Report to CFS Advisory Committee on: IACFS/ME Research and Clinical Conference

Fred Friedberg, PhD
President, IACFS/ME
January 13, 2017

IACFS/ME Sponsored Activities

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IACFS/ME Peer Review Journal

* Fatigue: Biomedicine, Health and Behavior
  * Founded 2013
  * Publisher: Taylor and Francis
  * ½ articles on ME/CFS

FATIGUE
BIOMEDICINE, HEALTH & BEHAVIOR

Contents

Knowledge management in engineering design: personalization and codification
Chris McMahon, Alistair Lowe, Steve Culley 000

Ontology-based systematization of functional knowledge
Yoshinobu Kitamura and Riichiro Mizoguchi 000

Techniques for the integration of expert knowledge into the development of environmentally sound products
Sebastian Leibrecht, Tri Ngoc Pham Van, Reiner Anderl 000

Knowledge-based support of rapid product development
Dieter Roller, Oliver Eck, Stavros Dalakakis 000

Product data management system-based support for engineering project management
Samir Mesihovic, Johan Malmqvist, Peter Pikosz 000

Plastics design: integrating TRIZ creativity and semantic knowledge portals
Gaetano Cascini and Paolo Rissone 000

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Taylor & Francis Group

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International Association for
IACFS/ME
Chronic Fatigue Syndrome

IACFS/ME Primer for Clinical Practitioners (2012, 2014)

* Provides information necessary to understand, diagnose, and manage the symptoms of ME/CFS
* 17,000+ views on the National Guidelines Clearinghouse

Available:

* http://iacfsme.org/portals/0/pdf/Primer_Post_2014_conference.pdf
* Bookpatch.com (print on demand)

IACFS/ME Newsletter

* 3x a year online (www.iacfsme.org)
* ME/CFS-related events
* Announcements
* Research news
* Clinical ideas

We welcome your submissions!

Lily Chu <lilyxchu@gmail.com>

* IACFS/ME Public Position Statements on Important Issues

IACFS/ME Public Position Statements

* PACE Trial
* DSM-5
* IACFS/ME representatives

  -state of the science at CFSAC

  -medical education at CDC

IACFS/ME Supports New Investigators

IACFS/ME 2016 conference travel awards

* NIH/NINDS grant funding

Six awardees (out of 40 applications!)

* Amit Arunkumar, BA
* Benjamin Eike, BA
* Ludovic Giloteaux, PhD
* Sarah Knight, PhD
* Katarina Lien, MD, PhD Candidate
* Jake Lindheimer, PhD

IACFS/ME Board of Directors

* Fred Friedberg, PhD (President)
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* Jon Kaiser, MD
* Sonya Marshall-Gradisnik, PhD

Interested in possible board membership?

* **Contact: ffriedberg12@gmail.com**

Conference Stats

* 60 oral presentations/symposia
* 80 posters
* Topics: ME/CFS and Gulf War Illness
* Close to 300 attendees, 200+ professionals
* 50 trainees or early stage investigators
* Attendees from all over the US
* 40% from 11 countries outside the US

Conference Program Book

* Full details of agenda and conference abstracts
* Available on pdf
* Presentation today is summary and highlights rather than complete listing

IACFS/ME Conference

* Highlights

Research Conference Topics

* Treatments
* Post-exertional malaise
* Epigenetics
* Gut microbiome
* Autonomic dysfunction
* Multi-site consortia

Plenary Speaker

Øystein Fluge, MD

Rituximab Treatment and CFS/ME Mechanisms

Keynote

Vicky Whittemore, PhD

New ME/CFS Developments at the National Institutes of Health

Keynote Speaker

Vicky Whittemore, PhD

Program Director, Channels, Synapses and Circuits
National Institute of Neurological Disorders and Stroke

New ME/CFS Developments at the National Institutes of Health

Professional Workshops

* ME/CFS office assessment
* Enteroviral infection in gut in ME/CFS
* Cardiopulmonary exercise testing
* Behavioral assessment and treatment of ME/CFS and fibromyalgia
* Diagnosing and treating orthostatic intolerance
* NIH grant writing workshop

Plenary Talk
Rituximab Treatment and ME/CFS Mechanisms
Oystein Fluge, M.D.

