS. 36% have a family history of CFS, fibromyalgia, rheumatic diseases and/or immunological. From the controls, 39% of families were suffering from fatigue, fibromyalgia and/or immune-mediated diseases and rheumatologic disorders. Note: 167 households were not healthy controls.

Discussion: In patients diagnosed with CFS, there is often a family history of CFS, fibromyalgia, as well as immune-mediated inflammatory disease (IMID) or rheumatologic, and the frequent familial aggregation. This advocates starting genetic susceptibility studies on them.

The UK ME/CFS Biobank: 2 years of experience
Eliana M Lacerda, Erinna W Bowman, Sunita Nagpal, Ronnie Chee, Luis C Nacul

Objectives: The UK ME/CFS Biobank was created by the CURE-ME group at the London School of Hygiene & Tropical Medicine as an open resource for high quality and ethical biomedical research, in particular for investigations to identify biomarkers for diagnosis and prognosis. Researchers utilizing the Biobank have access to well-catalogued, anonymized blood samples linkable to comprehensive clinical and risk factor data.

Methods: Following extensive discussions with people with ME/CFS, carers, and professional experts, we developed a robust protocol for the biobanking of tissue samples from people with ME/CFS (PWME) and controls. Residents of study areas in the UK with a clinical diagnosis of ME or CFS are recruited and categorized as cases according to Canadian, CDC-94 and three other diagnostic criteria, based on further assessment and investigations. Controls without fatigue (“healthy”) and with multiple sclerosis (MS; starting October 2013) are recruited using similar procedures. A sub-sample of participants are followed up at six months, and further follow-ups are planned, dependent on supplementary funding. We obtain relevant information enabling comprehensive characterization of the subjects and clinical phenotyping. Blood samples are taken from all participants and processed and separated into aliquots within 6 hours of collection and are then frozen in optimum conditions at state-of-the-art facilities at University College London / Royal Free Hospital (UCL/RFH) BioBank. Sub-samples are released for approved research studies.

Results: We will present the Biobank infrastructure and various procedures involved in ensuring quality of data and samples as well as legal, ethical, and logistic aspects of recruitment and assessment of participants, sample collection, and storage. We will also present selected outcomes (results) for over 250 Biobank participants and generated research hypotheses. By the end of August 2013, 104 cases (80% women) and 69 controls had donated blood samples and provided information on a range of clinical and socio-economic variables. The results confirm previous findings showing significant effects on various domains of quality of life, with some variation depending on the diagnostic criteria used.

Conclusion: The collection of high quality samples linked to comprehensive clinical and socio-demographic data functions as an open resource for research, with the potential to lead to biomarker discovery and research that will translate into better diagnosis and treatment of PWME. Working with standardized procedures in collaboration with other biobanks internationally greatly increases the potential for research outcomes with direct relevance to clinical practice.

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The lay-scientific partnership that shaped and development of the UK ME/CFS Biobank
“if we say ‘come on we are doing some research, and it will be like a blood party’…”
Eliana M Lacerda, Erinna W Bowman, Luis C Nacul

Objectives: To investigate the feasibility of setting up a biobank for the study of ME/CFS and to develop a protocol for its implementation that is acceptable, cost-effective, and complies with ethical and legal frameworks. The goals of the UK ME/CFS Biobank are to facilitate the structured collection and examination of human tissue of people with and without ME/CFS using carefully chosen approaches to recruit and follow up donors and to collect, store, and examine tissue samples (blood in particular).
Methods: We carried out a consultation process involving discussions with people with ME/CFS (PWME), carers, researchers, clinicians, and ‘experts’ in the fields of human tissue banks, law and ethics, to help delineate the specifications of the ME/CFS tissue bank. Qualitative methodology included focus group discussions with PWME (including both ‘expert’ and ‘lay’ patients) and carers.

Results: A participatory research approach established that setting up the biobank for the study of ME/CFS is both desirable and feasible. Participants highlighted the importance of a good definition of cases and controls; careful data collection methods by experienced people, especially in the severely ill; rigorous protocols for collection, transport, and storage of samples; and consideration of ethical and legal aspects, including clearly-worded informed consents addressing retrieval of clinical data and assuring anonymity and data confidentiality. A robust protocol for the setting up of the biobank informed by patients and experts was elaborated, and the facility was initiated in August 2011 with the expectation that it would help stimulate high quality ME/CFS research in a cost-effective manner.

Conclusion: PWME favoured the creation of a biobank for the study of ME/CFS that takes into account their wishes and concerns and are overwhelmingly willing to contribute with blood donations. Recommendations of PWME were fully taken into account alongside those given by professionals to create a protocol well-accepted by patients and the scientific community and responsive to the pressing need for further good quality biomedical research.

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SESSION: PUBLIC HEALTH RESEARCH - PART II

Session Chair: Elizabeth Unger, M.D., Ph.D.

Prevalence and Health-related Characteristics of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS), Fibromyalgia (FM) and Environmental Sensitivities/Multiple Chemical Sensitivity (ES/MCS): Results from the Canadian Community Health Survey (CCHS)

Parlor M, National ME/FM Action Network, Halapy E, Ontario Centre of Excellence in Environmental Health Business Case Project

Objective: In support of health care system planning in Ontario, the objective of this presentation is to quantify and interpret a broad range of health-related characteristics associated with ME/CFS, FM and ES/MCS based primarily on results from the 2005 and 2010 CCHS.

Methods: CCHS respondents are asked about chronic conditions including ME/CFS, FM and ES/MCS that have been diagnosed by a health professional. Measures of disability, health care utilization (including consultations with physicians and other health professionals), unmet health and home care needs, home care services received and socioeconomic factors were examined from the 2005 and 2010 CCHS. For each variable, estimates for the Total Canadian population as well as for four chronic health conditions (cancer, diabetes, effects of a stroke and heart disease) are presented as comparison groups.

Results: According to the 2010 CCHS, approximately 411,500 Canadians were diagnosed with ME/CFS, 439,000 with FM, 800,500 with ES/MCS and over 1.4 million with one or more of ME/CFS, FM or ES/MCS. The prevalence of one or more of ME/CFS, FM or ES/MCS increased from 4.2% (95% confidence interval (CI) 4.0%-4.3%) in 2005 to 4.9% (95% CI 4.6%-5.2%) in 2010. Canadians with these conditions are significantly impaired as demonstrated by high levels of being permanently unable to work and needing help with activities of daily living; require medical support as demonstrated by a high number of consultations with doctors; may receive inadequate care as indicated by high proportions of unmet health care needs and low proportions receiving home care services; are looking for help beyond the conventional medical profession through consultations with other health professionals; and, are experiencing socioeconomic disadvantage as demonstrated by high levels of moderate or severe food insecurity and sizeable proportions with low annual household income.

Conclusion: Analyses of CCHS data have indicated that ME/CFS, FM and ES/MCS are conditions with significant impact on individuals as well as the population. Unmet health care needs despite high physician utilization combined with lower rates of home care services may indicate that people with these conditions are receiving ineffective care or are experiencing barriers to and deficits in care. This information along with qualitative and clinical/academic information has been submitted to health system planners. Ongoing surveillance of these conditions is imperative to shed further light on the problem and to monitor the impact of health system initiatives.

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The Natural Course of Chronic Fatigue Syndrome: Evidence from a Multi-Site Clinical Epidemiology Study

Dana March, PhD; Assistant Professor, Department of Epidemiology, Columbia University Mailman School of Public Health

Objectives: To determine the natural course of chronic fatigue syndrome (CFS) in a multi-site clinical epidemiology study, and to compare the course of CFS to community-based epidemiological studies and other existing clinical epidemiology studies.

Methods: Patients (N=1430) with confirmed diagnoses of CFS for a minimum of 5 years were identified from four clinical sites specializing in CFS diagnosis and treatment: Miami, Florida (n=401), Sierra, Nevada (n=353), New York, New York (n=316), and Salt Lake City, Utah (n=360). A telephone interview was conducted with patients who had been in treatment at one of the sites for at least 5 years, with an emphasis on patients who initially presented to the clinical study site at least 10 years prior. A total of 960 patients completed the survey across the four study sites: Miami, Florida (n=237), Sierra, Nevada (n=221), New York, New York (n=256), and Salt Lake City, Utah (n=246). Patients were interviewed by trained interviewers and responded to questions addressing basic demographic information, onset type (gradual versus sudden), initial and current severity (absent, mild, moderate, severe) of CFS symptoms (post-exertional malaise, impaired memory or concentration, unrefreshing sleep/sleep difficulties, headache, muscle pain, joint pain, sore throat, lymph node pain/tenderness, and orthostatic intolerance), number and duration of remissions from CFS, comorbid conditions, and current functioning. Chi-square statistics were calculated to determine differences in groups by site. Ordinal logistic regression was used to obtain odds ratios and 95% confidence intervals to examine the associations between onset type, symptom severity, and functioning.

Results: In general, this survey sample comprises middle-aged (55.1±12.3 years), white (94.9%), women (79.8%), who were born in the United States (93.5%) and are highly educated (4-year college degree, 36.5%; graduate/professional degree, 27.4%). The mean duration since CFS diagnosis was 15.4±6.2 years. Approximately one-third of the sample had experienced an episode of CFS remission. Viral symptoms (sore throat and lymph node pain/tenderness) showed the most improvement with time. Many reported comorbid conditions including fibromyalgia (61.0%), depression (47.4%), anxiety (39.7%), and hypothyroidism (35.0%). Relatively few reported currently working (24.2%), attending school (4.2%), or engaging in regular activity equivalent to work or school (23.7%). There were differences across sites with respect to both demographic and clinical variables, with similar patterns observed for patients in Nevada and New York and patients in Florida and Utah.

Conclusions: The demographic composition of this sample is similar to other clinic-based studies of CFS. In this sample, CFS was shown to be a chronic condition for which the odds of permanent remission were extremely low.

Relation to Conference Theme: These results provide evidence on the natural course of CFS in patients from four clinical practices with diverse focuses and approaches to disease management.

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What Treatments Alter the Course of Chronic Fatigue Syndrome? Evidence from a Multi-Site Clinical Epidemiology Study

Lucinda Bateman, M.D., Adjunctt Assistant Professor, Department of Anesthesiology, University of Utah

Objectives: To examine the types of treatments that alter the course of chronic fatigue syndrome (CFS) in a multi-site clinical epidemiology study; specifically, to examine the association between treatment types and change in symptom severity over time.

Methods: Patients (N=1430) with confirmed diagnoses of CFS for a minimum of 5 years were identified from four clinical sites specializing in CFS diagnosis and treatment from different geographical areas of the United States: Miami, Florida (n=401), Sierra, Nevada (n=353), New York, New York (n=316), and Salt Lake City, Utah (n=360). A telephone interview was conducted with patients who had been in treatment at one of the sites for at least 5 years, with an emphasis on patients who initially presented to the clinical study site at least 10 years prior. A total of 960 patients completed the survey across the four clinical study sites: Miami, Florida (n=237), Sierra, Nevada (n=221), New York, New York (n=256), and Salt Lake City, Utah (n=246). Patients were interviewed by trained interviewers and responded to questions addressing initial and current severity (absent, mild, moderate, severe) of CFS symptoms (post-exertional malaise, impaired memory or concentration, unrefreshing sleep/sleep difficulties, headache, muscle pain, joint pain, sore throat, lymph node pain/tenderness, and orthostatic intolerance) and treatment effectiveness. Chi-square statistics were calculated to determine differences in groups by site. Ordinal logistic regression was used to obtain odds ratios and 95% confidence intervals to examine the associations between treatment type and change in symptom severity over time.

Results: In the total survey sample, the most effective CFS treatments included self-help strategies (65.2%) such as rest (37.2%), diet (20.9%), and exercise (18.9%), followed by traditional medicine (53.3%), such as prescription
medications (38.2%) and vitamins (16.4%). A small proportion of patients reported benefits with alternative/complementary medicine (16.9%) such as herbal remedies (7.4%) or acupuncture/reflexology/massage (6.8%). Self-help strategies (25.8%) and self-help strategies in combination with traditional medicine (25.9%) were the most effective treatment approaches. There were significant differences across clinical study sites with respect to the most effective treatments (individual and combinations, p=0.000 for both).

Conclusions: Evidence from this clinical epidemiology study suggests that there is substantial variation in the effectiveness of treatments, and that self-help strategies and traditional medicine are the most effective across a diverse sample of CFS patients. Although clinicians can prescribe medications to manage some symptoms, most CFS patients report greater improvements from employing self-help strategies.

Chronic Fatigue Syndrome and Comorbid and Consequent Conditions: Evidence from a Multi-Site Clinical Epidemiology Study
Salima Darakjy, MPH, Ph.D. Candidate, Department of Epidemiology, Columbia University

Objectives: To examine the prevalence of comorbid and consequent conditions (i.e. after CFS onset) in patients with chronic fatigue syndrome (CFS) in a multi-site clinical epidemiology study; to examine the prevalence of cancer in patients with CFS and compare it to data from the adult US population provided by the CDC’s National Cancer Registry.

Methods: Patients (N=1430) with confirmed diagnoses of CFS for a minimum of 5 years were identified from four clinical sites specializing in CFS diagnosis and treatment from different geographical areas of the United States: Miami, Florida (n=401), Sierra, Nevada (n=353), New York, New York (n=316), and Salt Lake City, Utah (n=360). A telephone interview was conducted with patients who had been in treatment at one of the sites for at least 5 years, with an emphasis on patients who initially presented to the clinical study site at least 10 years prior. A total of 960 patients completed the survey across the four clinical study sites: Miami, Florida (n=237), Sierra, Nevada (n=221), New York, New York (n=256), and Salt Lake City, Utah (n=246). Patients were interviewed by trained interviewers and responded to questions addressing a range of potential comorbid conditions: fibromyalgia, depression, anxiety, PTSD, bipolar disorder, hypothyroidism, type 2 diabetes or metabolic syndrome, PLMD or RLS, narcolepsy, severe spine problem, sleep apnea, endometriosis, menopause, low testosterone, cancer malignancy, autoimmune disease. Patients also reported cancer type (i.e. system affected or site of cancer). Chi-square statistics were calculated to determine differences in groups by site. Ordinal logistic regression was used to obtain odds ratios and 95% confidence intervals to examine the associations between treatment type and change in symptoms.

Results: Eighty-four percent of the CFS patient sample reported at least one additional significant diagnosis after CFS onset. Fibromyalgia (61.0%), depression (47.4%), anxiety (39.7%), and hypothyroidism (35.0%) were the most common post-CFS diagnosis conditions. A substantial proportion reported cancer malignancies (16.4%), which is four times the prevalence in the US adult population (4.1%). Nearly half of those occurrences (8.1% of the total sample) were skin cancer, predominantly among patients from Florida and Nevada; this prevalence is twice the prevalence in the US adult population (3.8%). Nine individuals had multiple cancer diagnoses. The initial severity of individual CFS symptoms was not associated significantly with the subsequent occurrence of cancer.

Conclusions: This diverse clinical sample of CFS patients is burdened with multiple chronic conditions, particularly pain, mental health, and hormonal disorders. In this sample, the prevalence of any cancer is substantially higher than in the adult US population. Further research designed specifically to determine whether individuals with CFS have an excess risk of cancer, and whether there may be shared pathophysiological mechanisms, is warranted.

Relation to Conference Theme: In order to effectively treat and manage CFS patients, clinicians must be cognizant of the wide spectrum of disorders that co-occur with CFS, and should be aware of a potential excess risk of cancer in this patient population.

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SESSION: PROVOCATION STUDIES

Session Chair: Staci R. Stevens, M.A.

Superior ability of a two-day CPET protocol to detect functional impairment in ME/CFS compared to either a single CPET, a submaximal exercise test, or a VO₂ prediction equation
Keller, Betsy A.  Ithaca College, Dept. of Exercise and Sport Sciences, Ithaca NY

Objective: Abnormal physiological responses to exercise have been reported in ME/CFS patients. This study assessed the ability of four methods to determine oxygen consumption at maximum effort (VO₂max) and/or ventilatory (anaerobic) threshold (VO₂@VT) to distinguish functional impairment in ME/CFS. These included, 1) a single cardiopulmonary exercise test (CPET), 2) two serial CPETs 3) a submaximal workload prediction of VO₂max and 4) VO₂max predicted from maximum workload and body weight.
Methods: 42 subjects (30 females, 12 males, age 43.25±11.45 yrs) diagnosed with CFS by a physician experienced in the diagnosis of CFS completed a CPET (T1) on a cycle ergometer followed by another CPET (T2) performed 24 hrs later to assess the effects of post-exertional malaise (PEM) on functional capacity. Measures at maximum effort and VT included VO₂, heart rate (HR), workload (W), minute ventilation (Ve), rating of perceived exertion (RPE) and respiratory exchange ratio (RER). RER is an objective indicator of subject effort during exercise.

Results: 1) One CPET VO₂max identified 18 subjects (43%) as functionally impaired. For VO₂@VT, 33/41 subjects (80%) were identified as functionally impaired (Weber & Janicki, AM J Cardiol 55(Suppl A), 1985). 2) Two successive CPETs identified 28 subjects (67%) as functionally impaired. For the entire sample, VO₂max decreased from T1 to T2 by 13.4%, with 23 subjects (55%) displaying an abnormal retest decrease in VO₂max of >6%. Similarly, for VO₂@VT, two successive CPETs revealed functional impairment in 39 subjects (95%). 3) Submaximal workloads (25, 50, 75 Watts) compared between T1 and T2 showed significant differences (p<0.05) in test variables indicating an inconsistent relationship between load and pulmonary measures from T1 to T2. Furthermore, stepwise regression analyses (N=32) revealed poor ability to predict VO₂max from any single or combination of variables for T1 or T2 (R²<0.34). 4) VO₂max predicted based on CPET workload and body weight (ACSM’s Resource Manual, 7th ed., 2014) was significantly different (p<0.05) from T1 to T2 for both VO₂max and VO₂@VT.

Conclusion: 1) A single CPET failed to identify functional impairment in at least 20% of subjects, using either VO₂max or VO₂@VT. Using only one CPET, diminished functional capacity due to PEM could not be detected, yet occurred in 55% of subjects, indicating poor ability of one CPET to identify functional impairment in ME/CFS. 2) Two serial CPETs revealed functional impairment, based on changes from T1 to T2 in VO₂max and/or VO₂@VT, in 98% of subjects. 3) Submaximal workload relationship with VO₂max differed between T1 and T2, making submaximal exercise tests poor predictors of VO₂max in ME/CFS. 4) Predicted VO₂max calculated using validated, standard prediction equations differed between T1 and T2, indicating that submaximal cycle tests are poor predictors of VO₂max in ME/CFS. These results demonstrate the superiority of two serial CPETs to delineate functional impairment in ME/CFS in contrast to either a single CPET, a submaximal workload prediction, or a standard validated VO₂ prediction equation.

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Diminished Pulmonary Ventilation in CFS Patients - Effects of Deconditioning and Post-Exertional Malaise.

J. Mark VanNess, Christopher R. Snell, Staci Stevens and Jared Stevens. University of the Pacific and Workwell Foundation, Ripon, CA.

Skeletal muscle fatigue likely contributes to post-exertional malaise in CFS. Objective: To determine if the ventilatory skeletal muscles display fatigue patterns like other skeletal muscles we tested the hypothesis that the muscles of ventilation are utilized differently in CFS. Methods: Graded exercise tests to maximal effort were performed and the ventilatory responses (VE = pulmonary ventilation L/min) at the anaerobic threshold (AT) and peak exercise were compared between CFS and sedentary control subjects. Results: In Study 1 the results from cardiopulmonary analysis during graded exercise showed reduced ventilatory responses to exercise in CFS patients at both the AT and during peak exercise. It is unclear if these differences are due to deconditioning since workload (WL) and oxygen consumption (VO₂) were both lower in the CFS group:

<table>
<thead>
<tr>
<th>STUDY 1 (means±SE)</th>
<th>Peak VE (L/min)</th>
<th>Peak WL (Watts)</th>
<th>Peak VO₂ (mL/kg/min)</th>
<th>VE@AT (L/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CFS (n=21)</td>
<td>71.9±4.4*</td>
<td>119.3±4.5*</td>
<td>24.3±5.4*</td>
<td>32.3±1.9*</td>
</tr>
<tr>
<td>Control (n=19)</td>
<td>101.1±3.37</td>
<td>173.7±24.9*</td>
<td>31.4±4.9</td>
<td>46.1±5.8*</td>
</tr>
</tbody>
</table>

* indicates p<0.05 vs Control

In Study 2 a serial exercise test-retest design was used where similar graded tests are performed on consecutive days. Similar differences were observed between groups on Test 1 – however the ventilatory response was diminished in the CFS patients to a greater degree on the second exercise test, especially when assessed at the AT.

<table>
<thead>
<tr>
<th>STUDY 2 (means±SE)</th>
<th>Peak VE-Test 1 (L/min)</th>
<th>Peak VE-Test 2 (L/min)</th>
<th>VE@AT-Test 1 (L/min)</th>
<th>VE@AT-Test 2 (L/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CFS (n=57)</td>
<td>67.5±2.7*</td>
<td>63.8±2.3*</td>
<td>25.6±1.1</td>
<td>23.1±1.0*</td>
</tr>
<tr>
<td>Control (n=12)</td>
<td>86.6±9.0</td>
<td>91.9±10.4</td>
<td>26.1±1.8</td>
<td>30.6±2.6</td>
</tr>
</tbody>
</table>

*indicates p<0.05 vs Control

Conclusions: The results from the first study provide evidence of diminished ventilation during exercise in CFS patients that would be due to deconditioning. The findings from Study 2 show that post-exertional effects seem to reduce the ventilatory response even greater in CFS patients. These effects may be due to diminished ventilatory muscle function during post-exertional malaise or reduced ventilatory neural “drive”.

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Submaximal exercise testing using near infrared spectroscopy (NIRS) may not differentiate those with Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) from healthy controls
Objectives: It is important to screen for mitochondrial dysfunction and other metabolic disorders in people with suspected ME/CFS. Maximal cardiopulmonary exercise tests (CPET) hold much promise for this in early studies, but frequently result in symptom flare. We investigated whether a novel approach to submaximal exercise testing might assist in screening for mitochondrial disorders and pose a possible alternative to CPET in distinguishing patients with ME/CFS from controls.

Methods: 16 individuals with ME/CFS and 14 healthy controls, all female and age matched <5 years, performed a handgrip exercise test of 30 contractions/min for 3 min at 40% maximal voluntary contraction. Muscle oxygenation and haemodynamics of the wrist extensor and flexor muscles were monitored using NIRS to generate information on the changes in oxyhaemoglobin and deoxyhaemoglobin (HHb). Borg’s rating of perceived exertion was also assessed. Response to the test was compared between cases and controls by calculating the area under the curve (AUC) of HHb over time.

Results: 13/16 ME/CFS cases and all controls completed the test. Time adjusted AUC of HHb was significantly lower for the ME/CFS cases compared to controls (P=0.004). However, total work performed throughout the experiment was also significantly lower for cases than controls (P<0.0001), and after adjusting for work, there was no significant difference in AUC of HHb between cases and controls (P=0.15), nor was there when further potential cofounders (age, BMI, haemoglobin and ferritin) were considered (P=1.0). Despite this, perceived work was significantly greater for cases than controls (P=0.01). When a group of 6 controls performed the test at 30% MVC, so case and control total work did not differ (P=0.94), there was no significant difference in AUC of HHb between groups (P=0.21). Despite being unable to differentiate between ME/CFS and healthy individuals as a whole, 3 ME/CFS cases had particularly low levels of HHb throughout the test prompting referral to a metabolic clinic, while two had adverse physical reactions (prolonged periods of muscle spasm and hypotension).

Conclusion: Our submaximal exercise procedure did not show sufficient predictive value to distinguish between ME/CFS cases and healthy controls. However, HHb levels did vary between cases, and a subset of 19% met criteria that prompted further testing for mitochondrial disease. The greater level of self-assessed exertion in light of lower total work for ME/CFS cases suggests sufferers have disproportionate perceived exertion. Even submaximal testing was intolerable for a subset of ME/CFS cases, indicating that healthcare professionals should be mindful of using exercise for testing or treatment of ME/CFS.

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Oxygen extraction and lactate are low during cardiopulmonary exercise test in patients with Chronic Fatigue Syndrome

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Objectives: The cause of exercise intolerance in Chronic Fatigue Syndrome (CFS) is poorly understood. The diversity of the syndrome and the complexity of metabolic adaptation to exercise attribute both to our lack of knowledge. We calculated the oxygen extraction and we measured post-exercise lactate to differentiate between possible causes of physical impairment.

Methods: We analysed the data of cardiopulmonary exercise tests of CFS patients, patients with idiopathic chronic fatigue (CFI) and healthy visitors. Continuous non invasive measurement of the cardiac output (Nexfin) was added to the cardiopulmonary exercise tests. The oxygen extraction by muscle cells and the increase of cardiac output relative to the increase of oxygen uptake (ΔQ/ΔV'O2) were calculated from the cardiac output and the oxygen uptake during incremental exercise. In a subgroup we measured lactate 2 minutes after peak workload.

Results: The peak V'O2 was 20.3 ± 5.0 ml/min/kg in 178 female CFS patients, 22.2±5.3 ml/min/kg in 172 female CFI patients and 27.4 ± 7.2 ml/min/kg in 11 healthy women (ANOVA: P=0.001). The peak V'O2 was 24.0 ± 7.2 ml/min/kg in 25 male CFS patients, 28.9 ± 7.1 /min/kg in 51 male CFS patients and 27.3 ± 3.7 ml/min/kg in 7 healthy men (ANOVA: P=0.019). Analysis of the functioning of lung, heart and circulation did not explain the differences. The peak oxygen extraction by muscle cells was 10.83 ± 2.80 ml/100ml in CFS women, 11.62 ± 2.90 ml/100ml in CFI, and 13.45 ± 2.72 ml/100ml in healthy women (ANOVA: P=0.001). The peak oxygen extraction by muscle cells was 13.66 ± 3.31ml/100ml in CFS men, 14.63 ± 4.38 ml/100ml in CFI, and 19.52 ± 6.53 ml/100ml in healthy men (ANOVA: P=0.008). The ΔQ/ΔV'O2 was >6 L/L (normal ΔQ/ΔV'O2 = 5 L/L) in 70% of the patients and 22% in the healthy group.

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The lactate in 75 female CFS patients was 6.39±2.58 mmol/l, 6.70±2.95 mmol/l in 46 CFI and 9.96±4.08 mmol/l in the 11 healthy females (ANOVA: P=0.001). Lactate was 7.21±2.40 mmol/l in 7 male CFS patients, 9.91±2.92 mmol/l in 14 male CFI patients and 11.40±2.52 mmol/l in 7 healthy males (ANOVA: P=0.024).

Conclusion: The low peak oxygen extraction and the high increase of cardiac output relative to the increase of oxygen uptake indicate a metabolic cause for exercise intolerance in a majority of CFS patients. The low lactate after exercise in a majority of CFS and CFI patients suggests that physical impairment in this group is caused by a downregulation of carbohydrate metabolism.

