

# **Chronic Fatigue Syndrome**

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# Outline

- Introduction
- Definition
- Status in ICD
- Epidemiology
- Etiology
- Comorbidity and differential diagnosis
- Treatment
- Conclusions



# Introduction



- **Fatigue-** a feeling of weariness, sleepiness or irritability after a period of mental or bodily activity
- **Tiredness-** A feeling of a lessened capacity for work and reduced efficiency of accomplishment, usually accompanied by a sense of weariness and fatigue

# Evolution of the concept



- In 1987 **Chronic fatigue syndrome (CFS)** first used to describe condition resembling "chronic active Epstein-Barr virus (EBV) infection" but with no evidence of EBV as its cause
- In 1988, "Chronic fatigue syndrome: a working case definition", **the Holmes definition**
- In 1994, **CDC (Centers for disease control and prevention)** gave its case definition

# CDC Guidelines



## ❖ MAJOR CRITERION

Severe chronic fatigue for  $\geq 6$  months

- Not due to ongoing exertion or other medical conditions
- Not substantially relieved by rest
- Significant interference with daily activities

# CDC Guidelines



## ❖ MINOR CRITERION

- Concurrent presence of 4 or more of 8 symptoms:
  - Post-exertion malaise lasting > 24 hours
  - Unrefreshing sleep
  - Impairment of memory or concentration
  - Muscle pain
  - Pain in multiple joints without swelling or redness
  - Headaches of a new type, pattern, or severity
  - Tender lymph nodes in the neck or armpit
  - Frequent or recurring sore throat

# ICD 10 CM (clinical modification)

## Chronic Fatigue Unspecified - R53.82



- For  $\geq 6$  months  $\rightarrow$  tired most of the time, trouble concentrating and carrying out daily activities
- Other symptoms include
  - mild fever
  - lymphadenopathy
  - headache
  - myalgia
  - arthralgia
  - depression, and memory loss
- Not caused by ongoing exertion, not relieved by rest

# Epidemiology



- Prevalence
  - 0.4% -2.5% (UK general population)
  - 0.2-0.4% (USA general population)
- Annual direct medical costs - \$7 billion in USA
- Mean age of onset 29-35 yrs
- 75% of affected patients are women



# Etiology- *Biological*



## 1. **Viral infection**

- Epstein-Barr virus initially proposed
- Later found to be not conclusive
- No clear causal relationship between infections and CFS

## 2. **Hypothalamic pituitary adrenal axis dysfunction**

- Mild hypocortisolism observed in cases of CFS
- HPA axis dysfunction not specific to CFS, symptoms like inactivity in CFS can decrease Cortisol levels
- Hypocortisolemia may predict a poorer response to CBT

# Etiology- *Biological*



## 3. Immunologic basis

- High pro inflammatory cytokines, high IL-1 levels in CFS
- NK cell dysfunction- either decrease in number or impaired function
- increased levels of T regulatory cells (CD25+/FOXP3+) CD4 T cells
- Lower activation of CD8 T cells
- Allergies (atopy) and CFS

# Etiology- *Biological*



## 3. Immunological basis (contd)

- Serotonin and CFS – anti 5-HT autoimmune activity could play a role in the pathophysiology of CFS and the onset of psychosomatic symptoms

# Etiology- *Biological*



## 4. Genetics

- Concordance 55% in monozygotic and 20% in dizygotic twins
- Sequence variation in genes coding for HTR2A serotonergic receptor potentially enhancing its activity may be involved in pathophysiology of CFS
- Differences observed in gene expression in exercise responsive genes in terms of gene ontology in attempt to explain fatigue which worsens post exercise in CFS

# Etiology- *Biological*



## 5. Neuroimaging

- Functional
  - Reduced basal ganglia function in terms of decreased activity of right caudate and right globus pallidus on MRI
- Structural
  - Reduced grey and white matter volume in the occipital lobe and reduced grey matter in the right angular gyrus and right parahippocampal gyrus on VBM (voxel-based morphometry) in CFS patients

# Etiology - *Psychological*



- Increased prevalence of maladaptive personality features and personality disorders
- Prevalence of paranoid, schizoid, avoidant, obsessive-compulsive and depressive personality disorders significantly higher in CFS compared to normal
- Neuroticism frequently associated with CFS; patients with CFS were found to be less extroverted

# Cognitive deficits in CFS



- Impaired information processing speed (reaction time)
- Impaired working memory and poor learning of information
- Alterations in motor speed

# Differential Diagnoses - Medical



## **VERY COMMON (~1 PER 100)**

Anemia  
Thyroid disorders  
Medications (statins)  
Sleep apnea

## **COMMON (~1 PER 1,000)**

Chronic infection: HIV, Hepatitis C  
endocarditis, osteomyelitis, Lyme  
disease, occult abscess