* 1st small study (N=30): Positive response:
  67% rituximab; 13%: controls; No adverse effects

* 2nd study (N=29) 63% clinical response; 37% no benefit
* 61% positive responders in remission at 3 years
* Adverse effects: allergic reactions; neutropenia; temporary symptoms worsening symptoms

Ongoing multicenter rituximab trial

* 152 patients; 2 infusions given 2 weeks apart
* maintenance infusions: 3, 6, 9, and 12 months.
* Results at end of 2017
* Possible mechanism: Drug diminishes autoantibodies that reduces energy enzyme pyruvate dehydrogenase; allows enzyme to function more effectively
* Hypothesis: defect in energy metabolism as major cause of ME/CFS

Treatment Studies

Treatment

* Low-dose methylphenidate plus mitochondrial support for ME/CFS. Lucinda Bateman

* Symptoms decreased, but non-significant
* 2 subgroups greatest response: severe group and those with both fatigue and pain.
* no obvious ill effects

Treatment

* Pilot ME/CFS Treatment with N-acetyl-cysteine (NAC).
  Dikoma Shungu
* Deficit in brain glutathione – an anti-oxidant; implicating oxidative stress in ME/CFS
* Rationale: NAC may alleviate cortical glutathione (GSH) deficit and improve symptoms in ME/CFS
* 4 weeks daily NAC to pts. and healthy controls with brain imaging and symptom assessments
* GSH rose to normative levels in patients; CFS symptoms significantly reduced

Treatment

* A reexamination of the cognitive behavioral theory of CFS Madison Sunnquist
* N=990 subjects with CFS
* Conclusions:

  -Individuals do not reduce activity level due to illness beliefs, as proposed by cognitive behavioral theory of CFS.

  -Exercise-based interventions may lack empirical justification and may not be appropriate, esp. with more strictly defined cases

* Post-exertional malaise

Post-exertional Malaise

* Difficult Clinical Cases Panel:
  Clinicians: most frequently reported symptoms related to **post-exertional malaise (PEM)** and orthostatic intolerance (OI)
* **Symptom provocation studies**:
  In ME/CFS: produce unique sxs of enduring PEM with pathophysiological alterations in tandem with real-time experimentally produced sxs flareups
  In Healthy Controls: do not move the needle toward abnormal physical responses

Post-exertional Malaise

* Characteristics of post-exertional malaise. Lily Chu
* 150 ME/CFS subjects: 89% experienced PEM after both physical/cognitive exertion and emotional distress.
* Fatigue most commonly exacerbated symptom, but sizable minority also reported cognitive difficulties, sleep disturbance, headaches, muscle pain, flu-like symptoms

* 11%: post-trigger delay of at least 24 hours, 23% endured PEM for 3 or more days
* Recommend: assess wide array of PEM sxs and duration.

Post-Exertional Malaise

Exercise testing and cytokine profiles. Jose Montoya

192 CFS patients and 392 healthy controls

24 hours post-exercise testing: 51 cytokines studied

* differences in cytokine profile between ME/CFS and controls
* abnormal cytokines and growth factor profiles in CFS, compared to resting values

* 13/17 cytokines correlated with symptom severity were pro-inflammatory
* May substantiate symptoms experienced by patients and immune nature of disease

Post-Exertional Malaise

* Mark Van Ness : 2-day exercise test (cardiopulmonary exercise testing, CPET) showed post-exertional chronotropic incompetence. (Heart rate doesn't increase with increased demands)
* Conclude: ME/CFS vs. healthy controls display post-exertional reductions in peak HR response to exercise
* Could contribute to exercise intolerance and reductions in oxygen consumption during PEM

Post-exertional Malaise

* CFS/ME patients: Lactate and 2-day CPET (exercise test).
  Katarina Lien (awardee)

* Patients: Higher blood lactate than heathy subjects at baseline and per work rate on both tests

* Suggests decreased physical capacity in CFS/ME compared to healthy subjects

Post-exertional Malaise

* Functional neural consequences of post-exertion malaise in ME/CFS. Dane Cook
* 30 min submaximal exercise on cycle ergometer
* Symptom assessments (fatigue, pain) and brain imaging data collected 1 wk prior to and 24 hr following exercise
* ME/CFS: large symptom changes compared to Controls; also affected brain function

* **Cognitive performance (PASAT) pre- to post-exercise**

  improvements for Controls

  worsening for ME/CFS

Post-exertional Malaise

ME/CFS patient responses to 2-day exercise test (CPET)

Betsy Keller

N=97 cases; Subsets:

* 73% failed to reproduce VO2 peak or VO2@VAT
* autonomic anomalies (43%)
* ventilatory anomalies (47%)
* Conclusion: multiple indicators of abnormal recovery following exertion in ME/CFS

Post-exertional Malaise: Non-exercise study

Neuromuscular Strain Increases Symptom Intensity in CFS

Peter Rowe

* 15 min neuromuscular strain: a supine straight leg raise (SLR) **vs.** Control: sham strain
* Higher symptom intensity changes during and 24 hr after leg raise compared to healthy controls
* Practical implication: better understanding why activities of daily life might be capable of provoking CFS symptoms.

