Chronic fatigue states

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

Can chronic fatigue be measured?

‘Neurophysiological’ fatigue: a failure of force generation in the muscle

What is chronic fatigue syndrome?

Definition

• 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?

**Definition**
- 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?

**Validated self-report questionnaires and interview schedule**

What is the natural history of chronic fatigue states?

- **Post-infectious fatigue** - Dubbo Infection Outcomes Study (DIOS)
- Prospective cohort study (n=613)
- Epstein-Barr virus, Ross River virus, Q fever

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Percentage (%) with disabling fatigue</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>50 10 10 10 6</td>
</tr>
<tr>
<td>3 months</td>
<td>50 10 15 15 5</td>
</tr>
<tr>
<td>6 months</td>
<td>50 10 15 15 5</td>
</tr>
<tr>
<td>12 months</td>
<td>50 10 15 15 5</td>
</tr>
</tbody>
</table>

* Meet diagnostic criteria for chronic fatigue syndrome

- **Post-cancer fatigue** - Follow-up after cancer study (FOLCAN)
- Prospective cohort study (n=218)
- Early stage breast cancer, adjuvant therapy

<table>
<thead>
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<th>Cohort</th>
<th>Percentage (%) with disabling fatigue</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast cancer (n=218)</td>
<td>24 48 15 11 6</td>
</tr>
</tbody>
</table>

* Meet diagnostic criteria for post-cancer fatigue

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

Dubbo Infection Outcomes Study (DIOS)

<table>
<thead>
<tr>
<th>Illness duration (days)</th>
<th>Low Illness severity</th>
<th>High Illness severity</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 50 100 200 300 400</td>
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</table>

Date Completed: ____/____/ 20____
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


Genetic risks for severe and prolonged fatigue

- High illness severity: interferon gamma (IFN-γ) +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-γ 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
- Ampligen (poly-I-poly-C)

Vitamins:
- vitamin B12
- co-enzyme Q10

Anti-depressants:
- moclobemide
- fluoxetine
- phenelzine
- selegine

Metabolic agents:
- fludrocortisone
- magnesium sulphate

Centrally-active agents:
- galantamine
- 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

Clinician 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 learning
  - Before and after assessment:
    - Self-reported confidence in knowledge of chronic fatigue
    - Self-reported confidence in clinical diagnostic skills
    - MOS 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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