Cancer

Pulmonary conditions: asthma,  
obstructive lung disease, interstitial lung  
disease

Symptomatic hyperparathyroidism

## **UNCOMMON (~1 PER 10,000)**

Polymyositis,  
Dermatomyositis,  
Myopathy  
Myasthenia gravis,  
Multiple sclerosis  
Narcolepsy  
Inflammatory bowel diseases



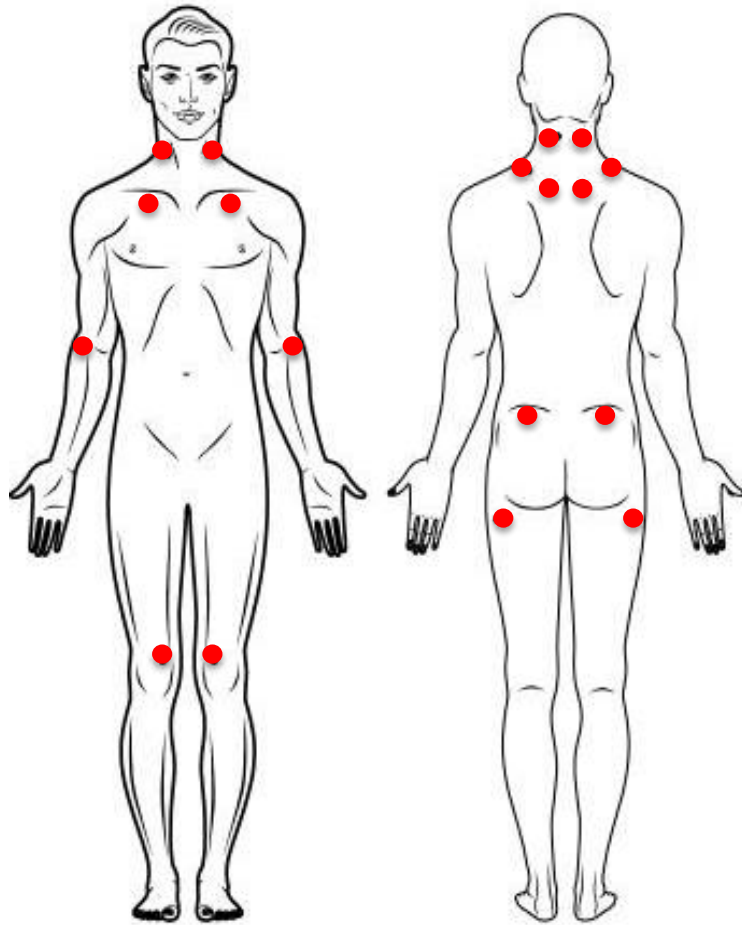
# Overlapping “Functional Syndromes”



## Functional Somatic Syndromes by Speciality

Gastroenterology	Irritable Bowel Syndrome, Non-Ulcer Dyspepsia
Gynaecology	Chronic Pelvic Pain Pre-menstrual syndrome
<b>Rheumatology</b>	<b>Fibromyalgia</b>
Cardiology	Atypical/Non-cardiac chest pain DaCosta's Syndrome
Respiratory Medicine	Hyperventilation Syndrome
Dentistry	Temporomandibular Joint Dysfunction/Atypical facial pain
ENT	Globus Hystericus
Allergy	Multiple Chemical Sensitivity

# Fibromyalgia



History of widespread pain (present for  $\geq 3$  mo)

**Definition:** Pain is considered widespread when all of the following are present: pain on both sides of the body, pain above and below the waist. In addition, axial skeletal pain (cervical spine, anterior chest, thoracic spine, or low back pain) must be present. “Low back” pain is considered lower segment pain

Pain in 11 of 18 standardized sites, commonly referred to as *tender points*, on digital palpation

Occiput (2)—at the suboccipital muscle insertions

Low cervical (2)—at the anterior aspects of the intertransverse spaces at C5 to C7

Trapezius (2)—at the midpoint of the upper border

Supraspinatus (2)—at origins, above the scapula spine near the medial border

Second rib (2)—upper lateral to the second costochondral junction

Lateral epicondyle (2)—2 cm distal to the epicondyles

Gluteal (2)—in upper outer quadrants of buttocks in anterior fold of muscle

Greater trochanter (2)—posterior to the trochanteric prominence

Knee (2)—at the medial fat pad proximal to the joint line

Digital palpation should be performed with an approximate force of 4 kg. A tender point has to be painful at palpation, not just tender