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Specific Fitness Profile To Effort In CFS

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Exercise intolerance in CFS is one of the most prevalent symptoms that conditions with more limited cognitive dysfunction. So, it is important to understand the basic mechanisms of cardiovascular and endocrine response to physical exercise to better understand the pathogenic mechanisms of this dysfunction and raise new potential treatments. One of the biggest problems of the CFS is the absence of specific biological markers, the diagnosis being limited to the purely clinical.

Objectives: For both patients and the medical community it would be important to determine an assessment protocol specific, quantifiable and objective of CFS that would end the controversy as to whether or not CFS. This study assessed cardio-ventilatory adaptation, metabolic and hormonal among a group of CFS patients and a control group using incremental exercise test repeated for 3 consecutive days (EEP).

Patients & Methods: The sample included 75 CFS patients (age 44.6 ± 7.5 years; BMI 26.1 ± 4.6), and 50 sedentary control subjects (age 40.6 ± 10.7 years; BMI of 25.6 ± 4.9). Both groups have performed an initial maximal exercise test and then after a week difference, we performed a specific test with supra-maximal workloads for three consecutive days are adjusted parameters: cardio-ventilatory (oxygen consumption (VO2), CO2 production (VCO2), FE final fraction of CO2 (FE2CO2), FeO2 final fraction (FE2O2), equivalent respiratory O2 (ERO2), respiratory CO2 equivalent (ERCO2) and True O2). Growth hormone, cortisol, prolactin and ACTH were done. Biochemical analysis included glucose, uric acid, CPK and free fatty acids.

Results: The results obtained PEE with statistically significant differences in the values of VE, QR, FR, VO2, FECO2, VCO2, O2 True are significantly higher in the control group with no differences between days (F= 17.48; p< 0.001). Regarding FeO2 values, the figures are significantly higher in the group of patients during the loading phase (F= 14.3; p< 0.001) with no differences between days. As for the parameters reflecting the ventilatory economy (ERCO2 ERO2) showed statistically significant differences higher values in the group of patients for the loads (F= 7.75; p< 0.001) with no differences between days. Regarding hormonal parameters observed with a statistically significant difference in the post-exercise hypocortisolism in the control group with no differences between study days ((F= 6.18, p< 0.001). As for the GH differences were not statistically significant although a clear trend towards lower values in the post-exercise in the group of patients with CFS.

Conclusions: Patients with CFS exhibit differences in adaptation to physical exercise from the cardio-ventilatory and hormonal point of view, showing a less economical ventilation and respiratory equivalents superficial FeO2 higher and higher in the group of patients having a lower O2 TRUE, reflecting a possible alteration of the alveolar-capillary exchange, or even a mitochondrial alteration to the cellular level. The hypocortisolism observed in the group of patients after the stimulus of exercise may explain why these patients do not adapt adequately to stress.
SESSION: ADVANCES IN PEDIATRIC ME/CF RESEARCH - PART I
Session Chair: Leonard A. Jason, Ph.D.

How is Pediatric Chronic Fatigue Syndrome/Myalgic Encephalomyelitis (CFS/ME) diagnosed and managed by Pediatricians? An Australian National Study
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Objectives The diagnosis and management of pediatric CFS/ME represent ongoing challenges for pediatricians, with limited research evidence to guide best practice. A better understanding of current approaches at a national level is important in informing guidelines for the diagnosis and management of CFS/ME and also in detecting gaps where education and research could improve consistency of care. We aimed to examine current diagnosis and management practices for CFS/ME by Australian general pediatricians.

Methods An online survey was sent to members of the Australian Paediatric Research Network (APRN). APRN comprises more than 40% of pediatricians registered with the Royal Australasian College of Physicians, with representation from all Australian states and territories. It aims to facilitate multisite research in the secondary care pediatric outpatient setting. The primary outcomes of interest for the current study included diagnostic criteria used, medical investigations and management practices in pediatric CFS/ME.

Results 178 (41%) of 252 eligible pediatricians responded, with 70 (41%) of responders reporting that they diagnose and manage CFS/ME as part of their practice. Most responders indicated that they had diagnosed 1-2 patients with CFS/ME over the past 6 months. Over 50% reported that they did not use published criteria or case definitions to make a diagnosis. Reported routine medical investigations used for diagnosis were variable. Conditions that more than half of the pediatricians reported as commonly co-occurring (i.e., present in >50% of cases) with CFS/ME included somatization disorders, anxiety, depression and fibromyalgia. There was wide variation in behavioral and pharmacological management strategies, with most pediatricians commonly engaging a school teacher, physiotherapist and/or psychologist as part of their management plan.

Conclusion Our data shows a wide variation in diagnostic and management practices which may reflect a lack of knowledge of diagnostic criteria and paucity of management guidelines. Given the estimated prevalence and variation in current practice, there is an urgent need to develop clear guidance and education for the diagnosis and management of CFS/ME in Australia.

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Impaired Range Of Motion In Adolescent Chronic Fatigue Syndrome
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From the 1Department of Pediatrics, Johns Hopkins University School of Medicine, Baltimore, MD, the 2Department of Health Behavior, University of Alabama at Birmingham School of Public Health, Birmingham, AL, and 3Violand and McNerney, PA, Ellicott City, MD, USA
Objective: To determine whether adolescents and young adults with CFS near the start of treatment have a higher prevalence of impaired range of motion (ROM) of the limbs and spine than healthy controls (HC) matched by gender and degree of joint hypermobility.

Methods: Eligible CFS subjects for this matched case-control study were participants in the Johns Hopkins Pediatric CFS Cohort Study, all of whom met the Fukuda CFS definition. HC were recruited from unaffected friends or family members of CFS study subjects, and from among families of staff members in the Department of Pediatrics. All cases and controls 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. Goniometers were used for all ROM measurements except prone press-up. Criteria for abnormal ROM were defined before the study began. The number of abnormal responses ranged from 0 (normal ROM throughout) to 11 (impaired ROM in all areas tested).

Results: Of the 55 subjects in the CFS Cohort Study, matched controls were identified for 48 (39 F). The median age was 14 years at CFS onset and 16 years at enrollment. The median number of areas with impaired ROM was higher in CFS cases than in HC whether measurements were made at the onset of stretch in the involved limb (5 vs. 2, P < .001; Wilcoxon signed ranks test) or at end-range (2 vs. 0, P < .001). The risk of more than 3 areas of impaired ROM was higher in those with CFS compared to controls (OR 6.0, 95% CI, 2.1-17.3; P < .001). CFS subjects were more likely to develop abnormal symptomatic responses to the individual tests and to the overall assessment (P < .001). To explore whether the ROM impairments could be explained by reductions in activity, we examined whether those with a score of ≤ 3 on the composite ROM score differed from those with a score of > 3. There were no differences in the SF-36 physical function normed score (39.4 vs. 41.3; P=0.48), the SF-36 vitality normed score (32.2 vs. 35.6; P=.19), or the Functional Disability Inventory score (21.8 vs. 19.8; P=.53).

Conclusions: Impaired range of motion is more common in subjects with CFS than in otherwise healthy adolescents and young adults matched by gender and joint hypermobility, and does not correlate with measures of inactivity. Adding a longitudinal strain to the nerves and soft tissues in those with CFS provoked symptoms in a subset. Taken together, these novel findings are consistent with reduced compliance in the neuromuscular system in subjects with CFS, and with the hypothesis that increased mechanosensitivity is a contributor to the generation and exacerbation of CFS symptoms.

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Tracking Post-infectious Fatigue in Clinic using Routine Clinical Lab Tests.

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Objectives. While biomarkers for myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) are beginning to emerge, they more often than not require the services of a highly specialized clinical laboratory. We hypothesized that combining commonly measured laboratory markers would identify subsets of such markers that would allow for early screening of infectious mononucleosis (IM) patients for potential long-term sequelae.

Methods. We studied 301 adolescents prospectively over 24 months following the diagnosis of monospot-positive IM. We found an incidence of ME/CFS at 6, 12 and 24 months of 13%, 7% and 4% respectively (n=13). At each time point 59 standard tests were performed including metabolic profiling (creatinine, calcium, potassium, etc...), liver enzyme panel, hormone profiles (sex, stress and thyroid hormones), complete blood count (CBC), differential white blood count (WBC), and standard urinalysis (bilirubin, ketones, leukocytes, protein, etc...). Linear classification models separating PI-ME/CFS from controls were constructed at each time point based on subsets of these markers selected iteratively using stepwise variable selection.

Table 1. Area Under the Curve (AUC) when re-adjusting coefficients at each time point.

<table>
<thead>
<tr>
<th>Test Result Variable(s)</th>
<th>Area</th>
<th>Std. Error</th>
<th>Asymptotic Sig.</th>
<th>Asymptotic 95% Conf. Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Lower Bound</td>
</tr>
<tr>
<td>six_months</td>
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<td>.001</td>
<td>.760</td>
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<td>.485</td>
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<tr>
<td>twentyfour_months</td>
<td>.856</td>
<td>.088</td>
<td>.004</td>
<td>.684</td>
</tr>
</tbody>
</table>

Results. At 6 months post diagnosis with IM, blood urea nitrogen (BUN), alanine transaminase (ALT), urine pH, mean corpuscular hemoglobin concentration (MCHC) and eosinophil count were selected as highly discriminatory markers for
eventual onset of PI-ME/CFS (AUC $p=0.001$) (Table 1). This sunset of indicators also supported classification of PI-ME/CFS subjects at 24 months post IM diagnosis (AUC $p=0.004$) although their respective contributions evolved over time. Elevated ALT increased in importance as did lower eosinophil count in PI-ME/CFS from 6 months to 24 months. Elevated urine pH and lower MCHC at 6 months reversed their contributions at 24 months whereas lower BUN remained a consistent feature of PI-ME/CFS.

Conclusion. These preliminary results suggest that dynamic response over time of hemoglobin, metabolic and inflammatory markers measured using standard clinical laboratory tests may support early assessment of risk of long-term sequelae in IM patients.

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Increased Prevalence Of Delayed Milk Protein Hypersensitivity Among Adolescents And Young Adults With Chronic Fatigue Syndrome

Peter C. Rowe, MD, Colleen L. Marden, Samantha E. Jason, Erica M. Cranston, Marissa A. K. Flaherty, Kevin J Kelly, M.D
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Objectives: To examine the prevalence, clinical features, and influence on illness severity of delayed milk protein hypersensitivity in adolescents and young adults with CFS who were enrolled in a prospective cohort study.

Methods: The Johns Hopkins Pediatric CFS Cohort Study followed 55 consecutive adolescents and young adults with CFS. All subjects had been referred to the Johns Hopkins Children’s Center Chronic Fatigue Clinic. Enrollment began in October 2008 and individuals were treated and followed for 2 years. In this investigation, we compared clinical features and quality of life measures in those with and without delayed milk protein hypersensitivity (also known as non IgE-mediated milk protein hypersensitivity). Delayed milk protein hypersensitivity was suspected if subjects reported (1) at least 2 of 3 of the following upper GI symptoms: (a) gastroesophageal reflux (GER), (b) early satiety, (c) epigastric or abdominal pain, and (2) improvement in upper GI symptoms on a rigid milk protein elimination diet, as well as at least 2 recurrences of upper GI symptoms following re-exposure to cow’s milk protein. No subject had anaphylactic responses to milk proteins.

Results: Of the 55 enrolled CFS subjects, 46 were female. The median age at onset of CFS was 14 and the median age at enrollment was 16 (range, 10 - 23 years). Fourteen (25%) met study criteria for delayed milk protein hypersensitivity. Affected patients had higher rates of emesis in infancy (50% vs. 15%; $P=0.01$) and, at the time of enrollment, a higher prevalence of GER (79 vs. 29%; $P=0.002$), early satiety (64 vs. 29%; $P=0.02$), epigastric pain (86 vs. 27%; $P=0.001$), and aphthous ulcers (57 vs. 10%; $P=0.001$). Those with milk sensitivity had lower Peds QL total scores (47.4[11.5] vs. 58.0 [14.9]; $P=0.01$) and higher scores on the Functional Disability Inventory (25.8 [9.4] vs. 18.8 [9.9]; $P<0.03$); the changes on both measures were consistent with worse HRQOL. Both groups received multi-modal therapy. With the addition of a rigid milk-free diet in those suspected of milk protein hypersensitivity, the significant differences in HRQOL at baseline had disappeared by 6 months.

Conclusions: Young people with CFS have a higher than expected prevalence of delayed hypersensitivity to cow’s milk protein. Delayed hypersensitivity to milk protein was associated with increased gastrointestinal symptoms and lower HRQOL. This condition warrants further attention as a com-morbid condition in CFS clinical care and in the design and conduct of clinical trials for CFS.

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SESSION: ADVANCES IN PEDIATRIC ME/CFS RESEARCH - PART II
Session Chair: Rosamund Vallings, MNZM, MB.BS

Impact Of Adolescent Chronic Fatigue Syndrome
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**Objective:** To compare the health-related quality of life (HRQOL) of adolescents and young adults with CFS to healthy controls (HC), as well as to published results of HRQOL in other chronic pediatric conditions.

**Methods:** Cross-sectional study comparing CFS subjects referred to a tertiary care Chronic Fatigue clinic and healthy controls. Eligible CFS subjects were age 10-30 years and met the 1994 International Chronic Fatigue Syndrome Study Group criteria for [Fukuda K, et al. Ann Int Med 1994;121:953-9]. Healthy controls were eligible if they were age 10-30 years, with self-reported good, very good, or excellent general health. Pediatric HRQOL was measured at the initial evaluation visit using the Peds QL, the Functional Disability Inventory (FDI), the Wellness score, and the Wood Mental Fatigue Inventory (WMFI). We enrolled 55 consecutive CFS patients (46 F). From a pool of 69 potential controls we selected 55 with similar age and gender distribution for comparison.

**Results:** Scores on all measures of HRQOL indicated worse function among those with CFS. There were significant differences on the median Wellness score (50 in CFS vs. 90 in HC; P < .001), median FDI scores (20 in CFS vs. 0 in HC; P < .001), median WMFI scores (13 in CFS vs. 1 in HC; P < .001), and all PedsQL domains (Figure; all P < .001). The mean [SD] PedsQL total score was lower for those with CFS (55.3 [14.8]) than for published reports of scores for children with cystic fibrosis (79.5 [13.1]), eosinophilic gastrointestinal disorder (67.5 [13.3]), epilepsy (75.9 [12.8]), type 1 diabetes (73.7 [14.6]), sickle cell disease (70.0 [16.5]), and renal transplants (75.2 [13.9]) (data from Ingerski LM, et al., J Pediatr 2010;156:639-44), and comparable to pediatric fibromyalgia (55.9 [15.2]) and paraplegic cerebral palsy (53.9 [12.2]) (data from Varni JW, et al. (Health Qual Life Outcomes 2007; 5:43).

**Conclusions:** Self-reported quality of life is significantly lower for adolescents and young adults with CFS near the start of treatment than for healthy controls, and is also lower than scores reported for cross-sectional samples of those with other pediatric chronic health impairments. Further research is needed to define predictors of low HRQOL and to identify optimal ways to improve function in this population.

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What do young people find helpful in managing their chronic illness? Lessons from Chronic Fatigue Syndrome.

Katherine Rowe, Royal Children’s Hospital, Murdoch Children’s Research Institute, Melbourne, Australia

**Objective:** To obtain feedback from young people referred with CFS as to which strategies, information, assistance and support was helpful and what was considered unhelpful or ineffective.

**Method:** 788 young people, age 6-18 years, with diagnosed with Chronic Fatigue Syndrome consistent with the Holmes et al (1988) and Fukuda et al (1994) criteria, were referred to a specialized clinic at the Royal Children’s Hospital between 1991 and 2009. They provided feedback regarding management received 1-21 years after referral. Management included: symptom management, an overall plan determined by severity of illness, stage of education, family circumstances and life interests, where the young person decided how to apportion their ‘energy use’ across social, educational and physical activities, with a pleasurable outside-of-home activity each week. There was a focus on maintaining an education in order to assist with achieving their lifetime and career goals. They monitored their recovery and evaluated the plan each month, increasing activities if appropriate. Ongoing supportive care was provided. The questionnaire included both quantitative and qualitative responses for functional outcomes, duration of illness, use of alternative health practitioners, and evaluation of management strategies.

**Results:** At least one return was obtained from 82% (644) of the group with half the group having the opportunity of providing feedback on a biannual basis. 1200 questionnaires were returned.

The management plan was appreciated for allowing them control over their lives again. ‘Believing them’, ongoing support, particularly assistance in navigating the education system were considered essential contributors to their quality of life and ability to cope. Alternative health practitioners were widely used but considered of little value (especially supplements and restrictive diets) but massage for muscle pain and ‘good’ dietary advice was helpful. Psychological assistance was most often sought when they were recovering and evaluating how they had managed adolescent developmental tasks.

Engagement in education was the best predictor of functional outcome.

**Conclusion:** Young people valued: regaining the control over their lives that was lost through illness; support to maintain social contacts; and assistance to achieve educational or life goals.
Sleep education during elementary school prevents school non-attendance in junior high school years.
Seiki Tajima1, Teruhisa Miike1, Tsutomu Maeda2.
1Hyogo children’s sleep and development medical research center, Hyogo, Japan.
2Nonprofit organization RIFOUMU WAKASA, Fukui, Japan.

Objectives: Japanese are one of the most sleep-deprived people and it causes chronic fatigue syndrome, especially in children and adolescents. Today, it is difficult to recover completely from chronic fatigue syndrome. Therefore, we believe that establishing prevention program is one of the essential themes for translating science into clinical care. Aim of this study is to reveal that sleep education during elementary school prevents developing pediatric chronic fatigue syndrome in junior high school years.

Methods: Sleep education has been performed at target elementary school since April 2007. Whole grade students were participated in this program with informed consent. Sleep education program consisted with lectures by MD and continuous lifestyle teaching by teachers according to MD’s comment to individual sleep log. It is difficult to make MD’s diagnoses to all participants in massive investigation. Joudoi et al reported that 83.6% of patients with school non-attendance or school phobia met the criteria for typical or atypical pediatric chronic fatigue syndrome. Therefore, incidence rate of school non-attendance during junior high school was used as indication of chronic fatigue syndrome morbidity.

Results: Numbers of students with school non-attendance are shown in following table.

<table>
<thead>
<tr>
<th>year</th>
<th>2005</th>
<th>2006</th>
<th>2007</th>
<th>2008</th>
<th>2009</th>
<th>2010</th>
<th>2011</th>
<th>2012</th>
</tr>
</thead>
<tbody>
<tr>
<td>number of newly developed school non-attendance</td>
<td>-</td>
<td>2</td>
<td>3</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>total number of students with school non-attendance</td>
<td>7</td>
<td>6</td>
<td>7</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>number of whole students</td>
<td>66</td>
<td>64</td>
<td>61</td>
<td>74</td>
<td>88</td>
<td>78</td>
<td>71</td>
<td>58</td>
</tr>
</tbody>
</table>

Incidence of school non-attendance decreased year-by-year. Finally, no student with school non-attendance was present in 2012. On the other hand, incidence of school non-attendance could not be suppressed completely yet in another trial which intervention was limited to 4th - 6th grade (data not shown).

Conclusion: Continuous sleep education and lifestyle teaching through whole elementary school grade are essential for preventing pediatric chronic fatigue syndrome.

Acknowledgment: This work has been supported by Grant-in-Aid for Scientific Research on Innovative Areas “Constructive Developmental Science” (No.24119004) from The Ministry of Education, Culture, Sports, Science and Technology.

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Does depression at presentation impact on outcomes for young people with CFS?
Katherine Rowe Royal Children’s Hospital, Murdoch Children’s Research Institute, Melbourne, Australia

Objective: To determine whether depression at presentation to the pediatrician impacts the functional outcomes, duration of illness or perception of recovery by young people with Chronic Fatigue Syndrome (CFS).

Method: 398 young people, age 6-18 years (M:F 22%:78%), referred to a specialized clinic at the Royal Children’s Hospital between 1991 and 2007 were diagnosed with CFS consistent with the Holmes et al (1988) and Fukuda et al (1994) criteria. A standardized history with symptom presence and severity and psychological measures that included Beck Depression Inventory, were collected immediately following the initial visit. In addition to routine clinical care, follow up questionnaires approximately each 2 years provided information regarding functional rating in social and physical activities, attendance at work or school as well as a global perception of functioning and whether they thought they had ‘recovered’.

Beck ratings were scored as ‘low’ (1-10 normal ups and downs, 11-16 mild mood disturbance); moderate (17-20 borderline clinical depression, 21-30 moderate depression); and significant (31-40 severe, over 40 extreme). Scores above 21 were considered as indicating depression. Ratings were analyzed using using Statistica 12 to determine if functional outcomes, duration of illness and perception of recovery were associated with initial levels of depression. Qualitative data provided by the young people also provided insights into other potentially significant factors.
Results: The average duration of illness prior to first visit was 15 months. Significant depression was present in 25% at baseline compared with a base rate of depression in adolescents of 20%. Those with severe depression identified, 'not being believed' either by family or professionals, difficulty remaining engaged with school and severity of symptoms as contributing factors and perpetuating factors. Mean duration until recovery was 5 years (range 1-14 years) with 60% reporting recovery by 5 years and 88% at 12 years reporting recovery. Those who were significantly depressed at the onset were more likely to rate themselves as 'not well' (42 of the 135) at follow up compared with 17 of 92 who considered they had recovered. (Chi square 4.54 p<0.05 df =1). Their functional rating also differed significantly (7.05/10 cf 7.77/10; p=0.005, df 228) but duration of illness and follow up period was not significantly different.

Conclusion: Depression is not as common as one might expect considering the impact on development at this stage, but the identified contributing factors provide many opportunities for advocacy by health professionals to ease their burden, and improve functioning.

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SESSION: ADVANCES IN BRAIN RESEARCH

Session Chair: Anthony Komaroff, M.D.

Neuroscience of fatigue and CFS/ME by using PET molecular imaging and functional neuroimaging
Yasuyoshi Watanabe1,2, Masaki Tanaka1,2, Kei Mizuno1,2, Akira Ishii1,2, Emi Yamano1,2, Sanae Fukuda1,3, Yasuhiro Nakatomi1,3, Kouzi Yamaguti1,4, and Hirohiro Kuratsune2,4
1RIKEN Center for Life Science Technologies, Kobe, Japan, 2Department of Physiology, 3Fatigue Clinical Center, Osaka City University Graduate School of Medicine, 4Department of Health Science, Kansai University of Welfare Sciences, Osaka, Japan.

The molecular and neural mechanisms of fatigue and chronic fatigue are still unclear because of the complicated and multi-factorial issue. However, we know the decrease in our performance by fatigue, and also the decrease in motivation for the tasks. It is of great value in our modern society to extensively analyze the causes of fatigue and motivational loss, and to develop the quantification methods on fatigue and motivation to develop the methods and therapies with better recovery and prevention from severe chronic fatigue.

We therefore organized the integrated research project on “The molecular/neural mechanisms of fatigue and fatigue sensation and the way to overcome chronic fatigue” from 1999 to 2005 and then 21st Century COE program from 2005 to 2009, both under the control of the MEXT, Japanese Government. The major contribution is: 1) Elucidation of the brain regions and their neurotransmitter systems responsible for fatigue sensation and chronic fatigue; 2) Development of a variety of methods and scales to quantitatively evaluate the extent of fatigue; 3) Development of methods of different causes of fatigue; 4) Elucidation of molecular/neural mechanisms of fatigue in humans and animals; 5) Invention of various methods or therapies on chronic fatigue and chronic fatigue syndrome; and 6) Development of the foods and drugs to overcome fatigue.

To further extend the research project for the people, we initiated a new center, Osaka City University Center for Health Science Innovation (OCU-CHSI), in July 2013. OCU-CHSI is aiming to promote consumer-industry-academia relationship for seeking better and healthy life. Here, the outlines of our work on neuroscience and innovation to overcome fatigue will be presented.


Yasuyoshi Watanabe, MD, PhD, Director of RIKEN Center for Life Science Technologies, Director of Osaka City University Center for Health Science Innovation, and Professor of Osaka City University Graduate School of Medicine, Kobe and Osaka, Japan. E-mail: yywata@riken.jp

EEG peak alpha frequency is associated with chronic fatigue syndrome: a case-control observational study
Marcie Zinn, Ph.D., Mark Zinn, MM, Jose Maldonado, MD, FAPM, Jane Norris, PA-C, Ian Valencia, BS, Jose G. Montoya, MD

Abstract
Objectives: The two cardinal symptoms of chronic fatigue syndrome (CFS) are ubiquitous, severe, disabling fatigue and cognitive impairment known as ‘brain fog.’ Remarkably, neuroimaging and neuropsychological studies have mixed results in finding structural changes commensurate with these two cardinal symptoms of CFS. The objectives of this pilot study
were to evaluate the relationship between electroencephalogram (EEG) peak alpha frequency (PAF) in CFS as compared to age- and sex-matched controls and to develop a diagnostic criteria using qEEG.

Methods: A 19-channel quantitative EEG and two fatigue measures were obtained on 50 CFS patients and 50 healthy control participants in a 3-minute closed condition using a resting-state only case-control design.

Results: Mixed ANOVA results found decreased PAF over 58% of the entire cortex in CFS patients when compared to controls, Wilks’ L = .66, (F(18,80) = 2.424, p = .006, partial h^2 = .31); bonferroni-corrected followup indicated significant differences in PAF at the following electrode sites: C3, C4, Cz, F3, F4, FP1, FP2, Fz, P3, Pz and T3 (p<.05). Two hierarchical multiple regression models found the best linear combination of predictors to predict fatigue: analysis 1 used the MFI-20 as the criterion variable;[ \( R^2 = .897, F(5,1894) = 3287.76, p = .000 \)] analysis 2 used the Fatigue Severity Scale as the criterion. \([ R^2 = .887, R^2 change = .865, F(5, 1894) = 3058.93, p=.000 ]\). To assess fatigue levels between groups, we used the Mann-Whitney U Test, first with MFI-20 \((z = -37.474, p < .000)\) then the FSS \((z = -37.757, p < .000)\).

Conclusions: These findings are consistent with reduced efficiency of thalamo-cortical connections in CFS participants. EEG PAF measurement of cognitive fog and fatigue in CFS may have prognostic value and facilitate the evaluation of CFS as part of a diagnostic regimen.

Keywords: Peak Alpha Frequency, Chronic Fatigue Syndrome, Myalgic Encephalomyelitis, Electroencephalography, Multidimensional Fatigue Inventory, Fatigue Severity Scale, alertness.

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qEEG measurement provides a quick, inexpensive and reliable diagnostic tool for most types of cortical issues. qEEG does not provide a stand-alone diagnostic, but integrates well into a clinical diagnostic regimen.

Cortical hypoactivation during resting state EEG suggests central nervous system pathology in patients with Chronic Fatigue Syndrome: A source analysis pilot study.

Marcie L Zinn, Mark A Zinn, Jose R Maldonado, Jane L Norris, Ian Valencia, Jose G Montoya

Objectives: Patients with chronic fatigue syndrome (CFS) are known to have a form of chronic cognitive impairment known as brain fog. To gain insight into how brain fog is produce, EEG was recorded from 19 scalp locations with link-ear reference during a 3-minute, eyes-closed task in 50 CFS patients and 50 healthy control subjects, matched for age (range 28 to 74 years), gender, educational level. The Multidimensional Fatigue Inventory (MFI-20) and the Fatigue Severity Scale (FSS) were likewise administered to the same group of patients. Using the EEG data, current densities were localized and computed from 1 Hz to 30 Hz with exact low-resolution electromagnetic tomography (eLORETA) from 6,239 cortical grey matter voxels based on each patient’s EEG. Non-parametric statistical mapping (SnPM) and linear regression analyses were used to evaluate the differences in current densities in each Brodmann area grouping of cortical grey matter voxels.

