Myalgic Encephalomyelitis/Chronic Fatigue Syndrome
Diagnosis and Management: The Basics and Beyond

Epidemiology and Science of ME/CFS
Diagnostic Criteria for ME/CFS
Physical Exam and Laboratory Workup

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Thursday October 6, 2011
RMS Stockholm, Sweden
ME/CFS Overview

- A complex fatiguing disorder of unknown etiology that persists for a minimum of six months
- Acute or gradual onset
- The debilitating fatigue is accompanied with multiple symptoms, such as:
  - Cognitive problems
  - Sleep disturbances
  - Headaches
  - Depression
  - Muscle and joint pain
  - Low-grade fever
  - Recurrent sore throat
- No diagnostic test available
- No known cure
Prevalence of ME/CFS

- Prevalence in the USA
  - Estimated 400/100,000 = over 1 million patients (CDC 2007)

- Prevalence in Sweden
  - Estimated 40,000 Swedes diagnosed
What is Known About Patients with ME/CFS World Wide

- High degree of activity limitation
  - Need help with tasks
- Experience socio-economic disadvantage
  - Permanently unable to work
  - Personal income under $15,000
  - Food insecurity
  - Very weak sense of belonging to the community
  - Experience difficulty in social situations
- Insufficient care
  - Unmet medical care needs
  - Unmet home care needs
Annual Economic Loss Due to CFS/ME

- $9 billion USD
- $61 billion Swedish Kronor
## Activity Limitation

<table>
<thead>
<tr>
<th>Question</th>
<th>Canadians with ME/CFS</th>
<th>Canadians in General</th>
</tr>
</thead>
<tbody>
<tr>
<td>Need help preparing meals</td>
<td>17%</td>
<td>3%</td>
</tr>
<tr>
<td>Need help getting to appointments and running errands</td>
<td>32%</td>
<td>3%</td>
</tr>
<tr>
<td>Need help doing housework</td>
<td>35%</td>
<td>5%</td>
</tr>
<tr>
<td>Need help with heavy household chores</td>
<td>56%</td>
<td>12%</td>
</tr>
<tr>
<td>Need help with personal care</td>
<td>9%</td>
<td>2%</td>
</tr>
<tr>
<td>Need help moving about both inside and outside the house</td>
<td>8%</td>
<td>1%</td>
</tr>
</tbody>
</table>

2005 Canadian Community Health Survey
## Insufficient Care

<table>
<thead>
<tr>
<th>Question</th>
<th>Canadians with ME/CFS</th>
<th>Canadians in General</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unmet healthcare needs over the previous 12 months</td>
<td>30%</td>
<td>11%</td>
</tr>
<tr>
<td>Unmet home care needs over the previous 12 months (ages 18+)</td>
<td>14%</td>
<td>2%</td>
</tr>
</tbody>
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## Socio-Economic Disadvantage

<table>
<thead>
<tr>
<th>Question</th>
<th>Canadians with ME/CFS</th>
<th>Canadians in General</th>
</tr>
</thead>
<tbody>
<tr>
<td>Permanently unable to work (ages 15-74)</td>
<td>18%</td>
<td>2%</td>
</tr>
<tr>
<td>Annual personal income &lt;$15K (ages 15+)</td>
<td>44%</td>
<td>29%</td>
</tr>
<tr>
<td>Food insecure</td>
<td>17%</td>
<td>5%</td>
</tr>
<tr>
<td>Weak sense of community belonging</td>
<td>19%</td>
<td>10%</td>
</tr>
<tr>
<td>Experience difficulty in social situations</td>
<td>27%</td>
<td>5%</td>
</tr>
</tbody>
</table>

2005 Canadian Community Health Survey
ME/CFS Diagnostic Criteria

Classification and Definitions
# History of “CFS”

