1. Day 1 - Welcome & introduction

1.1 Professor Holgate welcomed the participants to the workshop and introduced the format for the two days.

1.2 An overview was provided of the MRC CFS/ME Expert Group and its Terms of Reference. The aims of the workshop were then detailed as follows:

- Identifying the underlying \textbf{causes} and \textbf{mechanisms} of CFS/ME:
  - Clinical phenotypes
  - Novel technologies and methodologies to help identify sub-phenotypes
  - Molecular and cellular mechanisms of pathogenesis
- Consensus of priority areas.
- Encouraging new researchers into the field.

Areas proposed for consideration during the workshop included:
- capitalising on current issues and UK scientific strengths including national resources e.g. patient cohorts
- new technologies and technological platforms
- partnership models
- other issues

1.3 Professor Holgate referred to the recent interest in the publication of research linking the retrovirus XMRV to CFS/ME, before going on to summarise the key challenges in the field:

- A large clinical need without sufficient underpinning research.
- Low research capacity; need to encourage a multi-disciplinary approach.
- Grant applications that did not meet current competitive standards for funding.
- Absence of a clear pathogenetic mechanism(s) meant it was difficult to develop therapies “targeted” towards specific biological pathways. As a result current therapies tended to be directed towards symptom support rather than prevention or modifying/halting progress of the condition.
- The need to consider both physiological and psychological mechanisms in developing therapeutic approaches.
• The difficulties inherent in defining phenotype and sub-phenotypes for a complex condition without good knowledge on underlying mechanisms.
• Knowing how best to incorporate new science and technological platforms.

1.4 Professor Holgate advocated a more collaborative approach to move the field forward. A recent example of where such an approach had proved successful in increasing research capacity and impact was in respiratory research.

2. Presentations
(Full slide sets for each presentation are available at Annex 1)

2.1 Dr Esther Crawley provided an overview on the epidemiology of CFS/ME and the current research on phenotyping. The role of the British Association of CFS/ME (BACME) and the current specialist services available for patients were explained. The key points raised were as follows:
• Definitions of CFS/ME were important when investigating prevalence of the disease.
• In adults there were at least 3-6 different phenotypes identified to date and there were currently 3 paediatric phenotypes, suggesting the possibility of a stratified or targeted approach to treatment.
• CFS/ME was considered to be a heritable condition, and several latent factors and risk factors had been identified. Further gene/environment interaction studies were needed to understand the mechanisms at play in disease progression.
• BACME – in 2009 the 13 clinical service centres funded by Department of Health in 2004 were merged with the CFS/ME network. It was estimated that there would be 7,000-8,000 new patients/year assessed by the clinical teams.
• There were currently 30 teams contributing to the CFS/ME National Outcomes Database. Assessment data for more than 3,500 patients (adults and children) since summer 2009 had been collated. It was anticipated that this number would increase to 5,000 patients per year.

2.2 Professor Julia Newton presented an overview of the current research into the role of autonomic dysfunction in CFS/ME and briefly explained the research from her laboratory. She discussed the possible upstream and downstream mechanisms of autonomic dysfunction, such as those relating to control of blood pressure and heart rate, as well as treatment options. The key points raised were as follows:
• With regard to autonomic dysfunction in CFS/ME, there were currently problems regarding diagnosis of both CFS/ME itself as well as with the diagnosis of autonomic dysfunction. Further issues remained concerning the reproducibility, insensitivity of detection equipment and data interpretation.
• New assessment tools with increased sensitivity were progressively being made available.
Studies have shown that 50% of CFS/ME patients have neural-mediated hypotension.

There were overlaps between hypotension in CFS/ME and other diseases e.g. cirrhosis and rheumatoid arthritis.

A new treatment for patients with hypotension involving repeated daily tilt training was described.

2.3 Professor Jim Horne gave an overview of research into sleep disorders and the role of sleep dysfunction in CFS/ME. The key points raised were as follows:

- Some sleep disorders (eg apnoea/hypopnoea, restless leg syndrome, nocturnal myoclonus) can be manifested as CFS/ME, and it was important to screen for these.

- CFS/ME can produce sleep problems that can rebound back onto CFS/ME. For example, a disruption of the body clock (circadian rhythm), leading to sleeping excessively at the wrong time of day, to cause 'post-sleep inertia' (rather like 'jet-lag') with symptoms similar to/further aggravating CFS/ME.

- Stabilisation of the circadian rhythm can be helped by: 1) remaining under daylight/ fairly bright indoor light throughout daytime hours, and 2) using melatonin about 2h before bed-time (and avoiding bright light at night).

- Nevertheless, some patients with fairly normal circadian rhythms do take too many naps in the day, thus reducing sleep need at night and causing disrupted, unrefreshing night-time sleep.