Results: Frontal, temporal, parietal, limbic and sub-lobar regions of interest (ROI’s) demonstrated significantly different current densities in CFS patients when compared to healthy controls (HC). Statistically significant different were found in the delta (1-3 Hz) and in the beta 2 (19-21 Hz) frequency bands in both the left and right hemisphere. Delta sources were found predominantly in the frontal and limbic regions of interest (ROI) with beta2 sources found predominantly in the central and superior ROI’s. Linear regression models, predicting current density from the MFI-20 reduced motivation subscale, found increased delta in the left frontal, temporal, parietal, limbic, sun-lobar ROI’s. eLORETA was able to detect evidence of widespread cortical hypoactivation in CFS patients as demonstrated by increased delta and decreased beta2 sources. Delta is an index of overall arousal level produced by hyperpolarized neural populations driven by thalamo-cortical loops. Taken together, our findings provide objective quantification of central nervous system dysregulation in CFS sufferers. A model of prolonged subcortical deregulation is hypothesized to explain the results.

Cognitive Functioning in Chronic Fatigue Syndrome

Susan J. Cockshell, Jane L. Mathias, The University of Adelaide, Australia

Objective: To comprehensively investigate cognitive functioning in people with Chronic Fatigue Syndrome (CFS) by; (1) meta-analysing the available research in order to consolidate existing findings and identify core cognitive deficits and (2) using this information, examine the cognitive functioning of a group of people with CFS, in addition to a range of variables that may impact on cognition.

Study 1: Methods & Results: Detailed searches of the PubMed and PsycINFO databases identified 50 studies that diagnosed CFS using published criteria, included a control group, and assessed cognition using objective tests. Data for 54 published cognitive test were meta-analysed. Persons with CFS showed deficits in the domains of reaction time,
attention and memory, and performed at normal levels on tests of motor speed, visuo-spatial ability, verbal fluency, cognitive reasoning and flexibility, and global functioning.

Study 2: Method & Results: Participants were 54 people with CFS and 54 matched controls who completed a range of cognitive tests and self-report measures. Tests were chosen on the basis of the previous meta-analysis and examined domains that are affected by CFS (reaction time, attention, memory) and ones that are not (motor speed, verbal ability, visuo-spatial ability) in order to ensure that any deficits were not due to the global effects of fatigue. Participants were screened for test effort and completed self-report scales measuring CFS symptoms, fatigue, sleep quality, psychiatric status, depression, anxiety, and everyday functioning. Four people in each group demonstrated low test effort, albeit with an intention to perform well, and were excluded from all further analyses. The results revealed that people with CFS (N = 50) demonstrated large impairments in reaction time, when compared to healthy controls, but performed comparably on tests of attention, memory, motor speed, verbal ability and visuo-spatial ability. Poorer reaction times were not related to CFS symptoms, fatigue, sleep quality, psychiatric status, depression, anxiety or everyday functioning. People with CFS were significantly more fatigued due to cognitive testing and took an average of eight days to recover. Finally, subjective (self-reports) and objective (tests) assessments of cognitive functioning were not related in either the CFS or control group.

Conclusion: The main cognitive deficit in people with CFS appears to be a slowing in information processing speed, which cannot simply be explained by their higher levels of fatigue and depression. A small number of participants showed low levels of effort (both groups), but all demonstrated an intention to perform well, indicating that the test results provided a valid assessment of people’s performance.

Translating Science into Clinical Care: The ability to process information quickly and accurately is impaired in people with CFS. This impairment is not due to disingenuous performance, fatigue or depression. Self-reported cognitive problems appear not be related to cognitive test results but this is not unique to CFS.

Susan J. Cockshell, PhD Candidate; School of Psychology; University of Adelaide; Adelaide SA 5005; Australia; Email: susan.cockshell@adelaide.edu.au.

Session: Revised Primer

Guidelines Panel Chair: Fred Friedberg, Ph.D.
Panel: Lucinda Bateman, M.D., Kenneth Friedman, Ph.D., Leonard Jason, Ph.D., Charles Lapp, M.D., Staci Stevens, M.A., Rosamund Vallings, MNZM, MB.BS

This clinical session will highlight the significant changes that have been made to the original IACFS/ME primer during a two year effort led by the primer writing committee. These changes are based on feedback received from the professional and patient communities. The revisions are focused on an extensive presentation of the challenges of assessment of the severely ill patient with more practical recommendations for symptom management and clinical care. Also a more in depth discussion of treatment and management issues is contained in the revised primer. The committee welcomes feedback from the audience regarding the new edition.
Chronic Fatigue Syndrome from Vagus Nerve Infection: A Psychoneuroimmunological Hypothesis
Michael B. VanElzakker, M.A.

Chronic fatigue syndrome (CFS) is an often-debilitating condition of unknown origin. There is a general consensus among CFS researchers that the symptoms seem to reflect an ongoing immune response, perhaps due to viral infection. Thus, most CFS research has focused upon trying to uncover that putative immune system dysfunction or specific pathogenic agent. However, no single causative agent has been found. Here, I describe a new hypothesis for the etiology of CFS: infection of the vagus nerve. When immune cells of otherwise healthy individuals detect any peripheral infection, they release proinflammatory cytokines. Chemoreceptors of the sensory vagus nerve detect these localized proinflammatory cytokines, and send a signal to the brain to initiate sickness behavior. Sickness behavior is an involuntary response that includes fatigue, fever, myalgia, depression, and other symptoms that overlap with CFS. The vagus nerve infection hypothesis of CFS contends that CFS symptoms are a pathologically exaggerated version of normal sickness behavior that can occur when sensory vagal ganglia or paraganglia are themselves infected with any virus or bacteria. Drawing upon relevant findings from the neuropathic pain literature, I explain how pathogen-activated glial cells can bombard the sensory vagus nerve with proinflammatory cytokines and other neuroexcitatory substances, initiating an exaggerated and intractable sickness behavior signal. According to this hypothesis, any pathogenic infection of the vagus nerve can cause CFS, which resolves the ongoing controversy about finding a single pathogen. The vagus nerve infection hypothesis offers testable hypotheses for researchers, animal models, and specific treatment strategies.

Michael B. VanElzakker, MA., Graduate Student, Tufts University Psychology, Massachusetts General Hospital Psychiatric Neuroscience, 490 Boston Ave., Medford MA 02155 USA, michael.vanelzakker@gmail.com

Chronic Fatigue Syndrome, Myalgic Encephalomyelitis, ME/CFS: An Infectious Disease
Rosemary A. Underhill, MB,BS

Objectives: The names “Chronic Fatigue Syndrome” (CFS) and “Myalgic Encephalomyelitis” (ME) were both coined to describe cluster outbreaks of an illness, now also known as ME/CFS. The occurrence of cluster outbreaks of ME/CFS implies that it is an infectious disease. The purpose of this study was to conduct a narrative review of the literature with regard to infectious characteristics of ME/CFS.

Methods: A PubMed database literature search was done using the keywords chronic fatigue syndrome, myalgic encephalomyelitis, linked to prevalence, infections and immune system. References, concerning cluster outbreaks and epidemiology of ME/CFS were found in the proceedings of the Cambridge Easter symposium on Myalgic Encephalomyelitis/Chronic Fatigue Syndrome 1990.

Results: Sporadic ME/CFS is globally endemic. Cluster outbreaks of a similar disease, have also been reported globally, but using different names, e.g., Iceland disease, neuramyasthenia, Tapanui flu. Some patients who became ill in cluster outbreaks did not recover their health, and their persisting symptoms fulfill diagnostic criteria for CFS and/or ME. Patients affected in cluster outbreaks were closely associated in families, communities, hospitals, or schools. The illness typically affects one person at a time in a community, with an incubation period of 4-10 days and an attack rate of 4.4% to 8.3%. Sporadic cases are also often associated in families and 20% of patients report another family member with the illness. The prevalence of sporadic CFS was 3.2% in patients’ (genetically unrelated) spouses/partners and 5.1% in their offspring, compared to a community prevalence of 0.42%. Most close patient contacts do not develop the illness.

A febrile illness at onset, recurrent flu-like symptoms and enlarged cervical lymph nodes are common in sporadic ME/CFS. Immune system changes include: T cell activation; up-regulation of the innate human antiviral defense pathway 2-5A RNase L; low natural killer cell cytotoxicity; and changes in the levels of various cytokines. Comparable changes may be found in some other infectious diseases. Some healthy contacts of patients show similar immune system changes, including: similar T cell assays and low natural killer cell activity; the number and types of activated T cells in healthy controls from an area where a cluster outbreak of CFS had occurred resembled cases of CFS more closely than they resembled controls from where no outbreak had occurred; a statistically significant positive correlation between CD38 activation markers in patients and their genetically unrelated close family contacts was found.

More patients with ME/CFS harbor a variety of known pathogens than do healthy controls, but in spite of much research, no known pathogen has been shown to cause the illness.

Conclusions: ME/CFS shows characteristics of an infectious disease: 1. Cluster outbreaks of ME/CFS have occurred globally. 2. In sporadic cases, a febrile onset and recurrent flu-like symptoms are common. 3. Patients’ immune system responses may also be found in some other infectious diseases. 4. The prevalence of ME/CFS is higher in close patient contacts than in the community although most close contacts do not develop ME/CFS. 5. Some healthy patient contacts...
show immune system responses similar to those seen in patients, suggesting exposure to the same antigen (a putative pathogen).

Although no known pathogen has been shown to cause the illness, there is significant evidence that ME/CFS is an infectious disease, possibly caused by a novel pathogen.


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**Chronic Brucellosis Infection and Immune Response in a Patient Presenting as ME/CFS**

E. Martinez Duarte, MD, N. Swaebe, MD, N. Klimas, MD, I. Rey, MD, I. Rozenfeld, MSN, ARNP, P. Dilanchian, DO

**Institute for Neuro Immune Medicine, Nova Southeastern University, Fort Lauderdale, United States**

**Objective:** To review the presentation of a case presenting as ME/CFS determined to have chronic brucellosis, and compare clinical presentation, immunologic markers and other lab measures with those described in literature as seen in chronic brucellosis.

**Methods:** Review the evaluation of 28 year old man with extensive travel history presenting with acute onset ME/CFS, differential diagnosis and laboratory and immune studies followed by a literature review of immunological markers identified in ME/CFS and Chronic Brucellosis published in English using Embase and PubMed databases with no limitations regarding type of article, journal or date. The following MeSH terms were used: myalgic encephalomyelitis, chronic fatigue syndrome, brucella, brucellosis, immune, immunology and immunity. We then compared these immune markers that of our patient, including serology analysis and symptoms consistent with ME/CFS and Chronic Brucellosis infection. His clinical course in response to brucella treatment will also be reviewed.

**Results:** After literature analysis of serological markers for both ME/CFS and Chronic Brucellosis our patient's serology was consistent with low Natural Killer cells activity and enumeration, elevated TNF alpha, IL 1 beta, IL 6 and CD 4 count. His initial response to appropriate treatment antibiotic coverage was disappointing.

**Conclusions:** Recent literature states that ME/CFS may develop after chronic infections and cases have been reported of Chronic Brucellosis and exacerbation or and onset of ME/CFS symptoms. In our patient with both diagnoses immunological markers were found to have similarities among them and compared to those found in literature. Chronic infections inducing or exacerbating ME/CFS in the literature warrant further research. Response to antibiotic treatment in the setting co-morbid ME/CFS and brucellosis may be limited.

**A Comparative Study on Fatigue Characteristics among Patients with Different Child-Pugh Grades in Liver Cirrhosis Due to Chronic Hepatitis B**

XUE Xiao-lin, WANG Tian-fang, GE Jian, WU Xiu-yan LI Xin ZHAO Li-hong LI Ning Wang Si-ying

*(School of Preclinical Medicine, Beijing University of Chinese Medicine)*

**Objective:** To compare the difference of the fatigue characteristics among patients with different Child-Pugh grades in Liver Cirrhosis due to chronic Hepatitis B.

**Methods:** The 632 subjects with Liver Cirrhosis due to chronic Hepatitis B were divided into three groups that were Child-Pugh A group, Child-Pugh B group and Child-Pugh C group according to Child-Pugh classification criteria. The fatigue characteristics of all the subjects in three groups were evaluated with the fatigue Self-assessment Scale. The mean scores of physical fatigue (PF), mental fatigue (MF), general fatigue (GF), consequence of fatigue (CF) situationality of fatigue (SF) response of fatigue to sleep and rest (RFSR) in this scale for three groups were analyzed using statistical software.

**Results:** (1) The mean scores and standard deviation (\(\bar{X}\pm S\)) of PF, MF, GF, CF, SF and RFSR in Child-Pugh A group were 19.62\pm20.44, 18.44\pm19.96, 16.82\pm17.22, 18.08\pm16.66, 12.65\pm21.83, 40.68\pm28.37. All of them in Child-Pugh B group were 28.77\pm23.61, 22.04\pm19.75, 22.96\pm20.82, 24.35\pm19.29, 18.98\pm26.16, 38.51\pm25.97and in Child-Pugh C group were 39.99\pm27.36, 28.58\pm23.43, 30.65\pm23.47, 32.73\pm22.87, 25.54\pm27.68, 44.64\pm27.66. The mean scores of the above factors in three groups were statistically different (P 0.05) with the exception of SF.

**Conclusions:** There were differences about fatigue characteristics among three groups in Liver Cirrhosis due to chronic Hepatitis B. It suggests that the heavier illness, the more obvious level of PF, MF, CF and RFSR among the patients. Acknowledgments: The paper was supported by Major State Basic Research Development
Altered Gut Microbiome in ME/CFS Patients in Comparison to Healthy Controls

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Objectives. As well as the symptoms of fatigue, pain, malaise, immune dysfunction and exercise intolerance, Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) is associated with a variety of gastrointestinal complaints. In order to investigate the possible basis of this comorbid condition, we undertook a study to determine whether the gut microbiome in a ME/CFS population from the New York City area differs from healthy individuals.

Methods. We characterized the gut microbiota of a cohort of 48 patients with ME/CFS and 36 healthy controls from the New York City region by sequencing amplicons of the V4 region of 16S rRNA genes using the Illumina platform. Of the ME/CFS subjects, average age was 50.6 ± 13.3, 38 were female and 10 were male, while of the controls, average age was 46.5 ± 9.7, 29 were female, 7 were male. All patients fulfilled the Fukuda criteria for diagnosis of CFS. Levels of markers of inflammation, i.e. lipopolysaccharide (LPS), soluble CD14 (sCD14) and lactoferrin (LF) levels were also determined in plasma samples using standard assays.

Results. We obtained an average of 140,000 (± 86,000) high quality reads per sample. In both cases and controls, the most represented phyla were Firmicutes, Bacteroidetes, Proteobacteria, and Actinobacteria. Comparisons between cases and controls indicated a shift of diversity in the patient cohort. Statistical analysis revealed significant differences between groups, i.e. a reduction in members of the Bacteroidetes and an increase in members of the Firmicutes in the patient population, also reported in Crohn’s disease and acute ulcerative colitis. Specific species, including reduction of butyrate-producer Roseburia faecis (p = 0.001, q = 0.03) and increase of Ruminococcus spp. (p < 0.001, q = 0.004), were detected in subjects with ME/CFS. The amounts of LPS, sCD14 and LF in plasma in our cohort were not statistically different from controls and fell within normal ranges. Our data do not corroborate prior reports of significantly higher levels of Lactonifactor, Alistipes and Enterococci in the feces of patients.

Conclusion. Subjects with ME/CFS in our cohort have a shift in overall microbial composition in comparison to healthy donors, a finding also characteristic of patients with inflammatory bowel disease. Our analyses highlight the contrast between the distribution of anti-inflammatory species, such as Roseburia species, which are more prevalent in healthy individuals, and potentially pro-inflammatory Ruminococcaceae, which are associated with irritable bowel syndrome and found to be more frequent in ME/CFS cases. Despite the differences in gut microbiome, three inflammatory markers did not differ between patients and controls in plasma. Whether deliberate manipulation of the composition of the gut microbiome in ME/CFS patients may ameliorate symptoms in some patients remains to be investigated.

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Rapid rhythmic contractions of the internal organs of Varestrongylus klapowi, a CFS related parasite, serving respiratory and circulatory functions, explain it’s unusual anatomy, and distinguishes it from inanimate artifacts

Lawrence A. Klapow

Objectives: 1. Further demonstrate the vital nature of the Varestrongylus klapowi, the Vk parasite by video-graphing the rapid, rhythmic motion of its internal organs. 2. Show how Vk compensates for the apparent loss of gas exchange due to its abnormally thick cuticle through unique functional and anatomical adaptations.

Methods: Nematodes typically respire through their cuticle. Vk’s extremely thick protective cuticle appears to limit this function. Furthermore, it’s extreme opacity makes viewing of internal organs difficult. Polarized/analyzed lighting has proved to be effective in revealing Vk’s internal organs, but requires extremely intense cool illumination, now routinely available with LED illuminators. Live specimens were collected from infected CFS patients inhaling ethanol vapor for one minute, followed by nasal washing with warm, ~85 degree F, physiological saline (0.9 % NaCl). Collected washings (~80ml) were kept warm and settled in tapered 50 ml test tubes for a minimum of 30 minutes. The bottom few drops of fluid, containing settled worms, were gently pipetted to slides with glass coverslips, examined on a microscope equipped with a stage warmer (~85F), and video-graphed.

Results: A pair of closely spaced muscular bands surrounding the mouth, and an a ring shaped esophageal/intestinal valve, contract at about 100–150 beats per minute, pumping fluid through the short thin-walled esophagus. The intestine...
rhythmically contracts in unison with a pair of adhering rennet glands. Their combined motions act like a piston pumping oxygenated fluids near the “lung esophagus” to posterior portions of the body cavity. A pronounced forward curve of the rennet cell necks provides slack which keeps the rennet cells from being torn from their attachment to the body wall at the excretory pore, as they move in synchrony with the intestine. The loss of thick esophageal muscles, to allow efficient gas exchange, has lead to the evolution of elongated specialized lips which force food into the mouth, replacing strong esophageal suction force as the primary feeding mechanism. A uniquely modified barrel shaped chemo-sensory amphid, pumps at about the same rate, and may also serve a gas exchange function. Conclusions: The video documentation of vital internal movements helps explains the unusual anatomy of the “armored” Varrestrongylus klapowi nematode parasite, and clearly distinguish it from inanimate artifacts. High-speed video’s with polarized/ analyzed light, made possible by intense LED illumination, show it’s internal organs beating at 100-150 cycles per minute. This action, along with the evolution of related anatomical features, appear to serve respiratory and circulatory needs necessitated by diminished gas exchange through it’s thick, highly opaque, protective cuticle. Previous epidemiological studies, showing a significant association of the Vk parasite with CFS, as well as nematode related immunological studies should be pursued further.

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**Chronic Active Herpesvirus Co-Infections in Patients with CFS/ME**

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Background: Infections with the leukotropic herpesviruses [Epstein-Barr virus (EBV), human cytomegalovirus (HCMV) and human herpesvirus six (HHV-6)] have been strongly implicated as important factors in the development of chronic inflammatory/autoimmune diseases including multiple sclerosis, system lupus erythematosus, Grave’s disease, and rheumatoid arthritis. They have also been proposed as the cause of chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME). Their ability to establish life-long latent infections with the potential for periodic reactivations could account for the relapsing-remitting nature of autoimmune diseases and also of CFS/ME.

Objective: The goal of these studies is to develop an algorithm to identify an “infectious clinical phenotype” in CFS/ME, document immunologic and functional perturbations associated with this phenotype, and provide justification for the implementation of appropriate antiviral and/or immunomodulatory therapies.

Methods: Cross-sectional study of 152 adult patients with prolonged fatigue and signs and symptoms suggestive of an active, ongoing infection were tested for evidence of chronic active EBV, HCMV and HHV-6 infection. Nested Plasma PCR, HHV-6 and HCMV immediate early (IE) protein specific antigenemia, HCMV and HHV-6 IE rapid culture using human fibroblasts and IgG antibody titers for EBNA-1 were performed.

Results: There were 14/152 (9%) patients that were positive for CMV, HHV-6 and high EBNA-1 titers (triple positive). A subset of the population 35/152 (23%) was shown to be negative for all three viruses (triple negative). Age and gender data were not significantly different between the triple positive and triple negative patient populations. There were 18% of patients positive for two viruses and 49% were positive for one. The results on the triple positive and triple negative sub-populations will be discussed in the context of a medical record review of clinical and laboratory findings, including information on other immunological parameters, self reported questionnaires and functional studies including VO2 Max with expired gas exchange. This approach will identify patients with a higher pretest probability of an infectious etiology for their CFS/ME.

Conclusion: In these studies we introduce the concept of a “leukotropic herpesvirus swarm” in which two or more of the viruses reactivate simultaneously, or in close temporal proximity with each other on a frequent basis and collectively contribute to the clinical manifestations seen in CFS/ME. We postulate that the concurrent reactivation of these viruses can lead to synergistic cellular derangement and produce systemic immune dysregulation.

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**POSTER SESSION: TREATMENT**

Lipid Replacement Therapy using NTFactor, NADH and CoQ10 significantly reduces fatigue and improves mitochondrial function in long-term intractable chronic fatiguing illnesses

Nicolson GL1, Ellithorpe RR2 and Settineri R3

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IACFS/ME • 11TH BIENNIAL CONFERENCE • MARCH 2014
Objectives: To determine the effects of oral NTFactor 2,000 mg; microencapsulated NADH, CoQ10 35 mg; L-carnitine 100 mg) during a 60-day open label clinical trial in long-term (>15 yr) intractable chronic fatigue patients [1].

Methods: 58 patients (30 F, 28 M, av. age 55) used oral ATP Fuel in tablet form each day. Participants were patients with chronic fatigue syndrome (Canadian consensus) (n=30), chronic Lyme disease (n=17) or other fatigue-illnesses, such as fibromyalgia or Gulf War illness (n=16). Participants had been symptomatic for an average of 17.1 yrs, had seen an average of >15.2 physicians and had taken over 35 drugs or therapies without resolution of fatigue. Subjects were told to maintain normal activities and diet during the trial. Fatigue was scored using the Piper Fatigue Scale (PFS). The PFS is a validated instrument that measures dimensions of subjective fatigue, such as behavioral/severity, affective/meaning, sensory and cognitive/mood and has been directly related to mitochondrial function [1].

Results: Participants in the study responded to the combination test supplement, showing a 30.7% reduction in overall fatigue within 60 days (p<0.001). Regression analysis of the data indicated that reductions in fatigue were gradual, consistent, and occurred with a high degree of confidence (R²=0.960). Analysis of fatigue subcategories indicated that significant improvements (p<0.001) were present in every fatigue subcategory. Males responded slightly better to the combination supplement than females, and the patients with the most severe forms of fatigue responded slightly better than those with milder fatigue, independent of their medical diagnoses. One participant left the trial because of severe headaches, and one left because of gastrointestinal complaints, both of which had occurred intermittently before the trial.

Conclusion: The combination supplement ATP Fuel, containing NTFactor, micro-encapsulated NADH and CoQ10, was a safe and effective method to significantly reduce fatigue in long-term chronic illness patients with intractable chronic fatigue [2].

References:

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A Mind-Body Technique for Symptoms Related to Fibromyalgia and Chronic Fatigue Syndrome
Presented by Ashok Gupta MA (Cantab), MSc. Loren L. Toussaint, PhD, Mary O. Whipple, BA, Lana L. Abboud, MA, MAC, Lac, Ann Vincent, MBBS, MD, and Dietlind L. Wahnner-Roedler, MD (Mayo Clinic, Rochester)

Objectives: To examine the use of a novel mind-body approach called “Amygdala Retraining”, for improving symptoms related to Chronic Fatigue Syndrome and Fibromyalgia.

Methods: This was a single-blind, randomized controlled trial. The study was conducted in a tertiary-care chronic fatigue and fibromyalgia centre at the Mayo Clinic. Patients with a confirmed diagnosis of Chronic Fatigue Syndrome according to CDC Criteria, fibromyalgia, or both were included. Patients were randomly assigned to receive amygdala retraining along with standard care or standard care alone. Standard care involved attending a 1.5-day multidisciplinary program. The amygdala retraining group received an additional 2.5-hour training course in which the key tools and techniques adapted from an existing program were taught to the patient. A home-study video course and associated text were provided to supplement the on-site program. Both groups received telephone calls twice a month to answer questions related to technique and to provide support. Validated self-report questionnaires related to general health, well-being, and symptoms, including Short Form-36, Measure Yourself Medical Outcome Profile, Multidimensional Fatigue Inventory, Epworth Sleepiness Scale, and Fibromyalgia Impact Questionnaire.

Results: Of the 44 patients randomly assigned who completed baseline assessments, 21 patients completed the study (14 in the standard care group and 7 in the study group). Median age was 48 years (range, 27-56 years), and female subjects comprised 91% of the group. Analyses demonstrated statistically significant improvements in scores for physical health, energy, pain, symptom distress, and fatigue in patients who received the amygdala retraining compared with standard care.

We examined changes from baseline to follow-up in outcome measures across both groups using mixed-model repeated-measures ANOVA. Results of these analyses showed that patients receiving amygdala retraining showed significant improvements on several outcome measures from baseline to follow-up, whereas patients receiving standard care had unchanged outcome measures. This pattern of findings held for SF-36-physical, SF-36-energy, SF-36- pain, MYMOP-2, MDFI-motivation, MDFI-activity, and FIQ.

P Values for the various measures ranged from less than 0.1 to 0.05

Conclusion: The findings from this pilot randomized clinical trial of amygdala retraining provide reason for guarded optimism regarding the addition of mind-body techniques in helping patients cope with symptoms of fibromyalgia and chronic fatigue.
Future studies should emphasize improvements in recruitment, retention, and procedure. Specifically, future studies should aim to draw on larger patient samples and encourage retention of enrolled patients. Resources afforded by grant-funded, large-scale investigations would allow research staff to focus on broader and more intensive recruitment, and to offer more individualized attention. This would be more in line with the established approach currently offered by Gupta. Our hope is that this study provides a beginning point for further investigation into mind-body interventions for fibromyalgia and chronic fatigue. This study was funded internally at the Mayo Clinic, and no external funds were used.

A Prospective, Open Label, Phase II Trial of Methylphenidate plus a CFS-Specific Nutrient Formula in Patients with CFS and Decreased Alertness.

Jon D. Kaiser, M.D. - Clinical Faculty, UCSF Medical School

Objectives: To examine the clinical effects and safety profile of a currently available medication (generic methylphenidate) co-administered with a mitochondrial support nutrient formula (CFS Nutrient Formula) in patients with CFS and decreased alertness who meet the 1994 CDC case definition for CFS.