<table>
<thead>
<tr>
<th>Pre 1980</th>
<th>Global</th>
<th>Outbreaks of a disease that caused debilitating fatigue, mental confusion, sleep dysfunction, pain, memory problems. Ramsey coined the term ME and described the disease.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1980s to</td>
<td>Inclined Village and Lyndonville outbreak</td>
<td><strong>Focus on Fatigue</strong> <em>(in Definitions and Classification)</em></td>
</tr>
<tr>
<td>early 90s</td>
<td>CFS label designated; Holmes case definition</td>
<td>CFS added to ICD-9-CM under “Signs and Symptoms/Malaise and Fatigue”</td>
</tr>
<tr>
<td>In the US</td>
<td><strong>Focus on Neurological, Immunological, Endocrine, Post-exertional Malaise</strong></td>
<td>ICD-10 released. CFS was added to ICD-10 at G93.3 - Nervous System Diseases</td>
</tr>
<tr>
<td>Mid 90s to</td>
<td>ICD-10 released. CFS was added to ICD-10 at G93.3 - Nervous System Diseases</td>
<td>2004 and 2011 CFSAC recommendation to classify CFS as neurological in ICD-10-CM</td>
</tr>
</tbody>
</table>
Classification

- International Classification of Disease (ICD)
  - ME/CFS is classified as a neurologic disease in the World Health Organizations ICD

- Do not confuse chronic fatigue with ME/CFS
  - The “fatigue” of ME/CFS is a pathophysiologic exhaustion and is only one of many symptoms
<table>
<thead>
<tr>
<th>ICD 9 CM Diagnosis Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>780.71</td>
<td>Chronic Fatigue Syndrome</td>
</tr>
<tr>
<td>078.5</td>
<td>Cytomegaloviral disease</td>
</tr>
<tr>
<td>079.5</td>
<td>Retrovirus</td>
</tr>
<tr>
<td>780.79</td>
<td>Other malaise and fatigue: Asthenia NOS, Lethargy, Postviral (asthenic) syndrome, Tiredness</td>
</tr>
<tr>
<td>279.06</td>
<td>Common variable immunodeficiency</td>
</tr>
<tr>
<td></td>
<td>Dysgammaglobulinemia (acquired) (congenital) (primary)</td>
</tr>
<tr>
<td></td>
<td>Hypogammaglobulinemia: acquired primary, congenital non-sex-linked, sporadic</td>
</tr>
<tr>
<td>729.1</td>
<td>Myalgia and myositis, unspecified</td>
</tr>
<tr>
<td></td>
<td>Fibromyositis NOS</td>
</tr>
<tr>
<td>058.21</td>
<td>HHV-6 encephalitis</td>
</tr>
<tr>
<td>058.81</td>
<td>HHV-6 infection</td>
</tr>
<tr>
<td>058.12</td>
<td>HHV-7 infection</td>
</tr>
<tr>
<td>202.80</td>
<td>Other malignant lymphomas unspecified site</td>
</tr>
</tbody>
</table>
ICD-10 Code Recommendations from leaders in the field:

- **Before ICD-10-CM is implemented in 2013:**

- Move CFS from “Signs and Symptoms/Chronic Fatigue Unspecified” to G93.3 under “Diseases of the Nervous System”

- Do not split ME/CFS cases into ME for viral triggers and CFS for bacterial or other pathogens. Use the same code for ME and CFS.
ME/CFS Definitions

- Center for Disease Control (CDC)
  - The 1988 CFS Research Case Definition
  - The 1994 International Case Definition (Fukuda)


- ME International Consensus (2011)
This document provides a comprehensive, systematic, and integrated approach for the evaluation, classification, and study of persons with ME/CFS and other fatiguing illnesses.

Two criteria must be met:

1. Clinically evaluated, unexplained, persistent or relapsing chronic fatigue that is of new or definite onset, is not the result of ongoing exertion, is not substantially alleviated by rest, and results in substantial reduction in previous levels of occupational, educational, social, or personal activities.