American College of Rheumatology (ACOR) Criteria for Fibromyalgia

# Fibromyalgia vs CFS



- Most patients who have received the diagnosis of one are also likely to meet the diagnostic criteria for the other
- Simply put,
  - **CFS is fatigue with pain**
  - **Fibromyalgia is pain with fatigue**

# D/D vs Comorbidity - Psychiatric



- **Major Depression**
- **Anxiety disorders**
- **Somatoform disorder**
- **Hypochondriasis**
- **Neurasthenia**
- Debated - whether psychiatric conditions are  
Consequence / Cause / Co-incidental overlap of  
symptoms
- Main overlapping symptoms - fatigue, sleep  
disturbance, and poor concentration

# CFS vs Mood & Anxiety disorders



- A psychiatric disorder (in patients with an existing diagnosis of CFS) was diagnosed in 45.2%; mostly mood and anxiety disorder.
- Studies of clinic attenders with CFS reported that more than **25%** have a current DSM major depression diagnosis, and **50%–75%** have a lifetime diagnosis

	General Population	CFS Patients
GAD	3.5%	30%
Panic Disorder	5.1%	25%

# Barriers to making diagnosis



- Illness model- a biomedical approach by both doctors (GP) and patients
- Poor communication between the patient and the health professional
- Knowledge and attitudes- limited understanding, limited training
- Low priority in the health care setup

# Indian study



- Population survey- Goa
- 3000 women- between 18 and 50 yrs
- 'Chronic fatigue'- reported by 12.1%
- Factors indicating gender disadvantage (notably sexual violence by the husband) and poor mental health were strongly associated with chronic fatigue

*(Vikram Patel et al, 2005)*

# Treatment - *Principles*



- **Engagement:** Building rapport, empathic understanding of distress
- Developing a **therapeutic rationale - individualize**
- **Evolution of a treatment plan:** defined by objective performance targets and time frames.
- **Use psychopharmacology sparingly:** Only when a demonstrable symptom target can be seen
- **Avoid invasive and/or expensive medical testing.**
- Seek opportunities to clarify **importance of psychological factors** as the therapy proceeds



# Treatment - *Guidelines*



## **NICE Guidelines (2007)**

- General strategies
  - Symptom management
  - Function and quality of life management (sleep, rest period, relaxation, pacing, diet)
  - Equipment to maintain independence
  - Education and employment
- Complementary and supplementary care
- Referral to specialist

# Treating Co-Morbidities



- Depression/Anxiety - SSRIs/SNRIs
- Pain symptoms - TCAs/Duloxetine
- Sleep Disturbance - BZDs/Non-BZD Hypnotic

# Pharmacological treatment



## **Pharmacological interventions for symptom control**

- Prescribing of low-dose tricyclic antidepressants, specifically amitriptyline, for poor sleep or pain
- Melatonin may be considered for children and young people with CFS/ME who have sleep difficulties

# Pharmacological treatment



- Drugs with some evidence for CFS
  - vitamin B<sub>12</sub>
  - vitamin C
  - co-enzyme Q10
  - magnesium
  - NADH (nicotinamide adenine dinucleotide) or multivitamins and minerals

# Psychological treatment



- Best evidence base for CBT and GET
- CBT includes
  - educating patient about the etiologic model
  - setting goals
  - restoring fixed bedtime and wake-up time
  - challenging and changing fatigue- and activity-related cognitions
  - reducing symptom focusing
  - spreading activities evenly throughout the day
  - gradually increasing physical activity
  - planning a return to work, and resuming other activities
- The intervention, which typically consists of 12–14 sessions spread over 6 months, helps CFS patients gain control over their symptoms

# Psychological treatment



- Graded Exercise Therapy is based on the model of deconditioning and exercise intolerance and usually involves
  - a home exercise program that continues for 3–5 months.
  - Walking or cycling is systematically increased, with set target heart rates
- The primary component of CBT and GET is a reduction in fatigue is the change in the patient's perception of fatigue and focus on symptoms

# Course and Outcome



- Small minority of patients recover completely
- Most patients either achieve some improvement or remain status quo
- Long term follow up studies - Over time many individuals will not maintain a CFS diagnosis but will not return to their premorbid level of functioning.
- Psychological factors such as illness attitudes and coping style seem more important predictors of long term outcome than immunological or demographic variables

# Conclusions



- CFS predominantly described in the western literature
- Significant burden associated
- Dilemma over status as a psychiatric or medical condition
- No clarity over etiology
- Evidence lacking for pharmacological treatments
- Poor outcome
- Lack of studies in the Indian population



# Future Directions



- Multidisciplinary approach to research and treatment
- Interplay of biological and psycho-social factors in etiopathogenesis to be studied
- Need for cross-cultural research
- Enhancement of awareness in practicing physicians and psychiatrists



Thank you