Methods: This is an open-label single site, single arm Phase II prospective study to assess the effectiveness of generic methylphenidate co-administered with a CFS-specific nutrient formula in reducing fatigue and concentration disturbance symptoms in fifteen subjects meeting the 1994 CDC case definition for CFS. Fifteen patients with CFS were prospectively recruited and treated with immediate-release methylphenidate (10mg twice daily) plus CFS Nutrient Formula (4 tablets twice daily). Methylphenidate was initiated at 5mg bid for the first week and then dose escalated to 10mg bid from the second week forward if tolerated. Patients were instructed to maintain fluid intake of 6-8 glasses per day and not substantially change their activity level during the 12-week trial. Fatigue and concentration disturbance symptoms were measured using two clinically validated tools: 1) Checklist Individual Strength (CIS), a self-reported questionnaire used to measure fatigue in previous CFS clinical trials 2) Visual Analog Scale (VAS) for fatigue and concentration disturbance symptoms. Data was collected at baseline, 4-weeks, and 12-weeks. The primary endpoint was a clinically significant reduction in fatigue in more than 50% of the study subjects. For the purposes of this study, a clinically significant improvement was defined as an improvement of >25% in the total CIS score.

Results: At 12-weeks, a clinically significant reduction in the total CIS score (a decrease of >25%) occurred in 73% of the participants with a mean reduction in fatigue of 35%. The Visual Analogue Scale (VAS) for fatigue symptoms confirmed this trend with a mean reduction in fatigue of 52% at 12-weeks. A clinically significant reduction in concentration disturbance symptoms (as measured by the concentration subscore of the CIS) was observed in 66% of the participants with a mean concentration disturbance symptoms reduction of 43%. The Visual Analogue Scale (VAS) for concentration disturbance symptoms confirmed this trend with a mean concentration disturbance symptoms reduction of 58% at 12-weeks. All patients tolerated the treatment well.

Conclusion: The treatment of CFS patients with generic methylphenidate co-administered with a CFS-specific nutrient formula significantly improved fatigue, alertness, and concentration disturbance symptoms in a majority of study patients. The study treatment was effective and well tolerated in treating both fatigue and concentration disturbances associated with CFS. A Phase IIb multicenter double-blind, placebo-controlled trial powered for statistical significance (n=120) is scheduled to begin enrolling patients in December 2013.

Translating Science to Clinical Care: Because this intervention consists of a currently available medication (methylphenidate) possessing a well tolerated dietary supplement (CFS Nutrient Formula), further study and eventual clinical use of this intervention can move forward expeditiously. An oral presentation is requested.

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Differential Exercise Responses to Rintatolimod Exhibited by Patients with Severe Chronic Fatigue Syndrome (CFS)

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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 (Poly I : Poly C32U), a selective TLR3 agonist, in a Phase III prospective, 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) as the primary endpoint. The primary endpoint has been reexamined post-hoc as a function of dichotomization of individual patient responses.
Methods: Dichotomization of improvement in exercise performance from Baseline at the ≥25% and ≥50% levels was analyzed for the ITT population and as a function of pre-specified pre-treatment exercise duration strata (≤9 minutes vs. >9 minutes) at 40 weeks.

Results: For the ITT population a significantly greater percentage of rintatolimod patients (39%) vs. placebo patients (23%) improved ET duration by ≥25% (p=0.013) and 26% vs. 14% of rintatolimod vs. placebo patients, respectively, improved ET duration by ≥50% (p=0.028). For the subset of patients with Baseline ET ≥9 minutes, 33% vs. 12% of rintatolimod vs. placebo patients (p=0.004) improved ET duration by ≥25% and 23% vs. 4.5% of rintatolimod vs. placebo patients (p=0.003), respectively improved ET duration by ≥50%. In addition, a frequency distribution analysis of ≥25% improvement, ≤25% change and ≥25% worsening in ET from Baseline at 40 weeks for the Baseline ≥9 minutes cohort showed net improvement to be 18.3% for the rintatolimod cohort vs. -4.6% for placebo (p=0.015).

Conclusions: A responder analysis of rintatolimod vs. placebo patients improving ET duration from Baseline by ≥25% and ≥50% shows a clinical enhancement in ET effect in the rintatolimod cohort for the ITT population, as well as, for a subset of patients with Baseline ET duration ≥9 minutes as compared to placebo. Rintatolimod was generally well-tolerated in this CFS/ME population.

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The effects of cognitive retraining in eight patients with moderate to severe ME/CFS
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Objectives: As many as 9 of 10 patients with ME/CFS experience cognitive difficulties. Although coping with cognitive symptoms are one of the main issues for those affected with ME/CFS, treatment is lacking and no previous intervention has specifically targeted cognitive deficits.

Methods: The participants were all diagnosed with ME/CFS according to the Canadian criteria (2002) and participated in a multiprofessional rehabilitation program. To be able to participate in cognitive training program they had to have cognitive complaints self-rated with Cognitive Failure Questionnaire (CFQ), and a cognitive deficit in attention or working memory that was not judged to be congenital. In addition an overall evaluation was made whereas the patient had the capacity to undertake the intensive training.

A control group consisted of 15 patients who participated in the rehabilitation program but without specific intervention for cognitive deficits.

Cogmed QM is a computerized working memory training program and it aims to improve concentration, attention and impulse control. It has been evaluated earlier in several studies in other populations. The training takes 30-45 min per day and covers 25 times. The training is planned intensively for five weeks and in the study the participants performed the training in their homes. During the training program the participants were coached over the telephone 3-5 times.

Outcome measures: neuropsychological tests such as digit repetition backwards (from various test batteries) and The Rey Auditory Verbal Learning Test (RAVLT) were used before and after the working memory training program, and for the last four participants also the Canadian Occupational Performance Measure (COPM) was used to measure self-rated performance and satisfaction in working memory related activities before and after the training.

Results: Finally 11 participants were included. Six of the participants fulfilled the training within five weeks, two needed extended time (10 respectively 15 weeks). There were three dropouts: One due to severe increase of fatigue and other symptoms, one due to lack of motivation and one due to lack of time.
6 of 7 of the participants that fulfilled the training showed significant improvement of the Cogmed QM tasks. Results from the neuropsychological tests for memory and attention show significant improvements for the training group. In contrast the control group did not show significant changes in the testing results.

The COPM show significant improvements for both performance and satisfaction for two of four participants.

Conclusion: This study gives modest support for the idea that cognitive retraining can increase working memory capacity and performance and satisfaction in working memory related daily activities in patients with moderate to severe ME/CFS. This study also highlights that more research, understanding both mechanism of cognitive decline and treatments targeting cognitive difficulties in patients with ME/CFS is of need.

Case Report: Herbal Medicine and Meditation used in ME/CFS, Lyme and Fibromyalgia Patient
Lynn Anne Lafferty, Pharm.D., N.D., MBA, MH

This is a case report of a 47 year old woman who was diagnosed with ME/CFS, Lyme and Fibromyalgia. She had been to over 20 medical doctors who she said could not help her. Today, after using an integrative approach using herbal medicine, whole food nutrition and meditation for 1 year, she is living a normal life, she had been bed ridden for over 2 years.
Objectives: In this poster we will review her test results to identify and assess the markers of endocrine and immunologic conditions, pathogens and overall circadian rhythm; This presentation will also Review the scientific evidence of herbal and natural whole foods and other natural products on the HPA axis, herbal antimicrobials on viruses and other microbes; and herbal and other natural immune builders. This presentation will identify mediation and coaching as effective models to increase patient hope and treatment compliance.

Methods: The patient was tested using traditional blood tests along with saliva and stool tests. Saliva tests showed cortisol and other hormonal imbalances. Stool tests showed pathogenic microbes including gram + and - bacterial overgrowth. These Test results, a 200 question symptom survey, and interview were used to identify physiologic and biochemical imbalances. Herbal and whole food remedies were used to reduce and alleviate symptoms and pathologies with effectivenes as demonstrated by pre and posttests of symptoms severity and function. Meditation, prayer and individual coaching were used to increase the amount of hope of the patient and motivate her to stay with the program and to help her to better self-identify her progress.

Results: A patient case with ME/CFS and other diagnosis symptoms markedly improved after 1 year of treatment. Her chronic pain was totally alleviated, her depression and her digestive issues such as pain and constipation went from severe to none at all. Symptoms that improved by 50% were the amount of time it took to fall asleep and the restfulness. Her self-reported energy improved 75%.

Conclusion: An integrative approach can be successfully to alleviate symptoms and improve patient outlook should be considered with ME/CFS patients.

Translating Science into Clinical Care: The use of herbal and other natural products have not been extensively studied in this population, but many herbs have hundreds or even thousands of studies, which point to their anti-microbial and immune-building effects. Additionally there are herbs that address HPA axis dysregulation. Their use should be considered, and further studies in this complex population encouraged.

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In vitro peripheral blood response to exogenous IL-15 in Gulf War Illness and Myalgic Encephalomyelitis/Chronic Fatigue Syndrome in men

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Objectives. After returning from Operation Desert Storm, an alarming number of veterans presented with a constellation of symptoms eventually labeled Gulf War Illness (GWI). This complex disorder affects nervous, endocrine, and immune regulation. Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS), a complex illness affecting approximately 1 million people in the U.S alone, also impacts multiple systems and presents a significant clinical overlap with GWI. Both illnesses exhibit dysregulation of cytokines, specifically the observation of low IL-15. A profound impairment of NK cell function has been observed in both illnesses. We propose that stimulation with IL-15 may restore NK cell function in these patients.

Methods. Peripheral blood mononuclear cells from whole blood samples collected from GWI (n=5), ME/CFS (n=7), and healthy control (HC) (n=6) male subjects were recovered from cryopreservation in DMSO. Cell viability was determined using a ViCell 2.4, and viable samples were incubated in growth medium for 18 hours with and without 25 ng/mL of exogenous IL-15. NK cell cytotoxic function was assessed prior to cryopreservation and after stimulation using 51Cr labeled K562 target cells and lymphocyte abundance profiled with a fluorochrome multi-parameter cytometer on a 1:1 target to effector cell ratio.

Results. In vitro treatment with IL-15 improved NK cell function roughly 3-fold in both illnesses (ME/CFS p<0.05; GWI p<0.003), while CD3-CD56+ NK lymphocyte enumeration remained unchanged. Flow cytometry data exhibited significant increases in CD2+CD26+ (p<0.02) and CD4+CD26+ abundance in ME/CFS (p<0.01) and significant increases in CD8+CD26+ (p<0.02) and CD3-CD16+CD11a+ (p<0.03) abundance in GWI; no other significant cell population changes were observed.

Conclusion. Increased CD26+ lymphocyte expression and repair of natural killer cell cytotoxicity (NKCC) indicates that exogenous IL-15 has a positive effect on immune function in GWI and ME/CFS. Viral reactivation presents immune complications in ME/CFS, and thus repair of CD26+ subsets and NKCC is vital, especially in the context of the innate fight against cancer cells. Exogenous IL-15 presents itself as a viable intervention option for future immune therapy studies on ME/CFS and GWI.
Feasibility of Home-Based EMDR to Reduce Fibromyalgia Impact
Fred Friedberg, PhD, Jenna Adamowicz, MA, Indre Caukaisite, and Viktoria Seva, MA

Background: Fibromyalgia (FM) is a debilitating and medically underserved chronic illness with high rates of long-term disability, pain, and poor self-rated health (Kasman & Badley, 2004). Furthermore, the pain and limitations of FM pose a significant unmet medical need for millions of patients (Chopra et al., 2011). Notably, established interventions have significant limitations i.e., approved medications have relatively modest benefits, and cognitive-behavior therapy is time consuming and costly (Dobkin et al., 2006; Arnold 2006; Staud, 2010).

Objective: To document the feasibility of a brief, easy-to-use self-management technique utilized at home to reduce FM impact. The Eye Movement Desensitization and Reprocessing (EMDR) program was expected to reduce pain and fatigue impact such that FM patients could better control their symptoms.

Methods: Twenty-four women with FM diagnosed by their physicians were recruited for this pilot study. During the 3-month study period, participants were sent an EMDR program booklet, along with a MP3 player with ear phones to deliver the EMDR technique. Additionally, all participants were asked to complete a twice a day paper diary for the entire study period to record their symptoms and EMDR practice. The average compliance with the twice daily diary was 68%, but post-enrolment dropout was 50%.

Results: Feasibility issues included the high subject burden of completing daily paper diaries for three months (which appeared to contribute to the high dropout rate) and the possible need for a video-based form of EMDR instruction to clarify how the procedure is done. At the three-month follow-up assessment, significant improvements were found on pain severity and interference (Brief Pain Inventory- Short Form; p = .019 and .004, respectively.) A significant improvement was also found on pain magnification (Pain Catastrophizing Scale; p = .025). No significant changes were found in fatigue, depression or anxiety.

Conclusion: Brief utilization of the EMDR program at home can significantly improve the FM impact of pain; however, a high dropout rate indicates the need for adjustments in the protocol to lessen subject burden.
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The New Complex Chronic Diseases Program’s Integrative and Interprofessional Collaborative Practice Model: Integrating Evidence at Inception (2013) in a program to help patients with Fibromyalgia, Lyme disease and Myalgic Encephalomyelitis.
Alison C. Bested MD FRCP, Darci Rosalie RN and Nicole Prestley BA

Background: Over 100,000 British Columbians are affected by Lyme disease, Fibromyalgia and Myalgic Encephalomyelitis (Stats Canada). BC Women’s Hospital created the Complex Chronic Diseases Program (CCDP) using an integrated healthcare model to help patients with these conditions. The CCDP created an opportunity to integrate an Interprofessional Collaborative Practice (ICP) model of care from the program’s inception.

Objectives: Our aims: 1) to design an integrated clinical model of care 2) to define ICP within the CCDP and 3) to develop an ICP Action Plan.

Methods: Integrated model of patient care in the CCDP was designed then mapped and created Visit #1 with Allied Health professionals. CCDP staff was invited to participate in an “Advancing Interprofessional Collaborative Practice with Patients and Families” workshop from Michael Smith Foundation funding.

Results: The integrated model of care is helping the large number of referrals (930) to the CCDP. Participating in the workshop allowed the CCDP to integrate ICP into their model of care. Recent program changes include: improved role clarification allowing for the reassignment of workload, the Point Person role creation to provide support for patient involvement in their health care and the development a Patient Flow “Bookmark” to optimize engagement with patients during their CCDP health experience.

Conclusion: An integrative model of care with ICP integration into the program provides better patient care by encouraging effective patient participation and communication with their health care team. Support from administration is critical to the ongoing evaluation process and environment for incorporating evidence into clinical practice.
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Chronic fatigue syndrome: The development of an evidence-based self-management program in primary healthcare
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Objectives
Chronic fatigue syndrome (CFS) is an illness associated with physical and cognitive disability. Given the impact of the illness and the lack of curative treatments, it is important to develop effective interventions to promote better coping with the illness. Sufferers should have access to such interventions independent of place of residence. The potential role of patient education programs assumes increased importance. The aim of this pilot study was therefore to develop, carry out and evaluate a self-management program for people with CFS that can be organized in primary healthcare.

Methods
The process consisted of several steps. Firstly, we developed a program that was based on self-efficacy theory and concepts of client-centred practice and empowerment. Secondly, the program was carried out and consequently evaluated with evaluation forms as well as a semi-structured focus group interview. The results from the evaluation were used to adjust the program. The proposed changes were discussed with participants in a second focus group interview 4 months following participation in the program. The sample consists of 5 women and 1 man, with mean age 38.7 years (range 28 - 46), diagnosed with CFS from 1 week to 7 years (mean 2.3 years) ago. The interviews were analysed using thematic analysis.

Results
After participation in the program, the participants experienced better understanding of the illness, acceptance and coping with the illness. Participants proposed modifications concerning the presentation of topics, introduction of goals and action plans, need for client-centeredness and the practical organisation. In addition they supported adding a meeting for relatives. The results were used in the development of the final version of the program.

Conclusion
The developed self-management program for people with CFS appears to be a beneficial intervention, but needs modifications. The effects of the final program will be measured in a randomized controlled trial before implementation in primary healthcare.

Translating science into clinical care
Self-management programs appear to be a beneficial intervention that may be offered to people with CFS in primary healthcare.

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Acceptance & Commitment Therapy (ACT) for ME/CFS - does it work, and for whom?
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Introduction and objectives
To date, for many patients with ME/CFS, medical strategies alone appear insufficient to reduce symptoms and increase functioning. Cognitive behavioral therapy (CBT) is a promising treatment approach, but effect sizes are generally modest. Recently, Acceptance and Commitment Therapy (ACT) has gained increasing attention and research support, e.g. research evaluating ACT for chronic debilitating pain and tinnitus illustrate the utility of this approach for individuals with somatic disorders. In short, the treatment objective is to increase functioning and quality of life by promoting psychological flexibility, i.e. the ability to behave in accordance with important long-term goals/values in the presence of interfering experiences (fatigue, pain, anxiety). Also, mediation analyses indicate that psychological flexibility is central to functioning and quality of life. To date, the efficacy of ACT has not been evaluated for ME/CFS. Therefore, this pilot study will explore the utility of ACT for adults with ME/CFS as well as identify factors (e.g. physical activity, sleep, psychological, neurological, endocrine and immune) of importance to predict treatment outcome. An additional aim of this study is to identify subgroups of patients with different mechanisms in the genesis and persistence of the illness, with possible differential outcomes from behavioral interventions. Furthermore, we will evaluate the relevance of these factors in explaining functioning and quality of life.

Method
Treatment consists of 13 weekly individual ACT sessions. An open trial design is used, with assessments at pre- and post-treatment as well as at 3, 6 and 12 months follow-up. The primary outcome measures are mental and physical functioning (SF-36) and quality of life (EQ-5D). Secondary outcome measures include psychological flexibility (Psychological Inflexibility in Fatigue Scale, PIFS) and activity data assessed by an accelerometer. Measures for subgrouping include history data (presence of symptoms according to the Canadian case definition and grading of symptom severity, type of onset), psychological factors (e.g. psychological flexibility), dysfunction of the autonomic nervous system (e.g. HRV, SRS, tilt-table test, NPY), IBS (symptoms and laboratory investigations e.g. CD14), HPA-axis and stress (e.g. salivary cortisol, steroid hormone profile), immunology (e.g.; CRP, cytokine profile), physical activity and sleep (Astrand test of fitness test and VO2, accelerometer, pedometer).
Data will be analyzed using hierarchical regression analyses and linear multilevel modeling.

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Results and conclusion
Data collection is ongoing since March 2013. The poster will present preliminary findings regarding the relationships between psychological, neurological, immune and endocrine factors, as well as physical activity and sleep disturbances. Moreover, the possibility of identifying factors or combinations thereof (subgroups) central to the effects of treatment (predictors, moderators) will be discussed, as well as clinical implications of the preliminary findings.

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Can A Rehabilitation Program for Chronic Fatigue Syndrome Based On Gradual Activity Increase Be More Effective in Optimizing Capacity Than a Program Based On Pacing?
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Objectives: The purpose of this study is to compare two different rehabilitation programs for patients with a diagnosis of Chronic Fatigue Syndrome and/or Myalgic Encephalomyelitis.
(1) The first program was carried out between 2011 and 2013 and consisted of a psycho-educational part followed by individual interventions with a multiprofessional team. The main goal of this rehabilitation program has been to help patient to retain their current level of function according to the pacing model and increase quality of life. The preliminary results of this method have not, however, showed the expected increase in functional or occupational capacity. Yet, patients reported good satisfaction with the program and minor improvement in their quality of life.
(2) The second program starting 2014 emphasized a comprehensive multimodal approach with improvement within seven domains: physical activity, activities of daily life and leisure activities, cognitive activities, social activities, emotional reactions, activities related to work or education, and sleep behavior. After a systematic assessment of their current capacity in the seven domains, patients are offered a model of gradual increases in each domain with weakly monitoring with a team consultant.

Methods: 59 patients (45 females and 14 males) with a diagnosis of Chronic Fatigue Syndrome and Myalgic Encephalomyelitis according to the CDC and or the Canadian criteria, have been treated and 18 (15 females and 3 males) are under current treatment according to the first rehabilitation approach. The mean age of patients within the first model is 43.7 years (female: 44.8 years; males 39.7 years).
8 patients (only females with a mean age of 44.3 years) are currently assigned to the new program.

Results: The primary outcome measures of the study will be the results on the SF-36 health survey, the Multidimensional Fatigue Inventory (MFI-20), the Fatigue Severity Scale (FSS) and the Cognitive Failure Questionnaire (CFQ), the Visual Analogue Scale (VAS), the Patient Health Questionnaire 9 (PHQ-9).
Secondary outcome measures will be work or study activity at 2 years after completed program.

Conclusion: We expect that this study will help bring some clarity on which approach is most effective in treating CFS/ME patients: an approach characterized by pacing and conservation of current activity level or an approach characterized by an individualized graded increase in activity.

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Active B12 dosage in CFS/ME patients
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Vitamin B12 deficiency causes neurological damage and fatigue. The evaluation of vitamin B12 deficiency has improved with the dosage of active B12 in the serum. This testing seems much more relevant than homocystein, standard B12 dosage or search of macrocytosis. In my practice 10 patients suffering from CFS/ME with low active B12 have been clinically significantly improved after normalization of active B12 plasma level. Best improvement were observed for:
Translating Science into Clinical Care: new discovery concerning B12 evaluation seem to be very important for many CFS patients: evaluation and treatment

Poster Session: Genomics

Plasmacytoid dendritic cells cultured with siRNA or small molecule inhibitors of Toll-like receptors (TLR)-7 and -9 uniquely express proteins consistent to those observed in duodenum biopsies of subjects with myalgic encephalomyelitis.

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Objectives: Previously, we reported an infiltration of plasmacytoid dendritic cells (pDCs) in the gut of a statistically significant number of individuals with myalgic encephalomyelitis (ME). Additionally, we observed that approximately 50% of duodenum-associated pDCs expressed human endogenous retroviral (HERV) proteins, whereas no HERV protein expression was observed in any of the control biopsies. A previous report by Yu et al. (Immunity, 2013) describes the unique expression of HERV proteins by pDCs using a Toll-like receptor (TLR) 3-7-9 knockout mouse model. Consequently, we hypothesized that the expression of HERV proteins by pDCs may be a biomarker for TLR inhibition, and specifically, TLR inhibition of pDCs in the gut of ME subjects. Therefore, the objective of this study was to provide evidence that HERV expression by gut-associated pDCs in ME subjects is the result of TLR inhibition.

Methods: Purified pDCs from healthy donors were cultured for five days in the presence of small interfering RNA (siRNA) to TLR-7 and -9 or with the TLR inhibitors C661 and IRS-954. Non-treated cells and cells treated with an irrelevant siRNA were used as controls. HERV expression was established by immunohistochemistry and total RNA was collected on Trizol reagent, depleted of ribosomal RNA, and used to conduct transcriptional analysis by Next Generation Sequencing (NGS). Transcripts expressed by TLR-inhibited pDCs were deemed significant when their expression was four-fold greater than that of the control cells. Lastly, a monoclonal antibody specific for the most significantly upregulated transcript was used to screen duodenum biopsies of ME subjects to confirm in vivo expression.

Results: Consistent with observations in TLR-knockout mice, cultured pDCs expressed HERV proteins in the presence of TLR-7 and -9 siRNA as well as TLR inhibitors, but not control cells. NGS analysis identified several significantly upregulated transcripts, the greatest of which (500-fold increase) was phospholipase C-like 2 (PLCL2); a protein previously associated with multiple sclerosis. Monoclonal antibodies to PLCL2 were uniquely immunoreactive to pDCs in biopsies of ME subjects, but not in controls.

Conclusions: These data are consistent with an inhibition of TLR-7 and/or -9 in the gut-associated pDCs of subjects with ME; however, prospective studies will be necessary to identify the nature of the TLR inhibition. pDCs are key players in the type I interferon antiviral response as well as antigen presentation both in adaptive immunity and in the induction of tolerance; consequently, this work has potentially identified a defect in a critical component of the innate and adaptive immune response, which may lead to future targeted treatment strategies.

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Poster Session: Immunology

Disruption of cytokine pathways in chronic fatigue syndrome.

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Objectives: The literature on immune function in those with CFS has produced findings both for and against immunologic activation. Previous work on the part of our study group found a dysregulation of cortisol regulation to be associated with CFS. Expanding on that work, the intent of this investigation was to evaluate for the presence of differential cytokine activation in association with CFS. A group of patients with MS served as a disease control group, and a separate group of putatively healthy controls was used as a baseline reference.

Methods: Peripheral blood was obtained and the production of a select cytokine profile determined from stimulated and unstimulated cells. The cytokines and chemokines evaluated were: IL-1β, IL-2, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-12 (p70), IL-13, IL-17, BDNF, G-CSF, GM-CSF, IFN-γ, MCP-1, MIP-1α, and TNF-α. Values were determined using the BioPlex multi-analyte bead suspension array system. Statistically, pairwise associations were determined between blood protein levels for the CFS, control, and MS groups independently. Between every two protein combinations, we computed separate associations based on spearman correlation. Correlations with a significant threshold of less than 0.1 were used to model protein relationships using a graph model on which we then conducted neighborhood analysis.
Results: The control and MS sample produced a three neighborhood relationship regardless of cell condition. In contrast, the CFS sample in contrast displayed a three neighborhood solution when unstimulated, albeit one with stronger correlations among proteins, that changed to two factor model on stimulation. The stimulated CFS neighborhoods were one composed primarily of pro- and anti-inflammatory proteins, with the second neighborhood reflecting growth factors and factors associated with cellular differentiation. The model found in those with CFS was significant different from that found in the control or MS samples.

Conclusion: This study shows that CFS is characterized by a pattern of global immunologic activation in a differential pattern than seen in MS or control subjects. The connectivity between IFN and IL-12 is as expected, while there is also connectivity between IL-4, IL-5 and IL-13 in a manner consistent with anti-inflammatory activation. This differential pattern of activation amongst these groups provides evidence for a dysregulation of immunologic response in those with CFS.

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Innate Immune Cells in Severe and Moderately Chronic Fatigue Syndrome/Myalgic Encephalomyelitis.

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Objectives: There are consistent immunological abnormalities within the innate immune system in Chronic Fatigue Syndrome/Myalgic Encephalomyelitis (CFS/ME) patients. The most common innate immune abnormality is reduced Natural Killer (NK) cell cytotoxic activity. CFS/ME symptom presentation varies among patients who may be able to be characterised by their symptoms as moderate or severe. Few studies have assessed NK cells, neutrophils and monocytes in severe CFS/ME patients.

The purpose of this study was to assess innate immune cells, including NK cells, neutrophils and monocytes in severe and moderate CFS/ME patients.

Methods: CFS/ME patients were assessed using the 1994 CDC Case Definition and the International Consensus Criteria for ME. Health, mobility and quality of life questionnaires were used to distinguish CFS/ME participants as either moderately or severely affected. Blood was acquired from severe (n=18) and moderate (n=23) CFS/ME patient groups and non-fatigued controls (n=22). Using flow cytometric assays, analysis was conducted on NK cells, neutrophils and monocytes.

Results: In effector cell target ratios (12.5:1, 25:1, 50:1), there was a significant reduction in cytotoxic activity of NK cells in moderate (p = 0.001, 0.000, 0.017) and severe CFS/ME participants (p = 0.000, 0.000, 0.001) compared to non-fatigued controls. There was a further reduction in cytotoxic activity in those participants who were severe compared to those who were moderate although there was no statistical difference. CD56brightCD16dim and CD56CD16 NK cell phenotypes were increased in severe CFS/ME compared to moderate (p = 0.023, 0.049) CFS/ME patients and the NK phenotype CD56dimCD16 was significantly increased in moderate CFS/ME compared to non-fatigued controls (p = 0.045).