2. Concurrently have four or more of the following symptoms:
   - Post-exertional malaise
   - Impaired memory or concentration
   - Unrefreshing sleep
   - Muscle pain
   - Multi-joint pain without redness or swelling
   - Tender cervical or axillary lymph nodes
   - Sore throat
   - Headache

The symptoms must have persisted or recurred during six or more consecutive months of illness and must not have predated the fatigue.

A patient with ME/CFS will meet the following criteria:

1. Fatigue
2. Post-exertional malaise and/or fatigue
3. Sleep dysfunction
4. Pain
5. Neurological/cognitive manifestations (two or more)
6. At least one symptom from two of the following categories:
   - Autonomic manifestations
   - Neuroendocrine manifestations
   - Immune manifestations
7. Illness duration > 6 months with a distinct onset

ME International Consensus 2011: The four components

- Post-Exertional Neuroimmune Exhaustion
- Neurological Impairments
- Immune Impairments
- Energy Production / Transport Impairments

Post-Exertional Neuroimmune Exhaustion (2011 Consensus)

- The inability to produce sufficient energy on demand with prominent symptoms in the neuroimmune regions. Characteristics are:
  - Rapid physical and/or cognitive fatigability in response to exertion
  - Post-exertional symptom exacerbation: including flu-like symptoms, pain, and worsening of other symptoms
  - Post-exertional exhaustion that may occur right after exertion or be delayed for hours or days.
  - Recovery period is prolonged (usually 24 hours or greater)
  - Low threshold of physical and mental fatigability.

Neurological Impairments: At least one symptom from three of the following four categories (2011 Consensus)

- Neurocognitive Impairment
- Pain
- Sleep Disturbance
- Neurosensory, Perceptual and Motor Disturbances

Immune, Gastro-intestinal and Genitourinary Impairments

At least one symptom from three of the following five categories (2011 Consensus)

1) Flu-like symptoms that may be chronic or recurrent and are worse following exertion.
2) Viral susceptibility with prolonged recovery
3) Gastro-intestinal tract discomfort and dysfunction
4) Genitourinary dysfunction
5) New or increased sensitivities to food medication, odors, and chemicals

Energy Production/Transport Impairments: At least one at least one of the following symptoms. (2011 Consensus)

1) Cardiovascular: orthostatic intolerance, neurally mediated hypotension, POTS, palpitations with or without cardiac arrhythmias, light headedness/dizziness.
2) Respiratory: Labored breathing, fatigue of chest walls and muscles of respiration.
3) Loss of thermostatic stability
4) Intolerance of extreme temperatures

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6. At least one symptom from two of the following categories:
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   - Neuroendocrine manifestations
   - Immune manifestations
7. Illness duration > 6 months with a distinct onset
1. Fatigue

- Significant degree of physical and cognitive fatigue
  - New onset
  - Unexplained
  - Persistent
  - Recurrent

- Fatigue substantially reduces activity level
  - Activity level is reduced by approximately 50% or more
  - Some can be housebound or bedridden

Inappropriate loss of physical and mental endurance
Rapid muscular and cognitive fatigability
Tendency for other associated symptoms to worsen after activity
Pathologically slow recovery period – usually 24 hours or longer
3. Sleep Dysfunction

- Unrefreshed sleep, or
- Sleep quantity, or
- Rhythm disturbances, such as reversed or chaotic diurnal sleep rhythms

A small number of patients have no sleep dysfunction

4. Pain

- Significant degree of myalgia
- Pain in the muscles and/or joints, often widespread and migratory in nature
- Significant headache pattern, or severity

A small number of patients have no pain

5. Neurological/Cognitive Manifestations

- **Two or more** of the following should be present:
  - Confusion
  - Impairment of concentration and short term memory consolidation
  - Disorientation
  - Difficulty with information processing, categorizing and word retrieval
  - Perceptual and sensory disturbances (spatial instability, disorientation, inability to focus vision)
  - Ataxia, muscle weakness, and fasciculations
  - Overload phenomena: cognitive, sensory, emotional

