Lessons from research in Chronic Fatigue syndrome

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Incapacitating chronic fatigue

- Secondary to other disease
  - a most common complaint
  - commonly ignored by the doctor
- Chronic fatigue syndrome (CFS)
Doctor I'm so fatigued....

And what other complaints?
CFS

- Chronic incapacitating fatigue
- > 6 months
- Medically unexplained
- Associated symptoms
  myalgia/ arthralgia/ concentration disturbances/ memory disturbances/
  sleep disturbances/

See also CDC criteria (Fukuda et al)
Reasons for negative medical view on CFS:

- Information from outdated psychiatric textbooks
- Inability to diagnose and treat
- Irritation about selfdiagnosis “ME”*
- Strong physical attributions

*Myalgic encephalomyelitis
I know what I have got!
It is ME!
Why didn't you make that diagnosis?
Polarised discussions between

- Doctors who deny the existence of CFS/ME
- Doctors who are convinced it is a psychiatric illness.
- Patients, lay people and doctors who adhere to unscientific and uncritical explanations for CFS.
Can we measure fatigue?

- Questionnaires (CIS, SIP)
- Actometer
- Neuropsychological assessment
- Exercise assessment
CFS etiology & pathogenesis

Prins et al
Lancet 2006

Perpetuating factors

Predisposing factors

Precipitating factors

Prognostic factors

Complaints

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Predisposing factors

Somatic factors
- genetic (no convincing candidate genes)
- metabolic (no evidence)

Psychological factors
- physical inactivity in childhood
- trauma in childhood
- physical hyperactivity in adulthood
Precipitating factors

Patients attribute CFS to:
- Infection (e.g., EBV mononucleosis)
- Intoxication
- Surgery
- Anaesthesia
- Delivery
- Traumatic events
Precipitating factors

- Infection

So far, no unifying cause has been found, hence:
  - either: various causative organisms
  - or: unknown micro-organism
Model perpetuating factors in CFS
Vercoulen et al Psychosom Res 1998

Sense of control → Fatigue

Somatic attributies

Fatigue → Physical Activity

Physical Activity → impairment

Focus on complaints

Somatic factors? → Substrate?

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Somatic perpetuating factors

Causality? Association?
Largely irreproducible

Many investigations into the pathophysiology are flawed by the lack of adequate controls

Adequate controls:
- robust matching
- control for actual stress effects
- the same pre-analytical procedures

Neighbourhood controls (Nijmegen); Twins (Seattle)
TGFbeta-1 in CFS

All patients & controls

All patients

controls

Roerink et al unpublished
Substrate

Central fatigue, hence in the CNS

• Functional studies
• Blood (not where the action is)
• CSF
• Neuro-imaging
• Animal experiments
• Interventions

Netea et al 2007
Cognitive error-related responses are not disturbed

Affective/Motivational error-related response is disturbed

De Lange et al Brain 2004
Brain structure

Independent confirmation in 2 other papers, but:

N.0.
Recent large study
(Van der Schaaf et al Biol Psychiatry 2015)

2016 cohort                  2006 cohort revisited
Grey matter volume

CFS controls                  CFS controls

CFS controls
Pain is related to decreased grey matter
CFS, a perceptional disorder

- Sleep
- Exercise tolerance
- Concentration
- Memory
- Movement registration

Buchwald et al, Vercoulen et al, Bazelmans et al
Natural course of CFS over 18 months

- recovery: 3%
- improved: 17%
- unchanged: 60%
- worse: 20%

Vercoulen et al. 1996
INTERVENTIONS

- Fluoxetine (Prozac®) - no effect*
- Galantamine - no effect
- Food supplement - no effect
- Low dose steroids - effect?
- Cognitive behavioural therapy - effect
- Acclydine: no effect
- Ondansetron: no effect*
- Tryptophane depletion: no effect*
- Anakinra → results pending
CBT for CFS

**effect on fatigue severity**

![Graph showing the effect of CBT on fatigue severity over time.](image)

**CBT-SG** $p = .0001$

**CBT-NC** $p = .0001$

**CBT-SG** $p = .0015$

**CBT-NC** $p = .0016$

Prins et al Lancet 2004
Recovery after CBT

1. Fewer or no symptoms 73%
2. No physical impairment 64%
3. No social impairment 57%
4. No substantial impairment 58%
5. No serious fatigue 58%
6. No serious fatigue and not impaired 51%
7. Positive attitude to fatigue 45%

Knoop, Bleijenberg, et al 2007
Institute of Medicine Consensus: Systemic exertion intolerance disease

Diagnosis requires that the patient have the following three symptoms:

1. A substantial reduction or impairment in the ability to engage in pre-illness levels of occupational, educational, social, or personal activities, that persists for more than 6 months and is accompanied by fatigue, which is often profound, is of new or definite onset (not lifelong), is not the result of ongoing excessive exertion, and is not substantially alleviated by rest, and

2. Post-exertional malaise,* and
3. Unrefreshing sleep*

At least one of the two following manifestations is also required:

1. Cognitive impairment* or
2. Orthostatic intolerance
Prevalence of Postural Orthostatic tachycardia syndrome (POTS)

Adult

- CFS (n=331)  5.7%
- non-CFS (n=318)  6.9%

Adolescent

- CFS (n= 88)  18.2%
- non CFS  (NM=23)  17.4%

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