There was no statistical significance between any of the participant groups for neutrophil or monocyte phenotype markers.

Conclusions: These results have confirmed previous research where NK cell cytotoxic activity has shown to be reduced in CFS/ME. Data has further suggested that NK cells have immune perturbations related to cytotoxic activity and phenotypes in CFS/ME and this may be contributing to the overall immune profile demonstrated in this illness.

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Chasing a Shifting Immune Baseline in Women with Chronic Fatigue Syndrome.

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Objectives. Validation of biomarkers for myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) across data sets has proven disappointing. As immune signature may be affected by many factors, our objective was to explore the shift in discriminatory cytokines across ME/CFS subjects separated by duration of illness.

Methods. Cytokine expression collected at rest across multiple studies for female CFS subjects (i) 18 years or younger, ill for 2 years or less (n=18), (ii) 18-50 years of age, ill for 7 years (n=22), and (iii) age 50 years or older (n=28), ill for 11 years on average. Control subjects were matched for age and body mass index (BMI). Data describing the levels of 16 cytokines using a chemiluminescent assay was used to support the identification of separate linear classification models for each subgroup. In order to isolate the effects of duration of illness alone, cytokines that changed significantly with age in the healthy control subjects were excluded a priori.
Sex-hormone mediation of immune function as a driver of ME/CFS severity

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Objectives. While biomarkers for myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) are emerging, the mechanisms driving symptom severity remain poorly understood. We hypothesize that sex hormones and their mediation immune function may play a role. Our objective was to identify co-expression of cytokines and sex hormones that also coincide changes in ME/CFS severity.

Methods. As part of an ongoing study, blood samples were collected at rest from n=18 female ME/CFS subjects; 35-73 years of age. Illness severity was characterized using standard self-assessment instruments that included the multi-dimensional fatigue index (MFI), Beck Depression Index (BDI) and the short form 36 (SF-36). Blood samples were analyzed for concentrations of estradiol and progesterone as well as 16 cytokines using a chemiluminescent assay. Concentrations were log2 transformed and z scaled. Associations between symptoms and blood-borne markers were estimated based on partial correlation adjusted for age and body mass index (BMI). Null probability estimates were based on an asymptotic normal distribution and adjusted for false discovery using Benjamini Hochberg criteria.

Results. Analysis revealed direct and significant correlations (adjusted p<0.05) linking SF-36 measures for physical limit, emotional limit and pain with changes in progesterone (r=0.66), IL-4 (r=-0.71) and IL-1α (r=-0.76) respectively. The MFI measure for mental fatigue correlated positively with changes in IL-2 (r=0.62) while reduced motivation score correlated negatively with the interaction of progesterone and IL-17 (r=-0.63). In each case, symptoms correlating with blood-borne markers directly were part of a larger symptom cluster.

Conclusion. These preliminary results suggest that aspects of mental, emotional and physical fatigue including pain correlate significantly with levels of progesterone as well as that of specific Th1, Th2 and Th17 as well as inflammatory cytokines. Importantly the severity of a major symptom cluster may be driven by endocrine mediation of Th17 activity in ME/CFS.

Degradation of natural killer cell cytotoxicity over time after blood draw

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**Background.** Since the early 1990’s, natural killer cell cytotoxicity (NKCC) has been shown to be a biomarker for Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS). Deficient NKCC is the most reproducible finding for ME/CFS and has been validated across the globe. According to a CDC primer, 79% of Americans were found to have abnormal NKCC. While other methodologies exist, the most clinically useful assay is a whole blood method measuring cytotoxic cellular function on a 1:1 target to effector cell ratio. While the nature of the assay requires fresh whole blood, the complexity of such an assay prevents adoption by local clinical laboratories, giving rise to the need for shipment of whole blood to a central reference laboratory.

**Methods.** NKCC levels from patients seen in clinical practices across the country were collected. Laboratory data came from physician-ordered blood samples. These patients were previously found to have low NK cell function. While most patients had ME/CFS, others had various other chronic disorders, including cancer. The whole blood NKCC method involves incubating whole blood with Cr51 target K562 cells, then measuring radioisotope release using a gamma counter. We used flow cytometry to determine the CD3-CD56+ cell counts in whole blood, allowing for a non-linear regression that will provide cytotoxicity at a 1:1 target to effector cell ratio. NKCC values were then compared with the time elapsed since blood draw.

**Results.** From July 2012 to June 2013, patient’s (n=706) NKCC results were measured and compared against the hours elapsed from time of blood draw. A best-fit line of the degrading NKCC, plotted between 17-24 hours post blood draw, demonstrated a sharp decline as time elapsed. After 24 hours, NKCC values fell one standard deviation below the mean of the healthy control reference range.

**Conclusion.** Because the age of the sample affects the measurable result of the NKCC assay, patient samples must be compared to healthy controls of a similar blood age. Since the natural killer cellular function is affected by time, the assay is only reliable if samples are completed prior to the 24 hour mark. Fresh blood and timely delivery are a vital requirement of this assay.

### Comparison between Proinflammatory Cytokine in women versus men with Chronic Fatigue Syndrome.

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**Objectives**

This article reviews the measure of the Proinflammatory cytokines of a total of 100 patients of our institute to compare the difference between cytokines in women versus cytokines in men.

**Methods**

The authors selected a total of 100 patients with Chronic Fatigue Syndrome diagnosed by Fukuda diagnostic criteria without previous treatment, 80 women (40 Hispanic vs. 40 Non-Hispanic) and 20 men (10 Hispanic vs. 10 Non-Hispanic) between ages of 18 and 73 and they chose the cytokines report of the patient first visit. The report measured plasma interleukin-(IL)1α, interleukin-(IL)1β, interleukin-(IL)6, tumor necrosis factor (TNF)α and tumor necrosis factor (TNF)β.

**Results**

Tumor necrosis factor (TNF)α is significantly higher in women patients and interleukin-(IL)1β is significantly higher in women compared to men. The tumor necrosis factor (TNF)β and interleukin-(IL)1α are significantly lower in women patients compared to men. However, the interleukin-(IL)6 the mean remain the same in both sex.

**Conclusion**

The interleukin-(IL)1α, interleukin-(IL)1β, interleukin-(IL)6, tumor necrosis factor (TNF)α and tumor necrosis factor (TNF)β, all induce many inflammatory reactions. The results of the study suggest that there is a significant difference in the majority of the Proinflammatory cytokines between women and men.

### Comparison between Anti-Inflammatory Cytokine in men versus women with Chronic Fatigue Syndrome.

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Objectives
This article reviews the measure of the Anti-inflammatory cytokines of a total of 100 patients of our institute of Neuro Immune Medicine to compare the difference between cytokines in men versus cytokines in women.

Methods
The authors selected a total of 100 patients with Chronic Fatigue Syndrome diagnosed by Fukuda diagnostic criteria without previous treatment, 20 men (10 Hispanic vs. 10 Non-Hispanic) and 80 women (40 Hispanic vs. 40 Non-Hispanic) between ages of 18 and 73 and they chose the cytokines report of the patient first visit. The report measured interleukin-(IL)4, interleukin-(IL)5, interleukin-(IL)17, interleukin-(IL)23, interleukin-(IL)10 and interleukin-(IL)13 in plasma.

Results
The interleukin-(IL)5 and interleukin-(IL)23 are significantly lower in men patients and interleukin-(IL)17 is significantly higher in men patients compare to women. However, the interleukin-(IL)4, interleukin-(IL)10 and interleukin-(IL)13 the mean in all of the three remain the same in both sex.

Conclusion
The interleukin-(IL)4, interleukin-(IL)5, interleukin-(IL)17, interleukin-(IL)23, interleukin-(IL)10 and interleukin-(IL)13, all control the proinflammatory cytokine response and regulate the human immune response. The results suggest that there is a significant difference in some of the Anti-inflammatory cytokines between women and men.

Immune signatures associated with cognitive dysfunction in CFS
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Objectives: Mental fatigue, memory deficits and perceptual processing problems are major contributors to dysfunction in CFS, but the severity of cognitive disturbance varies both within individuals over the course of illness and across phenotypic subsets. Access to a robust biomarker of cognitive dysfunction in CFS would accelerate identification of patients responsive to select treatment strategies and also provide clues to pathogenesis. Although cytokine disturbances are reported in many CFS investigations, study populations and findings are heterogeneous, limiting their utility as biomarkers. We used feature selection and 51-plex immunoassays in an effort to define immune signatures associated with cognitive deficit in CFS.

Methods: Data from 298 CFS and 348 control subjects of the NIH CFS and the Chronic Fatigue Initiative studies, frequency-matched on age and gender, were pooled. High/low cognitive impairment subgroups were established using mean scores for 4 mental fatigue items from the Multidimensional Fatigue Inventory (MFI4, cases and controls; cutoff 1 SD > population mean): 142 high/147 low MFI4 cases; 29 high/312 low MFI4 controls. Plasma samples were subjected to immune profiling analysis. Principal components (PCA) and partial least square (PLS) feature selection approaches were applied to the 51-cytokine data set to derive latent variables for application as independent variables in logistic regression. Cytokines with odds ratios (OR) > 1.1 or < 0.9 (p=0.05) by PCA or PLS for the association with high MFI4 subgroups were included in the final logistic regression model along with age as a covariate.

Results: Elevated IFNγ levels were strongly associated with cognitive impairment in cases (high MFI4) (OR, 67.42; 95% CI, 5.34, 850.83; p=0.0011). Increased CXCL1 levels were also associated with more impaired case MFI4 (OR, 1.23; p=0.0285), with a trend in the same direction for IL13 (OR, 1.26; p=0.0018). The pattern within controls was similar to that within cases for IL13, with elevated levels predicting greater cognitive impairment (OR, 1.71; p=0.0088); however, other cytokines associated with cognitive impairment among cases did not show a similar pattern among controls. Stratified analyses showed no relationship with sex.

Conclusion: Cognitive dysfunction in CFS is associated with specific patterns of elevated cytokines. Increased circulating levels of IFNγ have a striking relationship with cognitive impairment. Individuals with CFS but without cognitive dysfunction did not demonstrate these disturbances. These results suggest immune homeostasis may be dysregulated in the subset of subjects with CFS with prominent cognitive disturbance. IFNγ elevations among cases with cognitive impairment may point toward a subgroup with higher probability of viral triggers and/or persistent infection.

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Poster Session: Pediatric ME/CFS
Pediatric Chronic Fatigue Syndrome: Complex Presentations and Protracted Time to Diagnosis
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**Objectives**
The diagnosis and management of pediatric Chronic Fatigue Syndrome (CFS) remain ongoing challenges for pediatric clinicians, particularly with unknown etiology and little research on effective treatments for this condition. The aim of this study was to describe the presenting features of new patients attending a specialist chronic fatigue clinic at a tertiary level Australian children’s hospital.

**Methods**
The medical records of all patients with an initial consultation at the chronic fatigue clinic over a 12-month period were reviewed using a standardized data collection template. Functional impact was based on school attendance and classified according to the National Institute of Health and Clinical Excellence guidelines (2007).

**Results**
A total of 99 patients attending the clinic were identified. Of these, 59 were diagnosed with CFS. Median age was 15.4 years with almost two-thirds of patients of female gender. Median time between symptom onset and diagnosis was 15.5 months. There was a high occurrence of fatigue, sleep disturbance, pain, post-exertional malaise, autonomic and cognitive symptoms in the group. The functional impact of CFS was classified as mild for 20%, moderate for 66% and severe for 14% of patients.

**Conclusion**
Most young people diagnosed with CFS experience symptoms for a protracted period with considerable functional impact prior to initial tertiary service consultation. This audit has identified important areas for research, practice development and education in relation to the management of patients with CFS.

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**Does The Presentation of CFS Differ Among Those With Joint Hypermobility?**
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**Objective:** Although joint hypermobility and Ehlers-Danlos syndrome have been associated with CFS, there has been very little study of the influence of connective tissue laxity on the clinical features of CFS. We examined whether the presence of joint hypermobility in adolescents and young adults with CFS affected the mode of onset, symptoms, and disease severity.

**Methods:** The Johns Hopkins Pediatric CFS Cohort Study has followed 55 subjects (46 F, 9M) with CFS since 2008. All subjects satisfied the Fukuda definition of CFS. Joint hypermobility was assessed at presentation using the 9 point Beighton score, which assigns one point for each side of the body on which the subject can 1) passively dorsi flex the metacarpophalangeal joint of the 5th finger beyond 90 degrees, 2) passively appose the lateral aspect of the thumb to the flexor surface of the forearm, 3) hyperextend the knee beyond 190 degrees, and 4) hyperextend the elbow beyond 190 degrees. One point is also assigned if the subject can perform forward flexion of the trunk with the knees straight so that the palms rest flat on the floor. Joint hypermobility was defined as a Beighton score of 4 or higher. All participants completed validated questionnaires assessing health-related quality of life (HRQOL), including the Functional Disability Inventory, the Peds QL, and the Wood Mental Fatigue Inventory.

**Results:** Of the 55 subjects aged 10-23 with CFS, 28 (51%) had a Beighton score of 4 or higher. There were no differences in age, race, or gender between those with and without hypermobility. When compared to the 27 without hypermobility, those with hypermobility had the same rates of abrupt onset of CFS (50% vs. 56%). Comparing CFS-defining symptoms at enrollment, hypermobile subjects reported more joint pain (43% vs. 15%; P<.05), sore throat (25% vs. 0%; P<.01), and tender glands (25% vs. 4%; P=.03). Although statistical comparisons were limited by the relatively small groups, numerically more hypermobile subjects had been diagnosed with co-morbid postural tachycardia syndrome (POTS) (82% vs. 56%; P=.12) or migraine headaches (39% vs. 15%; P=.09), and females with joint hypermobility reported more dysmenorrhea (40% vs. 10%; P<.05). Illness severity did not differ between groups, nor did measures of HRQOL.

**Conclusions:** Although joint hypermobility is a risk factor for CFS that is present from birth, and was hypothesized to be associated with a gradual onset of illness, those with and without joint hypermobility had similar rates of abrupt and gradual onset of CFS. There was a trend towards higher rates of POTS, migraines, dysmenorrhea, and some CFS-defining symptoms in those with hypermobility. These preliminary results will require further exploration in larger studies.

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**The development and implementation of a goal-focussed rehabilitation program for children and adolescents with CFS/ME.**
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Objectives: Little literature has been published regarding the treatment and outcomes for children and adolescents with CFS/ME; however there is increasing evidence supporting the efficacy of a cognitive behavioral therapy (CBT) - based rehabilitation approach. The development and implementation of a goal-directed interdisciplinary rehabilitation program for children and adolescents with CFS/ME will be presented. Details regarding the expert knowledge and available research evidence that contributed to the programs development, as well as preliminary findings will be presented.

Methods: An interdisciplinary team made up of a Clinical Psychologist, Education Specialist, Occupational Therapist, Physiotherapist, Pediatric Physiatrist, and a Nurse was formed to on develop the program, with support from a research team. On implementation of the program, participants diagnosed with CFS/ME by a pediatrician with expertise in CFS/ME participated in a combined inpatient and outpatient program over a four-week period. The program consists of a combination of group and individual sessions, focused on CBT, sleep hygiene, relaxation, activity balance, energy conservation, healthy eating, increased exercise tolerance, and participation in activities of daily living.

The Canadian Occupational Performance Measure (COPM), a widely used individualized outcome measure was used as a goal setting tool to direct therapy prior to program commencement, and to measure change in occupational performance and satisfaction of following program completion.

Results/Conclusion: Based on preliminary data, this evidence-based, goal focused rehabilitation program appears to offer potential to improve the occupational performance and satisfaction in children and adolescents with CFS/ME. Ongoing evaluation of our rehabilitation program represents a priority for future research.

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Yamada, J.Y. & Dean, N.J. (2014)

Objectives

Limited research exists regarding effective management of CFS in adolescents.

Our centre aimed to develop an interdisciplinary self-management program for adolescents with CFS utilising key psychological theory within a CBT framework. Specific principles and strategies of CBT are presented.

Method

Program development was derived from psychological theory including adolescent development, family systems, diagnostic models and CBT. Clinical experience has shown similarities between management of persistent pain, chronic disease and CFS. Program development was largely guided by the extensive literature base for pain and chronic disease management, and CBT. Clinical program development focused on 3 phases: assessment, treatment and follow-up. Both clinical and logistical issues were considered.

Results

A 4 week interdisciplinary self-management program was developed which adolescents attend as either inpatients or day patients. The program is based upon psychological principles applied within a CBT framework and aims to teach participants a range of active strategies to assist with self-management of their CFS. In general terms, the Program aims to review of the impact of CFS on the young person’s life in terms of mood, activity, relationships, school and other areas and the development of self management strategies to manage these issues. Maintenance of gains are planned and monitored.

Conclusion

Our centre has completed the first year of a CBT program for adolescents with CFS. Our program appears to be a good fit for adolescents with CFS. Group outcomes will continue to be measured and monitored for maintenance of gains. Future considerations include modification of parental involvement, review of duration and intensity of sessions and further investigation of individual population characteristics.

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Does Antinuclear Antibody (ANA) status or exposure to Ebstein Barr Virus (EBV) influence outcomes in young people with Chronic Fatigue Syndrome?

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Objective: EBV is a commonly recognized trigger for Chronic Fatigue Syndrome (CFS) in Australia and positive ANA titers are also common in young people with CFS. This study investigates whether exposure to EBV (glandular fever) or the presence of positive ANA titers has an influence on long term outcomes in CFS.

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Method: EBV serology and ANA results were available on 643 young people age 6-18 years, (M:F 1:3), diagnosed with CFS, who were referred to a specialized clinic at the Royal Children’s Hospital, Melbourne. A follow up questionnaire provided information regarding functional rating in social and physical activities, attendance at work or school as well as a global perception of functioning and whether they thought they had ‘recovered’. Positive ANA titers prompted investigation and exclusion of evidence of recognized autoimmune disease and were monitored during the illness to note changes. Analyses were conducted using Statistica 12.

Results: Evidence of exposure to EBV was present in 58% of the young people with CFS, with 20% having documented positive serology at the onset of the illness. Others had an illness suggestive of EBV but without definite serological evidence of titer change. There was not any difference in the duration of illness or the reported recovery for those with positive serology and those with no evidence of exposure to EBV. Of note, several young people contracted EBV during their illness, but recovered to their previous state within 6-12 weeks. Negative ANA of <1:160 was recorded in 75% with 12% recording a titer of 1:40 or 1:80 prior to revising norms. 25% were considered to have significant titers ranging from 1:160 to 1:2560 without evidence for SLE or other autoimmune disorder. The presence of positive ANA was not predictive of outcome, however there was a suggestion that ANA returned to normal with improvement in symptoms. Approximately 2% of those positive were later treated for autoimmune disorders such as SLE, often after they felt they had recovered from CFS. These were not generally associated with high titers at onset. Positive ANA titers were not associated with EBV exposure nor low levels of Vitamin D.

Conclusion: Higher than expected rates of positive ANA are present in young people with CFS without recognized autoimmune disease and often returning to normal with recovery. Neither EBV nor ANA status affected duration of illness or functional outcome although approximately 2% were later treated for autoimmune disease.

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Attentional and Motivational Deficits in Patients with Childhood Chronic Fatigue Syndrome
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Objectives: Cognitive and emotional features of patients with childhood chronic fatigue syndrome (CCFS) are loss of concentration, decrease in attention, and low motivation. However, the neural substrates associated with these impairments of the brain functions were not clarified.

Methods: We investigated the neural bases of reduced attentional and motivational processing in CCFS patients using functional magnetic resonance imaging (fMRI). In addition, we also conducted a behavioural study to evaluate the treatments effect of cognitive behavioural therapy (CBT) and selective serotonin reuptake inhibitor (SSRI) on the performance of attention control.

Results: We found that performances of divided and switching attention tasks in CCFS patients were decreased as compared with healthy children and adolescents (HCA). The fMRI study revealed that during the divided attention task, additional activity of the right prefrontal cortex of CCFS patients was observed, indicating the inefficient neural processing. The striatal activity of CCFS patients was lower than that of HCA during reward perception which is a driving force to muster up motivation. Decrease in performance of the switching attention task was improved after the combination of treatment with CBT and SSRI for 6 months.

Conclusion: The prefrontal and striatal processing of patients with CCFS are involved in attention control and motivation, respectively. Normalization of the frontal-striatal network is a treatment target to improve the cognitive and emotional symptoms of CCFS patients.

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Systematic Review of Paediatric Fatigue Measures in Health Conditions
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Objectives. Fatigue is one of the most common complaints across a range of childhood illnesses. There is a limited, yet growing, body of fatigue measures appropriate for the paediatric population but knowledge of how these available measures ‘map’ to our understanding of the multidimensional taxonomy of fatigue, and fit within a developmental framework is lacking. This study provides a review of parent and child-report measures of fatigue in children (0-18 years) with health conditions. Study objectives were to: 1) systematically review available tools for the assessment of fatigue in children and adolescents with chronic health conditions, 2) to describe the tools that have been used to measure fatigue in children and adolescents, 3) summarize the psychometric properties of the most commonly used assessment measures, 4) review the evidence base for assessment measures, using research on fatigue, 5) discuss the measures available from a developmental perspective.
Methods. We conducted a comprehensive literature search using the PRISMA guidelines and included the following databases: MEDLINE, CINAHL, PsycINFO. Databases were queried from 1990 to August 24, 2013. The search strategy included terms relating to fatigue, assessment and health conditions. The search was limited to studies including participants aged <18 years. This included proxy report for the younger age groups of children.

Results. A total of 1023 articles were retrieved. A small number of these met inclusion criteria. The most commonly used measures of fatigue were 1) PedsQL Multidimensional Fatigue Scale (parent report and self-report, PedsQL); 2) Chalder Fatigue Scale; 3) Fatigue Severity Scale (FSS); 4) Fatigue Scale (Child, Adolescent, Parent and Staff). Analysis of the psychometric properties of these scales suggests internal consistency is good for The Chalder, PedsQL and Fatigue Scale (child/parent/adolescent versions), with the exception of the Peds QL multidimensional fatigue scale, general fatigue subscale. Reliability has not been shown for the FSS in a child/adolescent population. All scales, however, showed good responsiveness (such as decrease in scores after treatment). Test-retest and inter-rater reliability are variable and infrequently reported across these scales. In terms of factor structure, the Chalder, PedsQL and Fatigue Scales (child/parent/adolescent) each load on two or three factors, including: General Fatigue, Sleep/Rest Fatigue, and Cognitive Fatigue; physical and mental fatigue; lack of energy, not able to function and altered mood. In contrast, the FSS provides an overall rating of fatigue severity (or intensity). Self-report is available for the PedsQL (5-18), Chalder (adolescents/> 18), Fatigue Scale (7-12; 13-18), and the FSS (age range unknown). Proxy reports are available for the Peds QL (2-18 years) and the Fatigue Scale (7-18 years).

Conclusion. A number of measures have been used to assess fatigue in pediatric health conditions. However, few of these adopt a multi-dimensional assessment of fatigue and are appropriate for use across the full age span of childhood, which is important from a developmental perspective. Of those that do, the Peds QL and Fatigue scales have the most reasonable psychometric properties. The importance of subjective (self versus parent) report needs to be considered. Informed and accurate assessment of fatigue is vital in order to better understand the impact of health conditions on children's functioning.

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POSTER SESSION: EPIDEMIOLOGY AND PUBLIC HEALTH

Comparison of 6 performance scales for differentiating individuals with Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS)

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Objectives: Performance scales are often used to measure the health of individuals with ME/CFS. While well used and validated, the Karnofsky performance score identifies extremes (death-normal) that may not be appropriate for measurement in ME/CFS. Alternative scales are often utilised, in particular the Functional Capacity Scale (FCS), although it has not been formally validated against Karnofsky for use in assessing patients with ME/CFS. We sought to compare the Karnofsky, FCS, Short Form 36 (SF36), Fatigue Severity Scale (FSS) and Pittsburgh Sleep Quality Index (PSQI) for their ability to distinguish between ME/CFS cases and healthy controls, and to describe changes in health for ME/CFS.

Methods: We performed a preliminary analysis of clinical data in the CCD metagenomic study. 13 cases with ME/CFS, defined using the Canadian definition, and 15 healthy controls, age matched <5 years were self-assessed using the aforementioned scales. ROC curves were generated to determine the predictive power of each scale to distinguish between cases and controls. To investigate spread within ME/CFS sufferers, participants were further investigated using Karnofsky and FCS to score their best and worst days since symptom onset.

Results: SF36-physical and FSS both had perfect predictive power to distinguish between ME/CFS cases and healthy controls (area under the ROC curve (AUC)=1.00). Additionally, FCS and Karnofsky both had high discriminatory power with AUC>0.99, while SF36-mental had the lowest predictive power (AUC=0.67). Separation of SF36 into its constituent parts revealed that role physical, physical function and general health all had very high predictive value (AUC>0.99), whereas role emotional and mental health were much lower (AUC<0.5). FCS had greater power to distinguish between participants in their best and worst states, (AUC=0.97) compared to Karnofsky (AUC=0.86).

Conclusion: Out of 6 scales investigated, SF36-physical, FSS, FCS and Karnofsky had very high discriminatory power for distinguishing ME/CFS cases from healthy controls. Karnofsky remains a well-validated and appropriate scale for employment in research studies, but, since FCS may offer greater power to describe a change in health, it might be considered a useful supplementary measure for evaluating ME/CFS patients.

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Objective: Complex chronic diseases of the neuro-endocrine-immune systems include Myalgic Encephalomyelitis/chronic fatigue syndrome (ME/CFS), fibromyalgia, and post-treatment Lyme disease syndrome (i.e. chronic Lyme disease). Early diagnosis and treatment are important to producing optimum outcomes in these patients. We sought to determine if these patients have access to knowledgeable healthcare of their disease, how long they must search for a diagnosis, and how many medical professionals they saw before being diagnosed. This information will be presented to public health providers and U.S. government agencies.

Methods: In the summer of 2012, people in North America who identify themselves as having ME/CFS, fibromyalgia, or post-treatment Lyme disease/chronic Lyme disease answered a 7-question survey that was distributed through emails to patient support groups, social media, and patient-oriented websites.

Results: Of the 1,294 respondents in the continental United States, 54.4% (n=705) said they were not satisfied with the medical care they were receiving because their physicians had not been adequately trained about their disease. Also, 71% (n=919) of the respondents in the continental Unites States visited four or more physicians before they received an accurate diagnosis. Additionally, 63% (n=815) spent two years or more searching before being appropriately diagnosed.

Conclusion: The current U.S. medical system has few specialty clinics for ME, CFS, ME/CFS, fibromyalgia, and post-treatment Lyme disease syndrome/chronic Lyme disease, and there is no specialty training about these diseases as a group in medical schools. As a result, the majority of these patients feel they do not have access to adequately knowledgeable clinicians. It is necessary to increase medical school education for these complex, multi-system diseases through a new specialty because they are not embraced by other specialties. There is also a need to establish additional multi-system specialty clinics in order to improve upon the notable delays in disease diagnosis and treatment.