6. Additional Symptoms

At least one symptom from two of the following categories:

**Autonomic Manifestations**
- Orthostatic intolerance - NMH, POTS delayed postural hypotension
- Light-headedness
- Extreme pallor
- Nausea and irritable bowel syndrome
- Urinary frequency and bladder dysfunction
- Palpitations with or without cardiac arrhythmias
- Exertional dyspnea

**Neuroendocrine Manifestations**
- Loss of thermostatic stability
- Marked weight change
- Loss of adaptability and worsening of symptoms with stress

**Immune Manifestations**
- Tender lymph nodes
- Recurrent sore throat
- Recurrent flu-like symptoms
- General malaise
- New sensitivities to food, medications, and/or chemicals

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7. Illness Duration

- Illness persists for at least 6 months
- Usually a distinct onset, although it may be gradual
- Preliminary diagnosis may be possible earlier than 6 months
- Illness duration of 3 months is appropriate for children

Some patients may have been unhealthy for other reasons prior to onset of ME/CFS and lack detectable triggers, and/or have more gradual or insidious onset

Exclusions

- All active disease processes that explain major symptoms
  - Specific diseases:
    - Addison’s disease
    - Cushing’s disease
    - Hypo- or hyperthyroidism
    - Iron deficiency or iron overload syndrome
    - Other treatable forms of anemia
    - Diabetes mellitus
    - Cancer
  - Treatable sleep disorders
  - Rheumatological disorders
  - Immune disorders
  - Neurological disorders
  - Infectious diseases
  - Primary psychiatric disorders
  - Substance abuse

Co-morbid Entities

- Fibromyalgia Syndrome (FMS)
- Myofascial Pain Syndrome (MPS)
- Temporomandibular Joint Syndrome (TMJ)
- Irritable Bowel Syndrome (IBS)
- Interstitial Cystitis
- Irritable Bladder Syndrome
- Raynaud’s Phenomenon
- Prolapsed Mitral Valve
- Depression
- Migraine
- Allergies
- Multiple Chemical Sensitivities
- Hashimoto’s Thyroiditis
- Sicca Syndrome

If a patient has unexplained fatigue for longer than 6 months and does not meet the diagnostic criteria for ME/CFS, classify as idiopathic chronic fatigue.

Definition Comparison

- Jason, et al compared patients meeting the Canadian clinical criteria and Fukuda criteria for ME/CFS against control patients with chronic fatigue due to depression.

- In summary, patients meeting the Canadian criteria appear to have more symptoms, more physical functional impairment, and less psychopathology compared to those in the CF-psychiatric group.

- In addition, the Canadian criteria identifies patients with more fatigue/weakness, neurological and neuropsychiatric symptoms than the Fukuda CFS criteria.

Epidemiology and Science of ME/CFS

Infectious, Immune, Endocrine, Autonomic, Exercise, and Sleep Research
Model of ME/CFS Pathogenesis

Genetic Predisposition

Triggering event / infection

Mediators (Immune, endocrine, neuroendocrine, psychosocial, viral reactivation or persistence)

ME/CFS

NKlimas-2007 Immunology and Infection
Summary of Genetic Predisposition Research for ME/CFS

- HLA DR haplotypes in 112 South Florida CFS patients, compared to 5,000 regional and national controls \(^1\)
- 4 to 6 fold increased relative risk for DR4, DR3 and DQ3 (Keller et al. 1992)
- Seattle CFS Cooperative Research Center Twin study - genetic predisposition, hereditability estimate of 51% (2nd World Conf); similar results in Sweden, Australian studies

1. NKlimas-2007 Immunology and Infection
Summary of ME/CFS Infectious Research

- **Viral infections associated with ME/CFS:**
  - Epstein-Barr Virus \(^1\)
  - Cytomegalovirus \(^1\)
  - Human Herpesvirus-6 \(^1\)
  - Human Herpesvirus-7 \(^1\)
  - Enteroviruses \(^1\)
  - Parvovirus B19 \(^1\)
  - XMRV \(^4\)

