Overview

- What is fatigue?
- What is the natural history of chronic fatigue states?
- What is the biological basis of chronic fatigue?
  - Acute sickness response and genetic studies
- How can chronic fatigue states be treated?

What is fatigue?

- Fatigue as a ‘sign’:
  - failure of force generation in the muscle
  - physiological or pathological
  - peripheral and central components
- Fatigue as a ‘symptom’:
  - everyday phenomenon
  - disease associated (infective, inflammatory, neurological, mood disorder,…)
  - ‘physical’ and ‘mental’ components

What is chronic fatigue syndrome?

- Unexplained, persistent or relapsing fatigue, that is:
  - of new, definite onset
  - not due to exertion
  - not relieved by rest
  - associated with a substantial reduction in daily activities
- Four or more of:
  - impaired short term memory or concentration
  - sore throat
  - tender lymph nodes
  - muscle pain
  - joint pain
  - headaches
  - unrefreshing sleep
  - post-exertional malaise
- Exclusion of medical and psychiatric disorders

What is post cancer fatigue?

- Significant fatigue, diminished energy, or increased need to rest, disproportionate to any recent change in activity level
- Five or more of:
  - Complaints of generalised weakness or limb heaviness
  - Diminished concentration or attention
  - Decreased motivation or interest in engaging in usual activities
  - Insomnia or hypersomnia
  - Experience of sleep as unrefreshing or nonrestorative
  - Perceived need to struggle to overcome inactivity
  - Marked emotional reactivity (e.g. sadness, irritability)
  - Difficulty completing daily tasks
  - Perceived problems with short-term memory
  - Post-exertional malaise lasting several hours


Can chronic fatigue be measured?

“Neurophysiological” fatigue: a failure of force generation in the muscle

What is the natural history of chronic fatigue states?

- Post-infective fatigue - Dubbo Infection Outcomes Study (DIOS)
  - Prospective cohort study (n=512)
  - Epstein-Barr virus, Rose River virus, Q fever

- Post-cancer fatigue - Follow-up after cancer study (FOLCAN)
  - Prospective cohort study (n=281)
  - Early stage breast cancer, adjuvant therapy

What is the biological basis of chronic fatigue states?

Chronic fatigue is:
- prevalent (~200/100,000)
- disabling
- costly

Chronic fatigue is not:
- a muscle disorder
- a psychiatric disorder
- an active infection
- an immunological disorder
- a sleep disorder
- a hormonal disorder
- a metabolic disorder
- …

Determinants of illness duration

Chronic fatigue is:
- prevalent (~200/100,000)
- disabling
- costly
Acute sickness response to infection

- Stereotyped symptom set associated with infection or inflammation:
  - fevers, sweats, musculo-skeletal pain,
  - neurocognitive difficulties, anorexia, hyperalgesia
  - social withdrawal, mood disturbance
- Immunologically (cytokine)-triggered
  - animal studies
  - cytokine administration in humans
  - correlative studies in natural infection
- Neurologically-mediated

Cytokine production and acute sickness response

<table>
<thead>
<tr>
<th>Reported Symptoms</th>
<th>High</th>
<th>Medium</th>
<th>Low</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td>0.30</td>
<td>0.50</td>
<td>0.70</td>
</tr>
<tr>
<td>Malaise</td>
<td>0.25</td>
<td>0.50</td>
<td>0.70</td>
</tr>
<tr>
<td>Anorexia</td>
<td>0.25</td>
<td>0.50</td>
<td>0.70</td>
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<tr>
<td>Hypoalgesia</td>
<td>0.25</td>
<td>0.50</td>
<td>0.70</td>
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</tbody>
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Genetic risks for severe and prolonged fatigue

- High illness severity: interferon gamma (IFN-\(\gamma\)) +874 T/A (\(p=0.004\))
  - Odds ratio (OR): T allele 2.5; TT genotype 2.9
- Low illness severity: interleukin-10 (IL-10) -592 C/A (\(p=0.03\))
  - OR: CC genotype 1.9
- High illness severity and combined genotype (IFN-\(\gamma\) TT / IL-10 CC) (\(p=0.001\))
  - OR: TT/CC 6.8

How should chronic fatigue be treated?

Double-blinded placebo controlled trials (n=100)

- Antivirals:
  - acyclovir
  - valganciclovir
- Immunological agents:
  - transfer factor
  - intravenous immunoglobulin
  - corticosteroids
  - Ampliten (poly-I-poly-C)
- Vitamin:
  - vitamin B12
  - co-enzyme Q10

Anti-depressants:

- moclobemide
- fluoxetine
- phenelzine
- selegiline

Metabolic agents:

- fluocortisone
- magnesium sulphate

Centrally-active agents:

- galphentra
- modafinil
- L-carnitine
How should chronic fatigue be treated?

- Level 1 evidence for graded exercise therapy (GET) and cognitive behavioural therapy (CBT)

Structure of UNSW Fatigue Clinic program

Outcomes of UNSW Fatigue Clinic program (n=264)

Fatigue severity

Physical function

Mood disturbance

Social functioning

Outcomes of UNSW Fatigue Clinic program (n=264)

Clinic education program for CBT / GET

- Knowledge and skills gap amongst key providers
- Online clinician assessment and training program
- Randomised trial for allied health practitioners
  - Wait list versus online eLearning
  - Before and after assessment:
    - self-reported confidence in knowledge of chronic fatigue
    - self-reported confidence in clinical diagnostic skills
    - MCQ and short answers on case vignettes
  - CPD accreditation
- ‘Open label’ access for GPs, nurses
  - Assessments (45 minutes)
  - Education (~5 hours)
  - https://aelp.smartsparrow.com/v/open/w1aweeta
- Information / advice
  - fatigueclinic@unsw.edu.au

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