Epigenetic studies

Epigenetic studies

* Epigenetics and disease: Disease may be caused by normal genes not turned on or off at the right time
* ME/CFS: significantly different gene expression patterns for genes involved in immune regulation, hormone regulation and mitochondrial function
* Epigenetic changes in ME/CFS suggest its potential role in disease manifestation:

  glucocorticoid hypersensitivity

  higher levels of EBV proteins more prone to viral reactivation

Epigenetic studies

* Single Nucleotide Polymorphisms in ME: Possible Genetic Factors Influencing Pathophysiology Benjamin Eike (awardee)
* SNP: most common type of genetic variation
* SNPs can act as biological markers, helping scientists locate genes associated with disease
* ME/CFS study using consumer available genetic tests
* 3/203 SNPs of interest: gene that codes for a subunit of NADH. NADH an important energy molecule in mitochondria; takes part in the production of ATP in aerobic respiration.

Gut Microbiome and ME/CFS

* Gut microbes synthesize
  -hormones and neurotransmitters
  -molecules of inflammation (cytokines, prostaglandins) and elicit production of those molecules by the gut immune system

Gut Microbiome and ME/CFS

- Reduced healthy gut *bacterial* diversity in ME/CFS
- L Giloteaux (awardee) found increased number of gut *viruses* in ME/CFS.
* Findings point to low-level gut inflammation
* Inflammation creates "leaky gut" allowing bacteria and bacterial toxins to enter the blood
* Hypothesis: changes in gut microbiome contribute to intestinal inflammation, bacterial imbalance and CFS symptoms (which includes many GI symptoms)

Polar metabolites

* Polar Metabolites Distinguish ME/CFS Patients and Controls Maureen Hanson
* Notable number of metabolites involved in energy metabolism, amino acids, and fat metabolism

  29/361 metabolites lower in ME/CFS patients, and

  4 were higher –described as hypometabolic state.
* Needs to be replicated: possible diagnostic test.

Brain studies

* Assessment of Neurobiological Dysfunction in Chronic Fatigue Syndrome. Benjamin Natelson

* Imaging and spinal fluid samples: ME/CFS vs. Healthy Controls

* Cerebral blood flow and glutathione significantly lower and ventricular lactate higher in CFS patients compared to controls (replication of prior study)

Autonomic Dysfunction

* Heart rate variability associated with ME symptoms : A population-based cohort study. Jose Alegre
* CFS/ME patients: higher autonomic symptom scores and decreased heart rate variability (HRV) compared to healthy controls
* Decreased HRV correlated with symptom severity in ME/CFS
* Implication: Autonomic response assessed by HRV could serve as potential biomarker and surrogate endpoint in intervention studies for CFS/ME.
* NIH funded study of HRV in ME/CFS (PI: Friedberg): volunteers needed

Criteria for diagnostic test

* Differentiates ME/CFS from healthy individuals
* Differentiates ME/CFS from other illnesses
* Many replications needed to show reliability/validity
* Convenient, relatively inexpensive

Multi-site consortia

Common Data Elements (CDEs) for Standardized Testing and Clinical Studies
Chair: Vicky Whittemore, Ph.D.

* Collaboration of NIH, NINDS, and CDC
* Development of CDEs for ME/CFS will facilitate comparison of results across studies and help to standardize analysis.
* Cf. NIH-produced PROMIS measures

Multi-site Clinic Assessment of ME/CFS (MCAM)

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

7 collaborating centers since 2012

* Biospecimens (serum, plasma, saliva, and white blood cell DNA) from nearly 700 ME/CFS cases and healthy control subjects.
* Objectives: use standardized questionnaires to measure illness domains; evaluate patient heterogeneity

* Describe course of illness and identify measures that best correlate with meaningful clinical differences
* Identify measures that best distinguish ME/CFS from the comparison groups and identify ME/CFS subgroups that may reflect different underlying causes.

Conference Summary

* Despite a very small universe of dedicated ME/CFS researchers: Gathering evidence for multi-system abnormalities
* Newer technologies and innovative studies

  -reveal micro frontiers of physiological dysfunction

  -better understandings of cause, pathobiology, potential diagnostic tests
* New symptomatic/ restorative treatments under study
* Need more researchers, funding, study replications

Acknowledgements

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* Department of Defense