- **Dysregulation of the 2-5A synthetase/ribonuclease L (RNase pathway in monocytes** \(^2\)

- **Bacterial infections associated with ME/CFS:**
  - Chlamydia \(^3\)
  - Mycoplasma \(^3\)
ME/CFS Infectious Research
Herpesvirus Infections in Blood Samples from Clinic Patients with ME/CFS

Summary of ME/CFS Immune Research

- Functional defects
  - Antiviral enzyme (RNase L) dysfunction
  - Low natural killer (NK) cell numbers and function
  - CD8 abnormalities
  - Decreased perforins and granzymes
  - Macrophage abnormalities
  - Antibody production

- Immune activation
  - Increased numbers of activated T cells
  - Increased production of inflammatory cytokines/chemokines
  - DR, CD26 expression

ME/CFS Immune Research

Evaluation of HHV-6, CMV, EBV infections and autoantibodies in 90 ME/CFS patients

Summary of ME/CFS Endocrine Research

- **Hormonal alterations in adolescent ME/CFS**¹
  - Plasma ADH was significantly decreased
  - Increased serum osmolality and plasma renin activity

- **Hypothalamic-Pituitary-Adrenal Axis Function**²
  - Despite contradicting studies, there is evidence of mild hypocortisolism, blunted ACTH responses and enhanced negative glucocorticoid feedback in a portion of patients with ME/CFS

Summary of ME/CFS GI Research

- Patients with ME/CFS are likely to report a previous diagnosis of irritable bowel syndrome (IBS) and experience IBS-related symptoms.\(^1\)
- Altered gut microbiota.\(^2\)
- Increased gut-intestinal permeability.\(^3\)
  - Translocation of LPS provokes immune response increasing serum IgA and IgM antibodies
- Altered fecal microbiota.\(^4,5\)
- High levels of H2S caused by intestinal overgrowth may play a major role in ME/CFS and lead to a series of reactions that leave cells devoid of oxygen and energy.\(^6\)
ME/CFS GI References


6. Kenny De Meirleir
Summary of ME/CFS Cardiovascular Research

- A characteristic repetitively oscillating T-wave inversions and/or T-wave flattening during 24 hour monitoring \(^1,2\)
- Decreased vagal activity \(^3\)
- Orthostatic Intolerance \(^4, 5, 6\)
  - POTS \(^7\)
  - Neurally mediated hypotension \(^8, 9\)
- Decreased total blood volume \(^10\)
- Lower blood pressure and abnormal diurnal blood pressure regulation \(^11\)
- Reduced cardiac stroke volume and cardiac output \(^12\)
ME/CFS Cardiovascular References

Summary of ME/CFS Exercise Research

- Symptom exacerbation ¹
- Elevated resting heart rate ¹
- Reduced heart rate at maximum workload ¹
- Reduced oxygen uptake ¹
- Decreased cerebral blood flow ¹
- Decreased body temperature ¹
- Breathing irregularities ¹
- Gait abnormalities ¹
- Cognitive function/reaction time is prolonged in post-exertional state ²
- Increased recovery period ³

Summary of ME/CFS Sleep Research

- Decrease in the length of periods of uninterrupted sleep \(^1\)
- Alpha intrusion into delta sleep \(^2\)

Diagnosing ME/CFS

Physical Examination and Laboratory Workup
Diagnosing ME/CFS

- Diagnosis of ME/CFS is primarily one of exclusion
- A detailed and thorough medical history are necessary for the diagnosis
  - Written assessment tools can be given to the patient to fill out ahead of time and reviewed before the patient’s first visit
- A vital part of the diagnostic process are the physical exam and laboratory testing
Physical Examination