Application to conference theme: This survey study shows that neuro-endocrine-immune disease scientific discoveries in recent decades are not improving clinical care for most patients. Our study proposes a solution to this problem. Tina Marie Tidmore, 7729 Shriner Drive, Pinson, AL 35126, tina@pandoraorg.net

Gender Differences in Spanish CFS Patients


CFS affects predominantly women, which means that there are few data on men with CFS.

Objectives: Analyze whether there are gender differences as well as clinical manifestations and quality of life between men and women with CFS.

Patients & Methods: Sectional study of consecutive cases on a population-based registry from a CFS Unit of a university hospital. CFS patients were diagnosed according Fukuda’s criteria between January 2008 and May 2012.

Variables studied: age, sex, occupation and employment status; clinic: apparent trigger, characteristics of fatigue and sleep, presence of recurrent headache and blocks grouped by clinical symptomatic, comorbidities and scores on the questionnaires of impact and intensity of fatigue and pain (McGill pain index), HADS, SCL90R, quality of life (SF-36) and the Fibromyalgia Impact Questionnaire (FIQ). We performed a comparative study between sexes of all variables. A p-value < 0.05 was considered significant.

Results: A total of 1,309 patients were included (91% female, average age: 47.4 ± 10.3 years). In men, the average age was 43 years and the age of onset of symptoms of 34, both being significantly lower (48 and 37 years for women, respectively). 30% were single and 32% had a skilled job vs. 15% and 20% in women (p< 0.001). In patients inactive, unemployed and grant a disability were more frequent in men (p= 0.006). The infectious triggering agent was more prevalent in men (27 vs. 14) and stressful life events in women. The fatigue and pain levels were lower in men (p= 0.013 and p= 0.002). In sleep disorders, nightmares and insomnia were less frequent in men. In symptomatic blocks, the presence of widespread pain, difficulty with fine movements, muscle spasms, dizziness, sexual dysfunction, Raynaud’s phenomenon, morning stiffness, migratory arthralgia, allergy drugs and metals as well as facial edema were less frequent in men. Comorbid phenomena were less frequent in men (fibromyalgia, regional myofascial pain, degenerative spinal disease, shoulder tendinitis, tennis elbow, carpal tunnel syndrome, plantar fasciitis, osteoporosis, panic disorder, ligamentous laxity, multiple chemical sensitivity, and thyroid disease (p< 0.05). In questionnaires measuring, in men, lower scores were found in the sensory and affective dimensions of McGill scale, the SCL-90R somatization, physical function, physical role and overall physical health SF-36 and physical function in the FIQ (p< 0.05).

Conclusions: In our series of CFS patients, 9% of them are men. The profile of men with CFS compared with women with CFS would be the youngest patient in the debut of the syndrome, single, with specialized work associated to infectious trigger. It is less muscular and immune symptoms and less comorbid phenomena. Their quality of life is better, preferably in the component related to physical function.
Post-exertional malaise symptoms and abnormal repeated cardiopulmonary exercise testing are associated with decreased physical functioning in myalgic encephalomyelitis/chronic fatigue syndrome subjects

Lily Chu, MD, MSHS

Objective: To explore the association between clinical characteristics and functional status among US residents with myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS)

Methods: During April and May 2013, I distributed an anonymous online survey to people affected by ME/CFS through patient-oriented websites, electronic forums, and state/local support groups. The survey included items addressing demographic traits, symptoms, test results (natural killer cell activity, neuropsychological testing, tilt table, brain imaging, repeated cardiopulmonary exercise test), work status, and functional status. Descriptive statistics followed by correlational analyses and one-way analyses of variance were used to analyze the data.

Results: 623 US residents responded to the survey; 86.2% were female, 96.1% self-identified as Caucasian, and the mean age was 51.2 years (SD 12.9 years). The average duration of illness was 17.9 years (SD 11.1). Mean SF-36 Physical Functioning score was 25.2 (SD 19.9); 71.0% reported being unemployed or dependent on disability benefits due to ME/CFS with 88.8% needing assistance with or modification of personal care activities. Even during their best days, 75.4% were unable to work and could only do light housework, walk around the house, or remain in bed. Subjects who reported the following characteristics had significantly lower mean SF-36 Physical Functioning scores than those who did not: abnormal repeated cardiopulmonary exercise test (22.0 vs. 30.2, p = 0.008), exhaustion/exacerbation of symptoms after mild activity as a major symptom (23.5 vs. 46.7, p < 0.001; 22.9 vs. 40.1, p < 0.001, respectively), disability benefits due to ME/CFS (20.6 vs. 38.1, p = 0.001), and unemployment due to ME/CFS (23.9 vs. 38.1, p = 0.01). Older age, longer duration of illness, and self-reported abnormalities on other tests were not significantly associated with lower SF-36 physical functioning scores.

Conclusions: Overall, respondents to this survey had very poor physical functioning. Symptoms and objective testing (abnormal repeated cardiopulmonary exercise testing) related to post-exertional malaise were most significantly associated with poor functional status. Clinicians and researchers interested in improving physical function in ME/CFS may wish to focus on eliminating or decreasing post-exertional malaise.

Relevance to conference theme: ME/CFS patients often have a multitude of symptoms which affect their functioning. This study reinforces the idea that post-exertional malaise is an essential symptom affecting function and may help clinicians prioritize what to focus on when seeing patients. It may also encourage greater use of repeated cardiopulmonary exercise testing as an objective measure of functioning. Finally, this study may reassure clinicians and patients that increasing age and longer duration of illness are not necessarily harbingers of decreased physical functioning.

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Trajectories of the course of CFS illness

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Objective: To analyze the clinical trajectory of illness in CFS patients from the clinician standpoint in the context of measurable illness variables.

Methods: The course of CFS is known to be variable. However, just what proportion gets better or worse is not known, and not much is known about what variables may be related to improvement. As part of a multisite study of 203 patients with CFS/ME physicians were asked to review charts and describe whether the patients improved, stayed the same, or worsened over both the entire course of the disease as well as within the past 6 months. They were also asked to describe the reasons why they think the patients improved or worsened. A variety of quantitative variables were considered in relation to improvement as well: acute vs. gradual onset, duration of illness (<3 years, >3 years), gender, CFS symptom cluster (fatigue, sleep, pain, GI disturbance, cognitive dysfunction, autonomic dysfunction, endocrine, inflammatory, neuromuscular symptoms), depression and anxiety.

Results: From the time the clinician first saw the patient to the time of data collection 43% improved, 31% stayed the same, and 26% worsened. Restricting this to the last 6 months 21% improved, 61% remained the same, and 19% got worse. Those with acute onset were more likely to improve over the course of treatment (44% of those with acute onset improved vs. 34% with gradual onset). In addition, those with shorter duration of illness (<3 years vs. >3 years) were more likely to have improved (31% versus 17%) over the past 6 months. No other variables tested were related to improvement. Qualitative reasons for improvement over the course of treatment were written in and will be described.
Conclusion: Although a significant number of patients with CFS improved over the course of treatment, many failed to improve. Those with acute onset and shorter duration of illness were more likely to improve. Further analyses of qualitative answers may give us more hypotheses about why some patients improve and others do not.

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ME/CFS: Trauma in the Context of Social Institutions
Geoffrey Hallmann, Dr Rosanne Coutts, Dr Yvonne Hartmann, Southern Cross University

Objectives: To examine the nature and impact of trauma upon 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. A focus for this paper was made on the incidence of trauma that participants reported as having experienced during interactions within institutional settings and attention was paid to the effect of such experiences. 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.

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. Relationships of power, politics, policies, practices and social relations were revealed to play an important role in the experience of ME/CFS. Trauma appeared to occur across every facet of the participant’s lives, particularly in dealings with the medical profession, insurance companies, educators, employment, family, friends and the media. Whilst apparently present such behaviour was often not named as such nor addressed.

Conclusion: When interacting with social institutions, persons with ME/CFS are subject to attitudes, beliefs, policies and behaviours (including bullying), that directly or indirectly arise because of their diagnosis and the contested nature of the condition. These experiences have an adverse impact upon the person - both physically and emotionally. Participants revealed that traumatic encounters and issues can influence their dealings with people within social institutions and impact adversely upon their condition and manner in which they address future interactions. Whilst trauma has at times been identified within the literature in the context of ME/CFS, there has been no thorough examination within an institutional context. The ability to protect themselves against traumatic experiences is difficult although avoidance is employed at times to limit exposure. Providing a more settled understanding of the condition and education within society is indicated as a counter measure to identify and counter traumatic experiences.

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ME/CFS: Social Security Accessibility and Experiences
Geoffrey Hallmann, Dr Rosanne Coutts, Dr Yvonne Hartmann, Southern Cross University

Objectives: To examine the accessibility and experience of social security for 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 incidence of trauma that participants reported as having experienced during interactions within institutional settings and attention was paid to the effect of such experiences. 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.

**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. The ability to engage with the social security provider (known as Centrelink in Australia) was hindered by physical and administrative barriers making the process of benefit accessibility difficult for persons with ME/CFS.

**Conclusion:** Persons with ME/CFS experienced difficulty in engaging in the process of accessing social security benefits, particularly the Disability Support Pension. Physical barriers (eg public transport, odours, smells, furniture, lines, distance, etc) impeded or prevented the requirement to physically attend the Social Security offices. The office set-ups were not appropriately designed for those with a physical disability like ME/CFS. Use of standing lines, long waiting times, and exposure to perfumes and other airborne smells/odours exacerbated symptoms or prevented entry into offices. Cognitive issues impacted the ability to interact with staff effectively. Attendance of offices of medical assessors for the purposes of assessment were not adequately set up to accommodate persons with ME/CFS, with chairs within waiting rooms not suitable for sitting or lying down, exposure to environmental exacerbators such as fluorescent lighting, smells, chemicals, noise and persons with communicable airborne ailments. Participants reported difficulty in engaging with Centrelink administrative requirements, including attendance at non-negotiable times that conflicted with the participants ability to function, excessive paperwork that they were unable to provide within the allotted time frame or without assistance, onerous medical requirements, assessments by persons with little knowledge of ME/CFS or preconceived and adverse beliefs about the condition, inappropriate methods of assessing disability/impairment unhelpful appeal processes and poor access to advocacy and assistance.

In contrast to select geographical locations with knowledge of ME/CFS provided through training from ME/CFS groups, other offices in other locations denied entitlement to disability benefits, forcing some participants onto benefits that required job search commitments or onto sickness benefits that provided less income and benefits. The ability to respond to adverse decisions 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. There are parallels between these findings and those for other disadvantaged/discriminated groups who depend upon social security services and welfare, such as sole parents and those on disability pensions.

**ME/CFS: Institutional Dependence**

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

**Objectives:** To examine the nature and impact of dealing with social institutions for persons with ME/CFS in the context of institutional dependence.

**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 incidence of trauma that participants reported as having experienced during interactions within social institution settings and attention was paid to the effect of such experiences. 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.

**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. In revealing their experience of “institutional dependency” all participants reported conduct and experiences that negatively affected them emotionally and physically when expressing interactions with various social institutions. Intrusive requirements by various institutions placed the participants in a constant position of investigation, scrutiny, judgement and accountability on an ongoing basis. Institutions such as social security, medical staff, insurers, educational bodies, allied health providers, housing, welfare services, the legal system, financial institutions, family and the like required a variety of reports, documents, verification checks, examinations, surveillance and the like to administer their particular dealings with the individual.

Conclusion: Each ME/CFS participant reported a variety of encounters with social institutions. All participants reported some form of obligation to or dependence upon more than one social institution. The condition was continually scrutinised and often questioned. Medical institutions required significant information, physical and personal invasiveness, and often questioned the validity and veracity of the condition, with many participants labelled with psychiatric attributions to causation. Insurance companies were identified as particularly intrusive and onerous and often questioned or denied the validity of the diagnosis. Paperwork, attendances to independent medical examiners, reporting of income, work hours, job search, family members, treatment regimes, medical attendances, symptoms and the like were a common experience. Social security obligations were one of the most commonly reported institutional involvement, with paperwork requirements on a regular basis necessary to obtain benefits.

Financial entitlement necessitated close scrutiny and carried with it the threat of termination of benefits for non-compliance or adverse decision. Educational institutions required reasons for non-attendance, accommodations, exam modifications, failure, special consideration, disability access and other entitlements. Medical certification was a regular and essential component. Again entitlement was assessed by the instruction with an adverse outcome possible.

Participants reported experiences of dishonesty, misstatement, threats, trauma, bullying and harassment within this process of instructional accountability. Such experiences were emotionally stressful and upsetting, whilst also causing exacerbation of the symptoms of the condition. The more stressful the event, the greater the potential severity of the symptom exacerbation. Institutional dependency of this type and duration has been shown to impact individuals and cause long term trauma.

A Novel Approach to Chronic Fatigue Syndrome (CFS) Education: Collaboration with a Professional Medical Learning Center
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Objective: There is an important need to educate medical students about chronic fatigue syndrome (CFS). Most medical schools in the United States have standardized patient (SP) programs using actors to simulate medical scenarios, and professors use online materials offered by MedEd Portal, which is credentialed and sponsored by the Association of American Medical Colleges. We partnered with the Center for Advanced Professional Education (CAPE) to develop CFS SP cases and curricula for MedEd Portal.

Methods: After conducting needs assessments with different stakeholders and educational experts, and using evidence-based data, we developed CFS SP videos using a five-step process. (1) We asked expert clinicians to develop SP case studies based on actual clinical encounters with CFS patients (anonymous). (2) We incorporated tenets from health behavior and communication theory into one-page vignettes and case studies. (3) Vignettes were converted into film scripts to train the SP actors. (4) Filming took place at CAPE in various settings including examination rooms, a physician break room, or a physician’s office. (5) For each video, we developed an educational curriculum including slides, learning objectives, references, and an instructor’s guide.

Results: We developed six different CFS SP videos and curricula. The educational cases included lessons on physician communication, physician peer education, adolescent CFS, CFS management in schools, CFS management and physical therapy, and diagnosing CFS. Several medical students volunteered to qualitatively evaluate video scripts and curricula prior to use in the MedEd portal. In comparison to other SP courses, they felt the scripts accurately portrayed patient visits and physician-to-physician communication. Students suggested adding a CFS resource list for physicians and patients.

Conclusions: CDC used evidence-based literature, focus group data, patient case studies, and health behavior theories to develop CFS curricula for medical students, which will be disseminated through the MedEd Portal. This project is an example of how partnering with a standardized patient education center enables CDC to reach a new target audience, in this case medical students.

Myalgic Encephalomyelitis: Patients’ Experienced Learning Needs - A Pilot Study
Eva Stormorken1, Irma Pinxterhuis2, Bengt Karlsson3

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Objectives
Myalgic Encephalomyelitis (ME) remains elusive without established pathology. Since no curative treatment exists and the
impact of the illness is devastating, there is a compelling need for patient education on how to manage daily life. An interdisciplinary educational program has been offered at a university hospital based outpatient clinic since 2004 to help patients improve their health and ability to manage every day life. Some studies of rehabilitation programs are published, but none have focused on the patients’ perception of learning needs immediately before enrolment. The aim of this study was to explore the patients’ learning needs before commencement in the educational program.

Methods
A focus group study using semi-structured interviews was conducted one week prior to enrolment. The Caucasian sample consisted of 9 women and 2 men who fulfilled the Canadian criteria. The sample was split into two focus groups with one man in each. Mean age was 45 years (range 29-57), illness duration 8 years (range 2.5-20). Antonovsky’s salutogenesis formed the theoretical framework. Theory driven qualitative content analysis was used to explore stressors and learning needs.

Results
The participants experienced a range of stressors that suggested lack of physical, material and psychological resistance resources, and they found it very difficult to manage daily life. Stressors were incomprehensibility, unpredictability, financial insecurity, losses and feeling overwhelmed. Emerged learning themes were facts about ME, how to gain control, cope with dysfunctions and emotional strains, energy conservation and relaxation techniques, assistive devices, nutrition, practical tips and how to obtain welfare benefits.

Conclusion
Identifying patients’ learning needs facilitates developing and offering more tailor made educational programs to help the patients manage their daily lives and improve health.

Translating science into clinical care
ME patients’ complex learning needs on areas such as physical, mental, social, and existential domains are best taken care of by interdisciplinary teams. According to Antonovsky’s salutogenesis more knowledge on health promoting aspects will increase resistance resources and subsequently result in better health, coping strategies and management in every day life.

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Experienced benefits of a group-based education program for people with chronic fatigue syndrome
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Objectives: Chronic fatigue syndrome (CFS) is a debilitating condition which often leads to extensive problems with occupational performance. Given the impact of the illness and the lack of curative treatments, it is important to develop effective non-pharmacological interventions. At our hospital a patient education program for people with CFS has been offered since 2004. The purpose of the program is to provide participants with information about the illness and coping-strategies, in order to promote better coping with the illness in daily living. The aim of this study was to elicit participants’ experiences with and perceived benefits of participation in the program.

Methods: A qualitative follow up study was conducted using focus groups. Semi-structured interviews were conducted immediately and nine months following participation in the program. The sample consists of 8 women and 2 men, with mean age 43.7 years (range 32 - 57) and average illness duration of 6.6 years (range 2.5 - 13.5). All participants met the CDC criteria and Norwegian diagnostic criteria for CFS. Data analysis was inspired by grounded theory, but instead of developing an entirely new theory the analysis was influenced by Fredrickson’s broaden-and-build theory of positive emotions.

Results: Participants experienced a mental process from before to after the program. Initially participants experienced chaos and insecurity, as well as confusion about coping with the illness. After participation in the program they felt more confident and relaxed, and experienced better understanding, acceptance and coping, especially after 9 months. Gaining more knowledge, learning coping-strategies, exchanging experiences, and meeting understanding and acceptance from both fellow participants and healthcare professionals seemed to facilitate the coping process.

Conclusion: This study showed that the patient education program promoted better understanding, acceptance and coping. Feeling more tranquil and confident seemed to make most participants more open minded. This in turn may have increased their ability to receive information and support from others as well as to learn new things, including coping strategies.

Translating science into clinical care: Patient education programs appear to be a beneficial intervention that may be offered people with CFS shortly after being diagnosed.

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Two age-peaks in the prevalence of CFS/ME in Norway. A registry study.
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1The Norwegian Institute of Public Health, Oslo, Norway.
2The Journal of the Norwegian Medical Association, Oslo, Norway
Objective: To estimate the prevalence of chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME) in the Norwegian population according to sex and age.

Methods: Diagnoses for all patients who are hospitalized or attend outpatient clinics in Norwegian specialized health services are reported to the Norwegian Patient Registry. We estimated sex- and age-specific prevalences by using the whole population (sized about 5 million) as denominator and registry cases with CFS/ME (ICD-10 code: G93.3) as numerator. We had access to registry data for the years 2008 through 2012.

Results: During these years, 5775 individual patients were registered with a diagnosis of CFS/ME as outpatients or inpatients in Norwegian hospitals. The overall prevalence was 0.133 % (95 % confidence interval (CI): 0.130-0.137). The female/male prevalence ratio was 3.0 (95 % CI: 2.8-3.3). The highest prevalence (0.416 %) was observed among women aged 15 to 19 years. A second peak (0.348 %) was found among women aged 35-39 years.

Conclusion: The estimates are most likely biased by forces of selection and variable use of the G93.3 diagnosis in clinical practice. However, the sex ratio and the two age peaks point to biological regularities that demand explanation.

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CFS/ME is associated with the pandemic H1N1 influenza virus, but not with H1N1 vaccination.
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1The Norwegian Institute of Public Health, Oslo, Norway.
2The Journal of the Norwegian Medical Association, Oslo, Norway.

Objective: To estimate the association between exposure to H1N1 influenza infection and/or H1N1 vaccination during the 2009 pandemic and later development of chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME) in the Norwegian population.

Methods: Norway has nation-wide registries for infectious diseases, vaccination as well as attendance to health care. We used regression methods to estimate the relative risk of CFS/ME in the years 2010-2012 according to exposure to influenza and/or vaccination with Pandemrix in the last months of 2009.

Results: During 2010-2012, 3645 new cases of CFS/ME were registered in the specialized health care system. The odds ratio for CFS/ME according to vaccination was 0.95 (95 % CI 0.89-1.01). Among the CFS/ME cases, 9 % had been registered with an influenza diagnosis in the primary health care system during the pandemic compared to 3.6 % for the rest of the population (OR=2.5, 95 % CI: 2.3-2.8). A positive H1N1 viral detection was registered in the Norwegian Surveillance System for Communicable Diseases in a subgroup (0.27 %) of the total population. For CFS/ME cases, the proportion registered was 0.57 %, giving an OR of 2.1 (95 % CI: 1.4-3.3).

Conclusion: These relative risks suggest that infection with the pandemic influenza virus (H1N1) increases the risk of CFS/ME. Vaccination does not appear to influence the risk. The results are preliminary and will be analyzed in more detail prior to the conference.

**POSTER SESSION: BRAIN RESEARCH**

Brain-derived neurotrophic factor is decreased in Chronic Fatigue Syndrome.
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Objectives: The study was designed to examine the levels of a major regulator of neuronal survival, brain derived neurotrophic factor (BDNF). BDNF is a protein involved in the maintenance and maturation of both peripheral and central neurons, and is believed to play a role in cognitive function and memory formation. In patients with multiple sclerosis (MS), BDNF expression is often decreased and believed to reflect ineffective repair mechanisms. As a preliminary exploration, we examined the production of BDNF on the part of peripheral blood mononuclear cells in three groups: patients with Chronic Fatigue Syndrome (CFS), patients with multiple sclerosis, and a set of putatively healthy controls.

Methods: Mononuclear cells were extracted from peripheral blood samples and cultured for 48 hours. Production of BDNF was evaluated from PMA/PHA stimulated and unstimulated cells. BDNF levels were determined using a commercially available enzyme linked immunosorbent assay (sensitivity: 62.5 - 4,000 pg/mL).

Results: Both the CFS and MS samples displayed nearly identical levels of BDNF (510 and 540 pg/mL, respectively), levels that were 25 percent of that displayed by the healthy control sample (2,018 pg/mL; p < 0.05). A logistic regression equation found BDNF level alone served to classify those with CFS from other study groups.

Conclusion: The deceased production of BDNF on the part of MS patients is consistent with the literature. However, the decreased production in those with CFS was unexpected and a novel finding. This finding could reflect a reduced ability to maintain neuronal structure and function in those with CFS. Future studies are needed to evaluate for neuronal damage in those with CFS.

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Advanced vascular ultrasound demonstrates venous flow aberrancies in the brain (CCSVI) and liver (CHVI) of Chronic Fatigue Syndrome (CFS) patients.
Paul R. Cheney MD, PhD
Background: The Chronic Fatigue Syndrome (CFS) is a disabling disorder characterized by significant cognitive dysfunction, mood instability and sleep/wake cycle disruptions that suggest brain dysfunction plus food as well as drug sensitivities that suggest liver/gut dysfunction. There have been published reports (Zamboni, 2009) of various venous blood flow aberrations called Chronic Cerebral Spinal Venous Insufficiency or CCSVI, primarily associated with MS patients but also seen in Chronic Fatigue Patients who are clinically indistinguishable from CFS (P. Coyle, 1997). This study attempts to prove or disprove the association of CFS with CCSVI and the related CHVI or Chronic Hepatic Venous Insufficiency (Cheney, 2013). Since global CNS hypoperfusion has been linked to CCSVI (Morovic, 2012) yet found in 0-23% of apparent healthy controls (Ghezzi, 2011), then any evidence of CNS hypoperfusion in CFS (see submitted IACFS abstract, Cheney, 2013) plus evidence of CCSVI in significant excess of 0-23% in CFS patients proves an association of CCSVI/CHVI with CFS.

Methods: A group of 15 consecutive CFS patients from a national CFS referral practice were referred to a national CCSVI referral center in Atlanta, GA (ccsvi-Atlanta). Using a Zamboni certified vascular ultrasound machine (Esaote’s Mylab Vinco) and a sonographer trained and certified in CCSVI methodologies, these 15 CFS cases were assessed for all 5 of the published criteria for CCSVI. The average patient age was 54 (range 27-67) and average KPS score was 59 (range 40-70). Sex distribution was typical for CFS with 10 females and 5 males. In addition, another 12 CFS patients were randomly selected to be evaluated for IJV reflux (left and right) using the iE33 Philips Healthcare Ultrasound machine. A dedicated iE33 vascular probe with 2-D color flow as well as time/velocity doppler images of the mid-IJV blood flow were used to screen for IJV reflux which is one of the CCSVI criteria. These 12 CFS patients were not significantly different from the 15 evaluated for CCSVI by age, sex or KPS score. Finally, these 12 patients were also evaluated for CHVI using a cardiac probe through the sub-xiphoid acoustic window and characterized by hepatic vein reflux confirmed by both color flow and doppler time/velocity measurements. An additional 35 patients were also evaluated for CHVI for a total of 47 consecutive CFS patients evaluated for CHVI.

Results: Of those who had CCSVI evaluation in Atlanta, 8 of 15 or 53% met the CCSVI criteria of at least 3 out of 5 criteria. 100% had at least 2 out of 5 criteria with B-mode defects of the IJV valve or proximal IJV stenosis occurring in 100% of these 15 cases done in Atlanta. The least likely CCSVI defect seen in Atlanta was IJV reflux where only 1/14 or 7% showed reflux. However, 14/15 or 93% showed Deep Cerebral Vein reflux in Atlanta. By contrast we saw significant IJV reflux using the new iE33 vascular probe in 9 out of 12 patients or 75% with 3 out of the 7 showing abolition of the reflux after VIP treatment in 20 minutes. Differences in the technologies or IJV reflux criteria used may account for this difference. As for CHVI, all 12 cases evaluated for IJV reflux in Asheville or 100% had CHVI or hepatic vein reflux. The larger group of 47 CFS cases showed an 87% (41 of 47) incidence of CHVI in CFS cases.

Conclusions: There is significant evidence of venous flow aberrancies in both the brain (CCSVI elements, 3/5 or 2/5) at 53% or 100% incidence respectively, and liver (CHVI) at 87% incidence and both are likely associated with CFS cases with an average KPS score of 56.

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Objectives: The Chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME) is a condition of unknown etiology, characterized by a persistent debilitating fatigue, the muscle-related symptoms and the neuropsychiatric symptoms. Although it is hypothesized that brain inflammation is involved in the pathophysiology of CFS/ME, there is no direct evidence of neuroinflammation in patients with CFS/ME. Here we show the existence of neuroinflammation in patients with CFS/ME by using the positron emission tomography (PET) with [11C]PK11195.

Methods: Activation of microglia or astrocytes is related to neuroinflammation. [11C]PK(11)- (2-chlorophenyl)-N-methyl-N-(1-methylpropyl)-3-isouquinoline-carboxamide ([11C]PK(11) 195) is a good ligand of positron emission tomography (PET) for a translocator protein that is expressed by activated microglia or astrocytes. Nine patients with CFS/ME and ten healthy controls underwent [11C]PK(11)195 PET and completed questionnaires about fatigue, fatigue sensation, cognitive impairments, pain, and depression. The binding potential (BP) was generated using a linear graphical analysis to measure the density of translocator protein.