- Conduct a standard PE with specific attention to:
  - Musculoskeletal system
  - CNS
  - Endocrine system
  - Cardiovascular system
  - GI system
  - Immune system
PE - Musculoskeletal System

- FMS tender point exam
  - Pain on palpation in 11 or more of the 18 designated tender point sites meets FMS diagnosis
- Check joints for inflammation, hypermobility, and restricted movement
- Document muscle strength
PE - CNS

- Reflex examination
- Tandem walk
- Romberg test
- Evaluate cognitive symptoms
  - Ability to remember questions
  - Cognitive fatigue
    - Serial 7 subtraction
  - Cognitive interface
    - Serial 7 subtraction and tandem done simultaneously

PE – Endocrine System

- Examine for signs of dysfunction in the following:
  - Thyroid
  - Adrenal
  - Pituitary
PE – GI System

- Check for the following:
  - Increased bowel sounds
  - Abdominal bloating
  - Abdominal tenderness

PE – Cardiovascular System

- Arrhythmias
- BP
  - Lying down
  - Immediately after standing
PE – Immune System

- Recurrent flu symptoms
- Sore throat
- Crimson crescents in tonsillar fossa
  - Red crescents are demarcated along the margins of both anterior pharyngeal pillars
  - They will assume a posterior position in the oropharynx in patients without tonsils
- Tenderness in the following lymph nodes:
  - Cervical
  - Axillary
  - Inguinal
- General malaise
- Examine for splenomegaly
ME/CFS Laboratory Workup

- Screening Diagnostic Tests
- Specific Studies
- Highly Specific Studies
- Functional Studies
- Neuro Imaging
- Other Useful Studies
- Experimental and Investigational Studies
Screening Diagnostic Tests

- Access previous lab diagnostics that have been performed
  - Repeat if greater than 3 months and reassess screening diagnostics for any diagnosable and treatable disorders
- Minimum diagnostic workup
  - CBC
  - Chemistry panel
  - UA
  - Thyroid panel
  - Sedimentation rate or equivalent
  - Testosterone
  - FSH and LH level II
- Additional diagnostics
  (depending on individual clinical presentation)
  - DHEA
  - Cortisol AM and PM
  - ACTH
  - Stool for WBC pathogens
  - Anitgliadin Ab
  - Iron
  - TIBC
  - Ferritin
  - Narcolepsy panel
  - Focused rheumatologic testing (ANA and rheumatoid factor)
Specific ME/CFS Studies

- Natural killer cell numbers and function
- Lymph enumeration panel
  - Specifically cytotoxic T cell testing
- B and T-cell function including:
  - IgG and IgG subclasses 1 - 4
  - IgA
  - IgM
Perforin is a molecule in cytotoxic lymphocytes necessary for killing of virus infected and tumor cells.
Highly Specific ME/CFS Studies

- Cytokine/Chemokine panel
- RNase L activity
- Amino acid profile
- Carnitine panel
- Magnesium
- Mycoplasma panel
- Chlamydia panel
- Determine past viral infections
  - Herpes virus screening panel
    - EBV early antigenemia
    - HHV-6 IgG and IgM
  - Parvovirus IgG and IgM
- Determine active viral infections with viral culture antigenemia and PCR
  - EBV
  - CMV
  - HHV-6
  - HHV-7
  - Parvovirus
Cytokine & Chemokine Profiling in ME/CFS

- Chronic Innate Immune activation by pathogenic triggers in a genetically susceptible host mediate the pathogenesis through a cytokine/chemokine storm

- Multiplex cytokine arrays afford the opportunity to analyze the complex relationships between the cytokines and clinical disease and to determine if clinical subgroups of disease could be identified based on distinct cytokine profiles
Cytokine & Chemokine Profiling in ME/CFS

- ME/CFS patients can be distinguished from healthy controls with 94% accuracy by measuring 5 Cytokines and Chemokines.
2-5A / RNase L Pathway in ME/CFS

- Positive Clinical Correlation
  - RNase L activity and MSQ score ($p < 0.01$)
    - MSQ = Metabolic Screening Questionnaire

- Negative Clinical Correlations
  - RNase L activity and KPS ($p < 0.002$)
  - Bioactive 2-5A and KPS ($p < 0.025$)
    - KPS = Karnofsky Performance Score

Status of the 2-5A synthetase / RNase L pathway in ME/CFS:

- 2-5 A synthetase is activated
- Bioactive 2-5 A is present
- RNase L is activated

**dsRNA** → **2’-5’ A synthetase** → **2’-5’ oligoadenylate (2-5 A)** → **RNase L (LATENT)** → **RNase L (ACTIVATED)** → **Degradation of RNA, Prevention of protein synthesis** → **Inhibition of viral replication**

Functional studies

- Sleep study (if indicated)
- Nocturnal oxygen screen
- Exercise tolerance testing with expired gas exchange
- Neuropsychometric testing
- SF-36
Exercise Tolerance Testing with Expired Gas Exchange

- Measures cardiovascular, pulmonary and metabolic responses at rest and during exercise
- Used to rule out other cardiopulmonary disease processes

- Key measures:
  - Peak Oxygen Consumption (VO2)
  - Anaerobic Threshold (AT)
  - Heart Rate (HR)
  - Blood Pressure (BP)
  - Ventilation (VE)

- All ME/CFS patients demonstrate low VO2 max

![Graph showing oxidative impairment in the post-exertional state](chart.png)
Neuro Imaging

- MRI with contrast
- Brain SPECT scan
- PET scan
Magnetic Resonance Images (MRI)

Increased $T_2$-weighted images in high white matter tracts

Fig. 2.—37-year-old woman with chronic fatigue syndrome.

A, Axial proton density–weighted MR image (4000/40) shows multiple foci of increased signal in internal capsules bilaterally and in white matter adjacent to left globus pallidus (arrows).

B–E, Axial SPECT images (5-mm-thick sections) show multiple foci of decreased perfusion throughout brain (arrows). Color scale ranges from black (low activity) to white (high activity).
Brain SPECT Scans: Regional Hypoperfusion

Fig. 2.—37-year-old woman with chronic fatigue syndrome.
A, Axial proton density–weighted MR image (4000/40) shows multiple foci of increased signal in internal capsules bilaterally and in white matter adjacent to left globus pallidus (arrows).
B–E, Axial SPECT images (5-mm-thick sections) show multiple foci of decreased perfusion throughout brain (arrows). Color scale ranges from black (low activity) to white (high activity).
Other Useful Studies

- Lumbar puncture
- 24-hour BP monitor
- Holter monitor
Experimental and Investigational Studies

- TCRγ Rearrangement
- DNA array
- mRNA array
- Viral array/human pathogen array
Clonal TCRγ Rearrangement Testing

What are γ T cells?:
- Play active role in regulation and resolution of pathogen induced immune responses
- Accumulate at sites of inflammation
- Associated with Viral, Parasitic and bacterial Infections
- Associated with autoimmune diseases
- Upregulate MIP1α, B, TNFα, IL-10, IFNγ

Rationale for testing:
- Suggest chronic active infection particularly CMV
- Predictive of lymphoma development

Clinical Criteria for Testing:
- Acute (viral) onset ME/CFS
- Lymphadenopathy and/or splenomegaly
TCR $\gamma$ Clonality in Nevada ME/CFS Cohort
Making the Diagnosis

- Making a Positive Diagnosis for ME/CFS
  - If the patient’s presentation meets the diagnostic criteria for ME/CFS and no specified exclusions are present, classify the diagnosis as ME/CFS
  - If the patient has prolonged fatigue but does not meet the criteria for ME/CFS, classify the diagnosis as idiopathic chronic fatigue

- New Symptoms
  - ME/CFS patients can develop other medical problems during the course of treatment
  - New symptoms need to be appropriately investigated