Results: The BP of [11C] (R)-PK11195 in the cingulate cortex, hippocampus, amygdala, thalamus, midbrain, and pons was higher in patients with CFS/ME than in healthy controls. In patients with CFS/ME, the BP of [11C]PK(11)195 in the amygdala, thalamus and midbrain positively correlated with cognitive impairment score, the BP values in the cingulate cortex and thalamus positively correlated with pain score, and the BP value in the hippocampus positively correlated with depression score.

Conclusion: Neuroinflammation is present in widespread brain areas in patients with CFS/ME, and was associated with the severity of neuropsychological symptoms.

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A Model-based Exploration of Cardiovascular Deficiency in ME/CFS with Orthostatic Intolerance.
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Objectives. Patients with myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) exhibit differences in cardiovascular control that are characteristic of this condition. Our objective was to use a simple electrical circuit model of brain perfusion to capture changes in vascular resistance and compliance in a cohort of healthy controls, patients with severe fainting and ME/CFS patients with postural orthostatic tachycardia syndrome (POTS).

Methods. We studied a pilot cohort of 8 subjects: 3 controls, 2 with severe fainting and 3 ME/CFS patients with POTS. Subjects were challenged with a tilt table test, raising them from a supine position to 70° inclination until blood flow and pressure stabilized. Blood pressure in finger and cerebral blood flow velocity (Doppler) were recorded. Cerebrovascular response dynamics were modeled for each individual using a simple Windkessel to represent systemic arterial bed resistance (Rs) up to the medial cerebral artery (MCA), arterial bed resistance beyond the MCA (Rp) and compliance of the arterial bed (Cs). Subjects were then compared on the basis of these three parameters.

Results. Estimates of Rs, Rp derived directly from windowed Fourier transform (WFT) analysis of impedance indicated that ME/CFS-POTS subjects tend to share higher values of resistance Rp in the fine vasculature and lower values of arterial compliance Cs than fainters and healthy controls. Moreover, the differences small vessel resistance Rp were especially important during post-tilt phase.

Conclusion. These preliminary results suggest that the dynamics of cerebrovascular perfusion during postural change in POTS may be quite specific to ME/CFS subjects and that these differences may arise from characteristic differences in arterial compliance and small vessel resistance to blood flow.

Fig. 1. Windkessel model describing cerebrovascular regulation


CFS/ME a neuro-lymphatic disorder? A review of new evidence supporting a possible re-classification of the disease.
Raymond N Perrin, DO, PhD

Objectives: To demonstrate how the recent discovery of the existence of new pathways involved in neuro-lymphatic drainage and two other new major research findings could be pivotal in understanding the pathogenesis of CFS/ME.

Methods: A review from a biophysical perspective of 3 recent research projects in the USA and the UK which were linked together with results from clinical trials carried out by the author over the past two decades.

Results: New scanning techniques have provided the first visible evidence of the existence of a drainage system for proteins and other large molecular structures from the central nervous system which involves cerebrospinal drainage through perivascular spaces into the lymphatic system. (Iliff J. et al 2012)

New evidence from biopsy has revealed that there is an increase in sympathetically-sensory innervation in fibromyalgia (Albrecht P et al, 2013)

New evidence from biopsy has revealed that there is an increase in sympathetically-sensory innervation in fibromyalgia (Albrecht P et al, 2013)

Also reviewed was recent research in the UK that has shown cerebral vascular control is closely related to an excess of skeletal muscle lactic acid leading to the fatigue in CFS/ME (Hea J, Hollingsworth K, Newton J and Blamiria A, 2013).

Conclusion: This latest findings support the long held view of the author that CFS/ME is a disorder of the neuro-lymphatic drainage system leading to neurotoxic build up within the central nervous system and the ensuing cascade of many symptoms of autonomic dysfunction seen in CFS/ME and fibromyalgia.

Viewing CFS/ME as a neuro-lymphatic disorder leads to diagnostic findings with specific physical signs which potentially aid in the early diagnosis of the disease. Also by improving the neuro-lymphatic drainage one can now understand why
specific manual techniques have helped patients on the road to recovery. Thus, by merging the scientific knowledge of all the aforementioned studies, this review explains how one can translate the combined science into improved clinical care.

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Prosp ective Evaluation of a Salivary Biomarker of Chronic Fatigue Syndrome (CFS)
Authors: Charles W. Lapp, John Kalns, Darren Michaels, Wendy Springs, S. Nicole Thompson

A pilot study performed by Hyperion Labs detected an endogenous salivary peptide three times greater in concentration in Persons with CFS (PWCs) than in non-fatigued controls [1]. The saliva samples evaluated were from 46 subjects meeting Fukuda criteria [2] for CFS and 45 subjects that were deemed to be non-fatigued. However, this study was performed using archival saliva remnants from the Centers for Disease Control (CDC) in Atlanta, Georgia. The provenance of the original samples was uncertain, subjects were not being treated for CFS, and saliva samples were collected at 8AM. In order to replicate more a more realistic scenario, samples for this current study will be obtained from PWCs attending the Hunter-Hopkins Center for routine appointments, on symptomatic medications, and at various times of the day. Saliva samples from CFS patients and non-fatigued controls will also be evaluated with the intent of finding new salivary markers that might be associated with CFS. A statistical method will be used to define specific groups of patients defined by levels of CFS biomarker, and levels of physical fatigue as measured by the Multidimensional Fatigue Inventory [3]. PWCs will be recruited consecutively from patients of the Hunter-Hopkins Center who meet 1994 Fukuda criteria for CFS and present for routine follow-up. Non-fatigued control subjects will be recruited from staff, friends or family of PWCs or staff, and office workers in the area of the Hunter-Hopkins office. Inclusion Criteria: female, age 18-65, and white non-hispanic. Exclusion Criteria: unable produce saliva, BMI greater than 40, or those who have eaten, consumed fluids, smoked or brushed their teeth within 30 minutes of the sample. The purpose of this study is to determine if a putative salivary biomarker of CFS is elevated in CFS patients compared to healthy non-fatigued controls. The results of this study could establish a unique biomarker for CFS.

References

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Liver volume changes during Valsalva manoeuvre measured with MRI - Application to autonomic function testing in chronic fatigue syndrome
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Objectives
Chronic Fatigue Syndrome (CFS) is associated with autonomic dysfunction (AD, >89%), where patients show abnormal responses to autonomic challenge such as the Valsalva manoeuvre (VM). The VM (blowing against a closed outlet to a target pressure of 40 mmHg for a duration of 16s) causes transient changes in mean arterial blood pressure, stimulating the sympathetic and parasympathetic nervous system. It has been hypothesized that rapid and transient changes in the distribution of blood in visceral organs such as the liver may be partially responsible for these changes in blood pressure. Here we report initial results of the development of an MRI based method of measuring and monitoring liver volume over the course of the VM.

Methods
Patients with CFS underwent MRI scanning of the abdominal region using a 3T MRI system. They performed a 270s long stimulation paradigm consisting of 30s baseline and 4 cycles of VM (16s each) interspersed with 44s rest periods. Patients received real-time visual feedback of their applied pressure. Scanning used an EPI-based scan
sequence allowing for the acquisition of an image of the full abdominal region every 2 seconds. Livers were manually traced by trained personnel on each frame of the VM cycles and for an additional 5 frames (10 seconds) afterwards. Liver volumes were computed from these tracings.

**Results**

Initial results showed marked decreases in liver volume over the course of the VM in 5 out of 6 currently analysed patients, followed by rapid volume fluctuations after the end of the manoeuvre (see right). The remaining patient showed a slight increase in volume, similar to one currently analysed control participant.

**Conclusions**

Our preliminary results seem to suggest that a majority of CFS patients exhibit decreases in liver volume over the course of the VM. This would be in contrast to previously reported findings from healthy individuals who show liver volume increases during VM. This novel method will allow us to examine whether autonomic dysfunction itself, or peripheral effects, lead to hypotension and associated symptoms in CFS. Further analyses will investigate interindividual differences of these volume changes and their relationship to CFS symptoms and clinical measures of AD.

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**Cerebral blood flow dramatically increased in real time by nasally applied Vasoactive Intestinal Peptide (VIP) in Chronic Fatigue Syndrome**

Paul R. Cheney MD, PhD

**Background:** The Chronic Fatigue Syndrome (CFS) is a disabling disorder characterized by significant cognitive dysfunction as well as sleep/wake cycle disruption and mood instability. We as well as others (Peckerman, 2003) have observed a low cardiac output state (Cardiac Index < 3.0) in CFS cases linked in this clinic (Cheney, 2009) to underlying diastolic dysfunction (DD). It is known that Vasoactive Intestinal Peptide (VIP) will lower tricuspid valve regurgitant pressure gradients or TRmaxPG by dilating the pulmonary vascular resistance vessels. The combination of reduced tricuspid valve regurgitant pressure gradients along with improved right to left heart filling gradients would be expected to improve both venous return to the right heart as well as left heart filling and therefore cardiac output, especially in DD seen in nearly all disabled cases of CFS.

**Methods:** 27 consecutive CFS patients (68% female, 32% male, ages 26-70, ave. age 54) from a national CFS referral practice were evaluated for IJV venous flow rates in the supine position at two ultrasound centers, one in Asheville, NC and one in Atlanta, GA. The left and right IJV flow rates in ml/min were determined at the mid-IJV level using advanced vascular ultrasound technologies available with state-of-the-art ultrasound machines (iE33 - Philips Healthcare at The Cheney Clinic and Esaote’s Mylab Vinco at CCSVI-Atlanta). Supine venous flow rates of both IJV’s were acquired with dedicated vascular probes and software algorithms using semi-automated TAV (time averaged velocities) together with the average CSA (IJV cross sectional area) associated with multiple sequences of venous flow patterns acquired and averaged over at least one breathing cycle over the left and right IJV’s. Following baseline IJV flow rate and TRmaxPG measurements, 200 mcg of VIP (Hopkinson Compounding Pharmacy, Boston, MA) was applied by nasal spray. 20 minutes following nasal VIP administration, IJV flow rates were re-measured at both ultrasound centers as well as TRmaxPG in Asheville, NC.

**Results:** The average brain blood flow in the IJV’s was below normal from 27 consecutive CFS cases at 282 ml/min (Normal > 400 ml/min). 15 of 27 CFS patients were measured in Atlanta and 12 were measured in Asheville. The IJV results were not significantly different so results were combined for analysis. Only 5 out of 27 had normal baseline flow rates above 400 ml/min so 81% were abnormally low. There was a weak positive correlation of baseline IJV flow rate with KPS score (r = 0.12, p = 0.037). 20 minutes following 200 mcg of nasal VIP, there was a significant and impressive rise in the average IJV flow rate from 282 ml/min to 636 ml/min. The average % improvement in IJV venous flow out of the brain was 126% (p < 0.0000003) or more than double the baseline IJV flow rate (range 20% - 765%). This was accompanied by clinical improvement on the echo table in a minority of patients ranging from improved energy, alertness, visual acuity and one case had improved anxiety levels. Finally, VIP improved significantly the TRmaxPG (average of 32% reduction) from borderline elevated at 21 mm/Hg to a mid-range normal at 15 mm/Hg also in 20 minutes (p < 0.002).

**Conclusion:** Nasal VIP produces a significant improvement (p < 0.0000003) in cerebral venous blood flow rates in CFS cases in real time (20 minutes) with likely clinical improvement expected over time in cognitive, mental and sleep/wake cycle status.

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**Reproducibility of Measurements Obtained During Cardiopulmonary Exercise Testing in Individuals With and Without Fatiguing Health Conditions: A Case Series**

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**Purpose:** The reproducibility of measurements obtained during cardiopulmonary exercise testing (CPET) is a longstanding tenet of exercise physiology. However, test-retest variation in CPET measures may be higher for individuals with chronic fatigue.
syndrome (CFS), which could explain the characteristic functional deficits of post-exertional malaise. The purpose of this case series was to demonstrate the potential variability of test-retest CPET measurements in individuals with and without fatiguing health conditions.

**Case Descriptions:**

Subjects (n=7) who were matched to age, body mass index, and gender received 2 maximal CPETs 24 hours apart. Cardiovascular, respiratory, and metabolic measurements were taken at both peak exertion and ventilatory threshold (VT). Standard criteria were used to verify a maximal test took place. Diagnoses included sedentary but non-disabled individuals (n=2), an active and non-disabled individual (n=1), multiple sclerosis (MS; n=1), human immunodeficiency virus (HIV; n=1), an individual with CFS who was low-functioning (n=1; Test 1 peak volume of oxygen [VO$_2$]: 17.2 mL/kg/min), and an individual with CFS who was high-functioning (n=1; Test 1 peak VO$_2$: 33.9 mL/kg/min).

**Outcomes:**

Subjects ranged in age from 33-46 years, and BMI ranged from 21.1-25.7. Test-retest CPET measurement variability for most peak variables including oxygen consumption (VO$_2$), workload (WL), heart rate (HR), and ventilation (VE) largely were reproduced, or even increased, between Test 1 and Test 2. However, both individuals with CFS showed significant decreases. The low-functioning individual with CFS demonstrated decreases of 16%, 67%, and 9%, and 19% in VO$_2$, WL, HR, and VE at VT, respectively. The high-functioning individual with CFS showed decreases of 30%, 33%, and 14%, and 9% in VO$_2$, WL, HR, and VE at VT, respectively.

**Conclusions:**

Variability in submaximal cardiac, pulmonary, and metabolic performance may be responsible for the waxing and waning symptoms and activity limitations in individuals with CFS. The findings of this case study merit further verification in the context of adequately-powered measurement validation studies that compare test-retest CPET measurement characteristics across fatiguing health conditions.

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**Chronic Fatigue Syndrome & Family Systems: A phenomenological inquiry**

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**Objectives:** The aim of this research is to explore the systemic themes that arise (if any) among people with chronic fatigue syndrome / myalgic encephalomyelitis (CFS/ME), using family/systemic constellations as the method of exploration.

**Methods:** We organized a group of twelve experienced family constellations representatives to conduct constellations for five people with medically diagnosed CFS/ME. First, all subjects completed surveys to indicate the current impact and severity of their fatigue. Then we conducted the family/systemic constellations processes with the whole group, and recorded audio and video of each of the constellation processes. Thirteen potential subjects with CFS/ME were scheduled, but because of unanticipated exhaustion, only seven showed up on the day and completed the process with the group. The digital and analog aspects of the recordings were coded, tabulated, and analysed for themes, and a framework was developed through an iterative approach.

**Anticipated Results:** The subjects with CFS/ME reported moderate to severe impact and severity of fatigue, having experienced the fatigue for an average of seven years. Each constellation was set up starting with representatives for the subject, the subject’s mother, the subject’s father, and the subject’s CFS/ME. Each constellation unfolded uniquely at the level of content and roles. However, themes arose on the level of systemic symmetry, ancestor entanglement, and interrupted development. All five subjects had entanglements with ancestors who had died but were not at peace. The CFS/ME either served a protective function (in two cases) or was a way of replaying the fate of a forgotten ancestor (in three cases). Four out of five of the subjects experienced interrupted reaching out toward one or both parents, and had a strong release experience when re-establishing proper reaching to that parent during the constellation process.

**Conclusion:** Although the content varied, the themes that arose at a systemic and developmental level were remarkably consistent, and warrant further validation with a wider sample, and longitudinal studies to validate long term outcomes. Conducting exhaustive tests until all other medical causes for fatigue are ruled out results in significant delays to diagnosis and treatment, which is both inconvenient and uncomfortable for patients. Translating the findings of this research into clinical care could lead to clinicians incorporating a systemic and developmental perspective into their current diagnostic approach. Because there are no negative side effects to avoid with this process, incorporating family/systemic constellations into a treatment plan early on could serve as both a valuable information gathering exercise as well as a beneficial therapeutic step that could help improve patient outcomes, even before a formal diagnosis is established.

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Diagnostic profile of plasma metabolites levels in tricarboxylic acid cycle and urea cycle in patients with chronic fatigue syndrome

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Objectives In order to identify metabolites/biomarkers involved in the pathophysiology of chronic fatigue syndrome (CFS) in an effort to establish new criteria for objective diagnosis of CFS, we performed a metabolome analysis with plasma from CFS patients.

Methods We performed a controlled study that analyzed plasma metabolites in 20 patients with CFS and in healthy control subjects. Subjects with psychiatric disorders or chronic diseases were excluded. Plasma samples were collected between 9:00 am and 11:00 am from fasting subjects. Concentrations of the plasma metabolites were determined using capillary electrophoresis time–of–flight mass spectrometry (CE–TOFMS). Patterns of changes in metabolite concentrations and the relationship between metabolite concentrations were assessed.

Results Concentrations of organic acids related to glycolysis and the tricarboxylic acid (TCA) cycle were significantly lower in CFS patients than in healthy control subjects, although there was no significant difference in glucose concentration. The ratio of concentrations of ornithine to citrulline in urea cycle was higher in CFS patients than in healthy control subjects.

Conclusions The profile of metabolism in CFS patients suggests decreased adenosine triphosphate production, and will provide biomarkers for objective diagnosis of CFS.

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Comparison of standard labs in CFS patients versus healthy controls reveals lipid abnormalities.

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Objective: To determine whether there are any abnormalities among standard labs given to ME/CFS patients in order to help guide clinical practice.

Methods: A multisite study was conducted which included the evaluation of 203 ME/CFS patients and 202 healthy controls (HCs) matched on age and gender. As part of this study, blood was drawn for standard labs including lipids, electrolytes, and various cell counts and measures. We report on these labs: Total Cholesterol, LDL, HDL, Triglycerides, Carbon Dioxide, BUN, creatinine, eGFR, potassium, sodium, alkaline phosphatase, albumin, LDH, and WBC, hemoglobin, hematocrit, sedimentation rate (Westergren), MCV, MCHC, RDW, platelets, and RBC counts. Vitamin B12 and Vitamin D (F5 Hydroxy) levels were also included. Chi-square analysis was used to compare distributions between CFS and HC’s (categorized into low, normal, high).

Results: The most marked abnormality was observed in the patients (vs HCs) lipid profiles. Although total cholesterol did not differ between groups, LDL cholesterol was high in 13% of CFS vs 4% of HCs ($\chi^2 = 9.73, p = .05$), and HDL cholesterol was low in 27% of CFS vs. 12.4% of HCs ($\chi^2 = 15.33, p = .00$). Triglycerides were also significantly higher in CFS (16%) vs. HCs (7%) ($\chi^2 = 17.19, p = .00$). The only other abnormalities found were in serum levels of Vitamins: Levels of B12 were significantly higher in CFS (19%) vs HCs (7%), perhaps due to supplementation ($\chi^2 = 14.45, p = .00$). Levels of Vitamin D (F5 Hydroxy) were also significantly higher in CFS, with 28% of CFS having low levels compared to 47% of HCs ($\chi^2 = 14.85, p = .00$), again, perhaps due to supplementation.

Conclusion: CFS patients exhibit lipid profiles characteristic of greater risk for cardiovascular disease with higher LDL’s and lower HDL’s, and higher triglycerides compared to healthy controls. Therefore it is particularly important for
Do glycolytic enzyme complexes provide a structural basis for compensating aerobic metabolic dysfunction in Myalgic Encephalomyelitis/Chronic Fatigue Syndrome?

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Objectives: Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) is a neuroimmune disease that leads to mitochondrial dysfunction and reduced production of adenosine triphosphate (ATP), a ‘high energy’ phosphagen required for cell function and homeostasis. Glycolysis appears to be a compensatory pathway for ATP production in some ME patient groups (Booth, Myhill & Howard, Int. J. Clin. Exp. Med. 5(3), 208-220, 2012). We postulate, as do others, that complexes of glycolytic enzymes not only enhance ATP production via metabolic channeling of substrate intermediates, but they provide a structural basis for regulating the production of ATP. To look for evidence of glycolytic enzyme complex formation in striated muscle, we used an animal model to examine the efflux of endogenous glycolytic enzymes from single demembranated muscle fibers bathed in a physiological salt solution. We reasoned: If glycolytic enzymes exist as complexes, then the complexed enzymes should diffuse together with the same low diffusion coefficient. If, however, the enzymes are not complexed, their diffusion coefficients should scale according to molecular size.

Methods: Single fiber segments from rabbit psoas muscle were skinned in oil and transferred to a series of drops of a physiological salt solution at 7°C. Cytosolic proteins that diffused into each solution drop were separated by gel electrophoresis and compared to load-matched standards for quantitative analysis.

Results: We observed a uniform initial lag and subsequent molecular-weight dependent efflux of glycolytic enzymes. The diffusion time courses were consistent with a radial diffusion model that incorporated the dissociation and dissipation of supramolecular complexes. The model also included terms representing protein crowding, myofilament lattice hindrance, and cytomatrix binding. Global fitting and optimization of the diffusion model to efflux data (RMS error between simulation and data of 20 best fits =1.66±0.02%) returned estimates of apparent diffusion coefficients that were uniformly low at the onset of diffusion (~10⁻¹⁰ cm² s⁻¹) but became differentially higher as the pool of cytosolic proteins became depleted. The very low initial value is consistent with a relatively immobile complex in situ, while higher subsequent values (e.g., 0.2 × 10⁻⁷ cm² s⁻¹ for phosphofructokinase) are consistent with molecular sieving and transient binding of dissociated proteins diffusing out of the skinned fiber.

Conclusions: Channeling of metabolic intermediates via enzyme complexes may enhance production of ATP at rates beyond that possible with randomly distributed enzymes, thereby matching supply with demand. Formation of complexes and up regulation of metabolic channeling may be the structural means, and potential therapeutic target, by which glycolytic enzymes compensate for reduced ATP production in ME and other metabolic diseases.

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Chronic Fatigue Syndrome and Cardio-Vascular Aging

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Background: Chronic fatigue syndrome (CFS) is a chronic syndrome affecting different organs or systems. The effect of CFS on the cardiovascular (CV) system are controversial and although some investigators suggest that patients with CFS have small hearts, this finding has not been validated in well matched studies. If this study, we will test the hypothesis that previously reported CV differences in CFS are due to selection bias and improper matching to the level of activity.

Methods: This is a prospective study designed to compare patients with CFS with matched sedentary and active healthy controls. A total of 132 patients were screened with a final enrolment of 81 subjects 25 in the CFS group, 26 in the sedentary controls group (SED), 26 in the active control group (ACT). Four subjects were excluded because of obesity or associated medical conditions. The CFS and SED and ACT groups were matched for age, sex, race, body mass index; in addition the CFS and SED group were also matched for level of activity using an international questionnaire. Each volunteer was evaluated with comprehensive questionnaires, electrocardiogram, femoral and carotid cardiovascular imaging and trans-thoracic echocardiography with emphasis on right and left ventricular function. ANOVA was used to compare vascular and ventricular remodelling parameters between groups.

Results: The majority of patients with CFS recruited were female (80%), with an average age of 46.86 ± 11 years, BMI of 23.5 ± 3.6 an MFI-20 score of 78.7 +/- 9.1. There was no significant different in age, sex, BMI, renal function, TSH and
level of activity between the CFS and SED group; the level of activity was as expected higher in the ACT group. Between the CFS group and the SED group, there was no significant different in arterial stiffness measures (aortic pulse wave velocity of 6.25 ± 1.24 vs. 6.94 ± 1.92 p=0.2 m/s) ventricular remodelling parameters (LV mass index 55.5 ± 9.8 vs. 56.3 ± 9.5 (g/m²)² p=0.8, LVID of 4.65 ± 0.43 vs. 4.78 ± 0.46 (mm) p=0.3, RVEDA index of 9.7 ± 1.7 vs. 10.1 ± 1.9 p=0.4 cm²/m²², LA volume index of 20.4 ± 7.0 vs. 21.75 ± 5.4 p=0.45 mL/m²², LVEF (64 ± 6.3 vs. 65.1 ± 5.6 (%) p=0.6) or left or right diastolic parameters. Although there was however a significant differences in ventricular remodelling parameters no arterial stiffness between the ACT and CFS group were demonstrated.

Conclusion: When compared to level of activity matched controls, there is no clinically significant difference in heart size or arterial stiffness between CFS and healthy controls. The study highlights the importance of level of activity matching in CV studies.

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**POSTER SESSION: PROVOCATION STUDIES**

**Cerebral Blood Flow Regulation, Orthostasis and N-Back evaluation in Chronic Fatigue Syndrome**
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Chronic Fatigue Syndrome (CFS), associated with orthostatic intolerance is characterized by neurocognitive deficits, impaired working memory, concentration, and difficulty processing complex information. We showed that in CFS/POTS subjects, upright tilting (HUT) caused decreased cerebral blood flow (CBF) related to hypocapnia and impaired cerebral autoregulation and increasing orthostatic stress during neurocognitive testing resulted in decreased cognition. We also showed an increased respiratory chemoreflex response to hypoxia and decreased respiratory chemoreflex response to hypercapnia. In CFS/POTS therefore, a lack of appropriate chemoreflex response to CO2 can account for the inappropriately sustained hypocapnia.

**Objectives:** Orthostasis-related neurocognitive impairment in CFS may be due to decreased CBF as a direct effect of CO2, altered cerebrovascular regulation or a combination of these.

**Methods:** We determined the effect of loading the baroreflex with sub-pressor dose phenylephrine to prevent hypopnea, by normalizing CO2 with exogenous CO2 to prevent hypocapnia, or by administration of acetazolamide, to alter CBF during HUT. We then performed N-Back testing of neurocognitive function.

**Results:** HUT increased heart rate (HR) in 8 controls by 23 bpm, while in 15 CFS/POTS, HR increased by 36 bpm. HUT also caused CBF to decrease 8.7% in controls, but fell by 22.5% in CFS/POTS. Exogenous CO2 to maintain eupacnea during HUT in controls mitigated the orthostasis-induced decrease in CBF (73.11±5.23 vs. 67.87±4.89 cm/s); baseline vs. treatment. Phenylephrine (69.75±2.02 vs. 69.93±3.74 cm/s) and acetazolamide (76.93±4.44 vs. 79.52±4.06 cm/s); baseline vs. treatment, resulted in no CBF decrease with tilt. The significant drop in CBF with tilt in CFS was prevented by CO2 (71.57±9.71 vs. 64.52±8.78 cm/s), phenylephrine (69.08±9.13 vs. 63.48±10.73 cm/s) and acetazolamide (67.13±7.86 vs. 71.58±10.93 cm/s); baseline vs. treatment. CBF measurements indicate that compared to control, CFS subjects are both more sensitive to orthostatic challenge and to baroreflex/chemoreflex-mediated interventions. These interventions can be used with N-Back testing to evaluate neurocognitive deficits with orthostasis in CFS subjects. N-Back testing showed no difference in the normalized response time (nRT) of control subjects comparing supine to HUT (106.2±3.1 vs. 97.3±2.3 msec at N=4), and no difference comparing control to CFS while supine (97.1±2.3 vs 96.5±3.9 msec at N=4). However, HUT of CFS subjects caused a significant increase in nRT (148.0±3.1 vs. 96.5±3.9 msec at N=4) compared to supine. Phenylephrine administration significantly reduced the HUT-induced increase in nRT in CFS to levels similar to supine (116±2.4 vs 96.5±3.9).

**Conclusions:** These interventions are effective in altering CBF. In CFS subjects, mitigation of the HUT-induced CBF decrease with phenylephrine has a beneficial effect on N-Back outcome in CFS subjects.

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**Psychological stress exacerbated low-grade fever in a chronic fatigue syndrome patient**
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Objective: Low-grade fever is a common symptom in patients with chronic fatigue syndrome (CFS). However, the mechanisms responsible for its development are poorly understood. We hypothesized that psychological stress contributes to low-grade fever in some CFS patients. The aim was to assess if psychological stress exacerbates low-grade fever and its mechanisms in CFS patients.

Methods: A 26-year-old female CFS patient was admitted to our hospital. She had been recording her axillary temperature (Ta) regularly and found that it was especially high when she felt stress at work. To assess how psychological stress affects temperature and to investigate the possible mechanisms for this hyperthermia, we conducted a 1-hr stress interview and observed the changes in the following parameters: Ta, tympanic membrane temperature, fingertip temperature, systolic and diastolic blood pressures, heart rate, plasma catecholamine levels, and serum levels of pyretic cytokines, including interleukin (IL)-1β and IL-6 and anti-pyretic cytokines, including tumor necrosis factor-α and IL-10.

Results: At baseline, her Ta was 37.2°C. It increased to 38.2°C by the end of the interview. In contrast, her fingertip temperature decreased during the interview. Her heart rate, systolic and diastolic blood pressures, and plasma catecholamine levels increased during the interview; there were no significant changes in either pyretic or anti-pyretic cytokines during or after the interview.

Conclusion: One-hr stress interview induced a 1.0°C increase in Ta in a CFS patient. Negative emotion-associated sympathetic activation, rather than pyretic cytokine production, contributed to the increase in temperature induced by the stress interview. This finding suggests that psychological stress may contribute to the exacerbation of low-grade fever and fatigue in some CFS patients.

Impaired Systemic Oxygen Extraction as a Cause of Unexplained Exertional Intolerance.

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Objective: Impaired systemic oxygen extraction (SOE) during exercise is a hallmark of a subset of mitochondrial myopathies, but its prevalence in a heterogeneous population of patients with unexplained exertional intolerance is unknown. We hypothesize that invasive cardiopulmonary exercise testing (iCPET) would reveal a subset of patients whose predominant exercise limit is due to abnormal uptake and utilization of O2.

Methods: We examined iCPET results of consecutive patients presenting to Brigham and Women’s Hospital between March 2011 and October 2013 for unexplained exertional intolerance who performed maximal incremental cycle exercise with catheters in the radial and pulmonary arteries. Systemic arterial and mixed venous blood gases were drawn at rest and every minute during exercise. Abnormal SOE was defined as (Ca-O2/Hb) ≤ 0.8 at peak exercise, a VO2max < 80% predicted, and the absence of pulmonary hypertension (PH) or heart failure (HF), specifically peak mean pulmonary artery pressure < 30, peak cardiac output ≥ 80%, and peak wedge pressure < 20. Normal controls were those with (Ca-vO2/Δ[Hb]) > 0.8 and a VO2max ≥ 80% predicted, as well as the absence of PH and HF. We also defined hyperventilators as those whose peak arterial PaCO2 was < [1.5xHCO3 – 8 - 2] as predicted by Winters’ formula.

Results: Of the 257 patients, prevalence of impaired SOE among the population of unexplained dyspnea was 12.1% (31/257) and 16% (41/257) were considered normal. 50% of the otherwise normal group and 73% of the impaired SOE group hyperventilated. VO2peak was 106±28% predicted for normal and 70±8% predicted for the poor SOE group (p < 0.001). At peak exercise, there was no significant arterial pH difference between the poor SOE and normal groups (7.38±0.05 vs. 7.37±0.04, p=0.31), but there was a trend towards decreased pCO2 in the impaired SOE group (29.6±5.3 vs. 31.9±6.1, p=0.11). The venous blood gas data at peak exercise showed increased pO2 (30.6±3.0 vs. 25.7±3.1, p=0.001), increased mixed venous O2 (46±5 vs. 33±7, p=0.001), decreased pCO2 (51±9 vs. 57±11, p=0.02), and a trend toward increased pH (7.28±0.06 vs. 7.25±0.05, p=0.06). Lastly, impaired SOE has a lower VO2peak/Qmax ratio compared to the normal group (93±11 vs. 129±21; p<0.001).

Conclusions: This iCPET study demonstrates that abnormal systemic oxygen extraction is common in patients with unexplained exertional intolerance. Associated hyperventilation may further compromise peripheral oxygen extraction by left-shifting the oxyhemoglobin dissociation curve and contribute to dyspnea on exertion. We speculate that mitochondrial dysfunction of the carotid body or skeletal muscle may account for the hyperventilatory and hypercirculatory responses. Invasive CPET can narrow the differential diagnosis of unexplained exertional intolerance and suggest an organic etiology for hyperventilation.

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Hot-wiring the immune communication network in ME/CFS
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Objectives. ME/CFS has been associated with characteristic differences in immune signal expression and cell demographics compared to healthy subjects at rest. Extending this observation, we hypothesize that the immune circuitry underlying the dynamic response of immune cell populations and cytokine signaling during exercise will be significantly altered 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 matched healthy control subjects. At each time, blood samples were analyzed for the concentrations of 16 cytokines using a chemiluminescent assay. A total of 12 lymphocyte fractions were profiled using a 5-color flow cytometer. For each subject, the trajectory of individual cytokines and cell fractions were fit to standard rate equations. Bipartite structure was enforced to emphasize cell signaling via the specific cytokines measured. The corresponding flow networks were combined across subjects using a voting scheme to create a consensus network for each group. These were analyzed for differences in immune information flow separating ME/CFS and healthy subjects.

Results. Betweeness centrality or the throughput of immune information managed by the CD3+/56+ cell fraction was dramatically increased in ME/CFS. This was followed by similar increases in throughput involving IL-2, 5 and 17 signaling as well as CD19+ B cells. Conversely, immune traffic involving CD8+/26+ and CD3+/8+ cytotoxic T cells along with IFN-γ and IL-6 signaling was essentially sidelined.

Conclusion. These preliminary results describing the detailed immune response dynamics, albeit in a small subset of ME/CFS subjects, suggest a disproportionate dependency on NK and B cell processing of immune information in ME/CFS. This coincides with a virtual collapse of T cell driven IFN-γ signal processing.

Fig. 1: Cytokine-lymphocyte immune signaling networks

Fatigue severity and cellular dynamics of immune response in ME/CFS
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Objectives. ME/CFS has been associated with characteristic differences in immune signal expression and cell demographics compared to control subjects at rest. Extending this, we hypothesize that dynamics of immune cell population and cytokine signaling during exercise will vary significantly ME/CFS severity.

Methods. As part of an ongoing study, blood samples were collected at 9 times during a maximal exercise challenge in n=4 female ME/CFS subjects. Illness severity was characterized using standard instruments that included the multidimensional fatigue index (MFI), Beck Depression Index (BDI) and the short form 36 (SF-36). At each time point, blood samples were analyzed for the concentrations of 16 cytokines using a chemiluminescent assay. A total of 12 lymphocyte
fractions were profiled using a 5-color flow cytometer. Trajectories for cytokine expression and cell abundance were summarized and projected onto symptom severity scores using a 3-way partial least squares (PLS) regression model. Marker contribution was ranked using variable importance in projection (VIP) score.

**Results.** Analysis revealed significant correlation of immune cell and signaling dynamics with indicators of symptom severity including the SF-36 general fitness and MFI general fatigue scores (Adj. $r^2 ≥ 0.87$). Response of NK cell fractions CD3+/16+ and CD3+/56+, as well as in CD3+/4+ T helper cell abundance were leading contributors to SF-36 general health score. Conversely MFI general fatigue score was most affected by the dynamic response in CD3+/8+ cytotoxic T cells, CD19+ B cells and the CD2+ NK T cell fraction. Leading cytokine signals contributing to these same symptom scores included IL-1α, IL-2, 2, and 5.

**Conclusion.** These preliminary results suggest, at least in this small preliminary set of subjects, that the dynamics of NK cell, B cell and cytotoxic T cell response during maximal exercise are directly affected and correlate strongly with general fitness and fatigue severity in ME/CFS.

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**Chronic Exercise in Mice as a Mediator for Immunological Diseases**

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**Objectives:** To study the effect of several forms of exercise, running and swimming, on cardiac function and inflammatory markers To evaluate a mouse model of exercise for possible use in study of myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFW) and gulf war illness (GWI).

**Methods:** Adult male (C57BL/6) mice were assigned to three groups: wheel running exercise (RE) (n=10), swimming exercise (SE) (n=5), and sedentary control group (n=6). Mice were subject to exercise for 1 hour, 3 days/week, for 7 weeks. RE were forced to run at a velocity of 8 m/min in a wheel running system, while SE group performed voluntary swimming in warm water. Echocardiography was conducted at baseline and 7 weeks. At experiment termination, mice were sacrificed and plasma was collected for inflammatory cytokines analysis.

**Results:** Cardiac measurements showed a significant decrease ($p<0.05$) in ejection fraction (EF %) in SE compared to RE and control (54.23±1.71% vs. 64.31±2.27% & 63.61±2.20 respectively). Fractional shortening (FS %) was lower in SE compared to RE and sedentary (0.28±0.02% vs. 0.37±0.01% & 0.35±0.01% respectively, $p<0.05$). End systolic area (ESA) was markedly increased in SE group (0.116±0.002 cm²) compared to RE and control (0.092±0.005 ±0.095±0.002 cm²). Inflammatory cytokines assays revealed greater murine tumor necrosis factor (mTNFa) in SE (31.34±9.3 pg/ml) vs. control group (1.894 ± 1.0 pg/ml), $p<0.05$. mIL-1α was elevated ($p<0.03$ in the RE group compared to controls. There was a significant effect of treatment ($p<0.05$) between groups for the chemokine murine growth-regulated alpha protein (mKC) as determined by one-way ANOVA. During inflammation, mKC contributes to neutrophil activation.

**Conclusion:** The findings indicate that chronic exercise paradigms may result in different pathologies specifically related to cardiac and immune effects.

Our research group has reported differences in exercise effects in both ME/CFS and GWI, compared to each other and to controls. The results presented indicate that this murine model may be useful in both ME/CFS and GWI.

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Objectives: Chronic Fatigue Syndrome/Myalgic Encephalomyelitis (CFS/ME) 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. It is believed that a combination of inherited, environmental and viral factors cause CFS/ME. In recent years it has been shown that EBV encodes microRNAs (miRNAs). These small (19- to 24-Nt) noncoding RNAs negatively regulate gene expression through binding target miRNAs. Many miRNAs are known to be associated with diseases.

Methods: 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 (VO₂ 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.

Results: We evaluated both human (hsa-miRNA) and viral microRNAs at the respective time points (t0, t1 and t2). We found that at all time points expression of human hsa-miR-103, hsa-miR-146a, hsa-miR-106b, hsa-miR-191 and hsa-miR-223 was significantly decreased in PBMCs of CFS/ME patients. These microRNAs play important role in the regulation of inflammation processes, cell differentiation and regulation of transcription. Overall expression of viral miRNAs was also decreased in PBMCs of CFS/ME patients. Analysis of one specific EBV miRNA, ebv-miR-BART21, calculated regardless of collection time or patient gender, shows that CFA/ME patients had as average fold change of -2.03, indicating that these cells express about half of the HC viral miRNA levels. Separating the overall average data with regard to collection time, we observed fold changes of -2.08, -2.20 and -1.78 for time points t0, t1 and t2, respectively. Further dissecting the data by taking into consideration patient gender, we observed that females at all time-points showed a more pronounced decrease in fold change for ebv-miR-BART21 than males.

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. 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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POSTER SESSION: COMORBID CONDITIONS

Prevalence of depressive symptoms assessed using the Structured Clinical Interview for DSM-IV in chronic fatigue syndrome.
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Objectives: Diagnostic criteria for chronic fatigue syndrome (CFS) and major depressive disorder (MDD) have some shared symptoms; notably sleep disturbance, fatigue and poor memory and concentration. Differentiating between CFS and MDD in clinical practice can, therefore, be a challenge. Moreover, neither the aetipathogenic significance, the functional impact, nor the optimal treatment of depressive symptoms in CFS is known. Patients with CFS report that they are often erroneously labelled as having depression and state that “trials” of antidepressant medication are often used and then continued indefinitely. This study aims to further our understanding by examining the prevalence and nature of past depressive disorder and symptoms in a cohort of well-characterised patients with CFS and to look at the associated use of antidepressants.

Methods: The sample consisted of consecutive patients recruited for the MRC funded CFS Autonomic Study. Fifty-one patients have been recruited to date. All were required to meet Fukuda criteria. At screening participants were interviewed using the research version of the Structured Clinical Interview for DSM-IV (SCID). A diagnosis of past or current depressive episode requires criteria to be met for five specified symptoms, which must include depressed mood or loss of interest, and which must be present for a period of two weeks and be associated with functional impairment. The structure of the SCID determines that patients who do not meet criteria for depressed mood or lack of interest are not asked about other depressive symptoms.

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Results: Recruitment and data collection is on-going. For the data available 16 (31%) participants had symptoms of at least two weeks of either depressed mood or loss of interest or pleasure. Further assessment revealed that three (6%) had two or fewer symptoms, ten (19%) had three or four symptoms and three (6%) had at least five symptoms and met criteria for a past major depressive episode. Seven (14%) participants were taking antidepressants. Five of these had no recorded current or past DSM-IV depressive symptoms. A significantly greater proportion of patients taking an antidepressant fulfilled criteria for past MDD (n=2 of 7, 29%) than patients not taking antidepressants (n=1 of 44, 2% p=0.07).

Conclusion: Previous symptoms consistent with depression are common in the CFS sample that does not currently meet criteria for MDD. Further research to help characterise these symptoms and to better understand the overlap with CFS is needed to avoid the potential for misdiagnosis of depression. Antidepressants appear to be used in patients who have previously been depressed but also in patients in whom no previous depressive symptoms have been recorded. Further analysis of the dataset will hopefully allow us to better understand the nature and impact of depressive symptoms in CFS and the role of antidepressants.

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Sleep disturbances in patients with ME/CFS
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Objectives: To investigate the prevalence of Restless Legs Syndrome (RLS) and Obstructive Sleep Apnea Syndrome (OSAS) in patients with fatigue-related problems.

Methods: Patients were referred to Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS)-project for suspected diagnosis of ME/CFS. Ninety-seven patients completed Karolinska’s Otolaryngology Sleep Questionnaire which includes questions related to diagnosis of Restless Legs Syndrome (RLS), morning and daytime tiredness as well as Epworth Sleepiness Scale (ESS). To fulfil the criteria of RLS all 4 questions should be rated positively. The severity of RLS was also graded according to numeric scale. A subpopulation of 38 patients who fulfilled the criteria underwent a full night polysomnography ( PSG).

Results: Of 97 patients (81% women and 19% men), 57 patients were diagnosed with ME/CFS according to CDC and/or Canadian criteria while 40 suffered from another disorders explaining the fatigue. There was no significant difference in age between these groups (ME/CFS vs other diagnosis, 43±11 and 41±11 years, mean ± standard deviation) or BMI (25±6 and 23±6). Results from RSL-related questionnaire showed that 40% of patients in both groups rated positively for all 4 questions for RLS diagnosis. 2/3 of those patients graded RLS symptoms as mild-severe.

PSG data of 38 patients (32 women and 6 men, mean age 45±10, mean BMI 24.9±3.8) was analysed. Diagnosis of ME/CFS was given to 31 patients (82%), while 7 patients had other disorders explaining fatigue. PSG showed that 29 (76%) patients fulfilled the criteria of OSAS with Apnea-hypopnea Index (AHI) >5. Six patients (16%) patients had normal PSG, among them 5 diagnosed with ME/CFS.

Conclusion: The prevalence of RSL in patients with fatigue and suspected ME/CFS was approximately 40%, and to our knowledge was not sufficiently diagnosed and treated. The prevalence of OSAS in patients referred to PSG was 76%. These sleep disturbances should be evaluated and treated before the final ME/CFS diagnosis is set.

Fatigue Reporting of Interference Relative to Severity Covaries with Clinically Elevated Depression in Chronic Fatigue Syndrome/Myalgic Encephalomyelitis Patients
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Background/Objective: Chronic Fatigue Syndrome/Myalgic Encephalomyelitis (CFS/ME) patients have an increased risk for developing depression, which can negatively impact quality of life. CFS/ME patients perceiving more interference in their daily activities given their level of fatigue may feel more “set back” and depressed by their chronic fatigue. The objective of this study was to ascertain whether depression is associated with reporting of higher fatigue interference relative to severity, as this may elucidate a useful clinical tool to gauge if a CFS/ME patient would benefit from psychological support.

Methods: For this study, 61 women with CFS/ME completed measures of fatigue (Fatigue Symptom Inventory; FSI) and depression (Beck Depression Inventory-II, BDI-II). A ratio of FSI fatigue interference score to the severity score (I:S) was calculated for each participant. ii. A Receiver-Operating Curve analysis was then used to explore the true positive rate
(sensitivity) and the false positive rate (1-specificity) of the I:S ratio to predict depression using a clinical cutoff score of 20 (moderate severity) on the BDI-II.

**Results:** Overall, 13 (21%) participants had at least “moderate” depression scores on the BDI-II. The AUC statistic was .74 (SE=.07), with 95% CI (.61-.88). When sensitivity and specificity were weighted equally, an optimal I:S ratio of .94 yielded a sensitivity of 84.6% and a specificity of 64.6%.

**Conclusion:** Findings indicate that CFS/ME patients whose perceived interference given their level of fatigue is approximately greater or equal to 1 are likely experiencing clinically-elevated depressive symptoms. Physicians working with patients with CFS/ME should note relative interference and severity of their patients’ fatigue, and consider psychological follow-up if the I:S ratio is 1 or greater. Future investigation is needed to determine directionality and potential mediators of the depression-fatigue ratio association, as well as appropriate interventions to ameliorate symptoms of each.

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The prevalence and possible significance of thyroid disorders to Chronic Fatigue Syndrome patients diagnosed in CFS specialty clinics.

*Lucinda Bateman, Nancy Klimas, Daniel Peterson, Susan M. Levine, Donna Felsenstein, Gail H. Ironson and the CFI Study Group**

**Objectives:** Examine the occurrence and/or treatment of thyroid conditions in CFS patients diagnosed in CFS specialty clinics.

**Methods:** Data from the Chronic Fatigue Initiative (CFI) were analyzed to assess how many patients are diagnosed with a thyroid condition, taking levothyroxine, and/or have abnormal thyroid stimulating hormone (TSH) results compared to age, gender and regionally matched healthy control subjects. The study cohort has 405 subjects, 203 with CFS and 202 matched controls, divided evenly across five CFS Clinics in the U.S (Salt Lake City, Miami, Incline Village, New York, Boston), collected between Dec 2011 and Dec 2012

**Results:** Hypothyroidism is listed as a diagnosis in 30% versus 7% (p=.000), hyperthyroidism in 3% versus 0% (p = .014), and thyroiditis in 7% versus 0% (p = .001) of CFS patients versus matched healthy controls. Levothyroxine is taken by 23% of CFS patients versus 5% of controls. Of all subjects on levothyroxine (n=51), 23 reported they are significantly improved, 16 somewhat improved, 12 unchanged, and no one reported being somewhat worse or significantly worse on this treatment. There was no difference in effectiveness of levothyroxine for CFS patients (n=42) vs. controls (n=9). (The effectiveness data are from the medication history in the core questionnaire). TSH lab values are available from 199 CFS and 199 control subjects. There is no difference between the mean TSH values of CFS patients and controls (including 42 CFS patients and 9 Control subjects taking levothyroxine). Of the total cohort (on or off levothyroxine) 14% of the CFS patients had abnormal TSH (16 low, 12 high) and 7% of the health controls had abnormal TSH (7 low and 7 high).

**Conclusions:** The diagnosis of thyroid disorders and treatment with thyroid hormone is much higher in CFS patients than the normal population. This may be from the detection and treatment of subclinical hypothyroidism (defined as a TSH 5-10 with normal T4) during a vigorous diagnostic search for underlying chronic illness, but the background rate in the general population is 3%-8%, as is reflected in our control subjects. It is possible that patients are receiving chronic thyroid hormone supplementation without a true diagnosis of thyroid disease in an attempt to treat CFS symptoms, a practice that does not have established long term efficacy or safety. The data may also suggest an underlying mechanism of illness in CFS that leads to primary or secondary hypothyroidism. Because the main causes of hypo- and hyperthyroidism in the general population are auto-immune, further analysis of these findings may lead to better understanding of CFS pathophysiology and to more effective treatments.

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Endometriosis as a Comorbid Condition in Chronic Fatigue Syndrome: Prevalence and Impact on Health
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Objectives and Background. Endometriosis (EM) is estimated to be a comorbid condition in 20% of women with chronic fatigue syndrome (CFS), while its general prevalence among all women is estimated to be 4 to 7%. It is not well known whether women with EM and CFS are in worse health than women with CFS only. This study aims to examine whether health characteristics and laboratory parameters differ between women with CFS and EM (termed ‘CFS+EM’) and those with CFS only (termed ‘CFS-only’).

Methods. Data were derived from a population-based case-control study of CFS in Wichita, KS, conducted between 2002 and 2003. This analysis concerned a subset of the source sample on 84 women: 36 CFS cases and 48 controls with no CFS. Self-administered questionnaires collected information on gynecologic conditions (e.g., endometriosis, pelvic pain, etc.) and health characteristics (measured by the 20-item multidimensional fatigue inventory (MFI-20) for fatigue domain profile, the Short Form Health Survey (SF-36) for functional impairment or well-being, and the CDC Symptom Inventory (SI) for CFS case-defining and associated symptoms (symptom presence, frequency and intensity were used to calculate the SI score). Obstructive sleep apnea (OSA) scores were derived from an overnight polysomnography. Laboratory parameters of interest included: complete blood counts (CBC); serum C-reactive protein (CRP), IL-6 and TNF-alpha (inflammatory markers); and cortisol. We used chi-square tests to compare proportions for categorical variables, parametric and nonparametric tests to compare continuous variables (e.g., age, BMI, sleep, and laboratory parameters), and logistic regression to calculate odds ratios (OR) with 95% confidence intervals (CI) to estimate the magnitude of association between the CFS+EM group and the selected health/laboratory characteristics. Statistical significance was set at alpha=0.05 (two-sided).

Results. Thirty-six percent of the 36 women with CFS reported EM (CFS+EM) versus 17% of controls reported EM (termed ‘EM-only’ group), p=0.04. There were no significant group differences in age (50.9±1.5 years, mean±SEM), body mass index (BMI), mean scores of the MFI-20 and the SF-36 subscales, or laboratory parameters. The CFS+EM group had a significantly greater number of CFS case-defining symptoms from the SI 6.8±0.3 (mean±SEM) vs. 5.5±0.3 in CFS-only, but the total CFS SI score, while higher, was not statistically different (51.4±5.7 vs. 43.0±4.3, p=0.3). Chronic pelvic pain was more common in the CFS+EM group (46.2%) than the CFS-only (8.7%) [OR=9.00 (95% CI, 1.47-55.25)] and also more frequent than in the EM-only (12.5%, p=0.17). Menopause and hysterectomy were significantly more common in the CFS+EM group than in the CFS-only group (menopause: 92.3% vs. 56.5%; hysterectomy: 84.6% vs. 34.8%; OR=9.23 (1.02-83.33) and OR=10.31 (1.82-58.37), respectively). Notably, mean age at menopause onset was lower in the CFS+EM group (36.4±3.0 years) than in the CFS-only (47.0±2.7). Mean scores for OSA episodes were higher in the CFS+EM group than in the CFS-only, but did not reach statistical significance (20.3±11.3 vs. 4.4±2.3, p=0.14).

Conclusions. Although a small sample size, our study found a higher prevalence of endometriosis in women with CFS than in controls. Further, presence of co-morbid endometriosis was associated with having more CFS symptoms, chronic pelvic pain, and earlier menopause; however it did not significantly impact function, fatigue level, inflammatory markers or other laboratory parameters.

Disclaimer: The findings and conclusions expressed in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

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POSTER SESSION: NEUROENDOCRINE STUDIES

Getting Down to Detail: Exploring the Sometimes Pathogenic Versatility of Discrete Immune Logic
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Objective: Feedback mechanisms in the immune and endocrine systems play a significant role in maintaining stable homeostatic states. Specifically, the hypo-thalamic-pituitary-adrenal (HPA), and hypo-thalamic-pituitary-gonadal (HPG) axes contribute important regulation of immune activity. We propose that these components form an over-arching regulatory system capable of supporting multiple stable regimes. Here we explore the role of these interactions in perpetuating chronic endocrine-immune dysfunction in chronic fatigue syndrome (CFS) and Gulf War Illness (GWI).

Methods: We represent documented interactions within and between components of the HPA-HPG-immune system as a set of logic circuits. Logical analysis of these regulatory circuits reveals the allowed stable homeostatic states of the overall system. Using standard t-tests clinical endocrine/immune profiles of male GWI and CFS subjects, obtained from an ongoing study, are compared against controls. A meta-analysis technique is then used to combine the resulting significance measures into the probability of alignment with model predicted states.

Results: In the absence of external perturbations the HPA-HPG-immune model supports three stable homeostatic states. Endocrine-immune profiles observed experimentally in GWI and CFS males were both distinct from the normal resting state. Male GWI aligned closely with a state corresponding to persistent hypercortisolism, decreased testosterone, and inflammation. While male CFS was also closest to this state, it was relatively distant from all three predicted states.

Conclusion: Our results suggest that endocrine-immune regulatory circuitry is largely intact in male GWI and that the persistent immune dysfunction in this illness may at least in part be facilitated by the body’s own homeostatic drive. For male CFS, results suggest a continued influence of an exogenous agent or lasting changes to the regulatory circuitry.

Succumbing to the Laws of Attraction: Gender Differences in Homeostatic Drive and the Perpetuation of Chronic Illness
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Objective: A key component in the body’s stress response, the hypothalamic-pituitary-adrenal (HPA) axis, orchestrates changes several biological systems, although few models of its function account for these interactions. HPA dysfunction has been associated with numerous chronic diseases including Gulf War illness (GWI) and chronic fatigue syndrome (CFS). Here we model HPA function and it’s interaction with sex hormone regulation and immune response to explore the role of gender in homeostatic regulation and the perpetuation of chronic illness.

Methods: We use documented data of molecular/cellular signaling from biochemical/physiological literature to construct a diagram of interactions between the HPA, immune system and sex hormone axis. Logic rules are applied to this connectivity diagram to predict the stable homeostatic behaviors of the total system. Clinical endocrine/immune profiles of male GWI and female CFS subjects, obtained from an ongoing study, are compared against controls using standard t-test statistics. Using a meta-analysis of these statistical significances the probabilities of alignment of GWI and CFS with model predicted states are calculated.
**Results:** Male GWI subjects showed the greatest alignment with a predicted state of hypercortisolism, low testosterone and a shift towards a Th1 immune response. Female CFS subjects aligned most significantly with a predicted hypocortisolic, high estradiol, and a shift towards an anti-inflammatory Th2 activation state.

**Conclusion:** Results support a role for homeostatic drive in perpetuating dysfunctional cortisol levels through interaction with the immune system and sex hormone axis. Additionally, results suggest that this drive can perpetuate sexually dimorphic responses in GWI and CFS due to the inherent differences in the male and female sex systems.