2.4 Professor Maria Fitzgerald provided a comprehensive overview of the complex mechanisms and processes involved in pain. The role of pain in CFS/ME was also discussed. She highlighted the importance of pinpointing when pain became chronic. The key points raised were as follows:

- The purpose of pain was primarily defensive and a warning mechanism. However this mechanism could become maladaptive.

- Pain processing occurred at multiple sites. Furthermore, pain mechanisms were complex, combining sensory, motor, autonomic and affective components which could also lead to altered brain function resulting in, for example, anxiety and insomnia. These changes were dependent on individual differences, age, gender and culture.

- It was unclear whether pain in CFS/ME comprised either of peripheral components, altered central nervous system (CNS) processing and altered endogenous factors or a combination of these. In other conditions such as fibromyalgia, both altered CNS processing and altered endogenous factors were a feature of pain. There was also evidence of altered cortical pain processing in the brain.

- Potential causes of pain in CFS/ME may include an increased limbic system involvement, decreased endogenous descending control, enhanced temporal summation, nociceptor sensitisation, genetic determinants and early life experience.
• Improved animal models of pain in CFS/ME were needed as a basis for research into underlying mechanisms, as were improved ways of defining and quantifying fatigue.

2.5 Professor Gijs Bleijenberg presented an overview of current research in clinical psychology in CFS/ME and outlined possible future directions in this area. The key points raised were as follows:

• The aetiology of CFS/ME could be divided into multi-factorial predisposing, precipitating and maintaining factors.
• Predisposing factors included neuroendocrine dysfunction; gender; psychiatric illness; high physical activity in adulthood; low physical activity in childhood.
• Precipitating factors included infectious triggers; fatigue; pain; physical inactivity.
• Less was known about perpetuating factors and the key question was how and when did certain factors become perpetuating.
• Current treatments were aimed at symptom management and included cognitive behavioural therapy and graded exercise therapy.
• Neurobiological changes were reported in CFS/ME e.g. changes in patterns of cerebral activity and decreased grey matter volume. However, it was not yet known whether these changes were as a result of the condition or whether they were central to the disease process.
• Possible future directions for research:
  o Large population based studies to increase insight in the development of CFS/ME.
  o Smaller cohort studies of groups at high risk for developing CFS/ME with an emphasis on the development of the maintaining factors.
  o Research and mediation analyses of treatment studies; experimental studies to discover mechanisms.
  o Studies investigating neurobiological or physiological markers of CFS/ME in relation to treatment effect.
  o Early detection of CFS/ME by physicians and promoting healthcare seeking by patients.

2.6 Professor Phil Cowen provided a summary of imaging techniques and studies in CFS/ME and other disorders. The key points raised were as follows:

• Technologies such as PET/SPECT, ligand PET, MRI, MR Spectroscopy and fMRI could be useful tools in helping to understand CFS/ME pathophysiology.
• In some respects, imaging studies of CFS/ME patients have shown similar findings to those using subjects with depression. For example:
  o Structural morphometry studies have shown reduced grey matter volume.
o Decreased binding of brain 5-HT1A receptors using PET.

o Increased neural activation during tasks of working memory. Specifically in CFS/ME patients proton MRS detected an increase in ventricular lactate, which had been postulated as a potential biomarker for CFS/ME, perhaps representing evidence of mitochondrial dysfunction.

- Currently there was an overall lack of understanding of neural correlates of central fatigue in relation to functional brain imaging.
- The current evidence base in the field was unreliable due to the small patient numbers involved and the lack of consistency in experimental design. Increased sample sizes were needed coupled to more robust methodological approaches.

2.7 Professor Chris Ponting discussed new technologies in relation to genetic studies and their potential for use in CFS/ME research. The key points raised were as follows:

- Susceptibility: were viral or other environmental triggers impacting on a vulnerable host? Further study of gene/environmental interactions was needed.
- For successful genome wide association studies (GWAS) large sample numbers from well phenotyped patients were needed.
- It was possible to identify gene variants for low-moderate effects, which may be an issue for CFS/ME. For example a GWAS on height found that 40 genes account for only 5% of heritability.
- It was important to discover biological pathways implicated by genetic studies, as opposed to single abnormalities as these might prove to be more informative.
- Most complex disease associations appear in non-coding regions of the human genome whose mechanisms mostly remain enigmatic.
- There were currently limitations in analysis, storage and interpretation of the large data sets that will be generated in genomics and genetics in the next 5 years.

2.8 Professor Anthony Pinching gave an overview of the possible role of immunity and infection triggers in CFS/ME. The key points raised were as follows:

- Whilst chronic infection has been investigated for many years as a possible pathogenetic mechanism, the balance of evidence now tends to favour persistent immune activation or dysregulation, triggered by infection or other events that have similar impact.
- Patient histories indicate the common triggering role of a wide range of infections, and also provide clues to altered immune function in association with ongoing disease.
- Altered immune factors, e.g. decreased natural killer cell function, Th1-Th2 cell imbalance, elevation of both pro and anti-inflammatory cytokines have been associated in CFS/ME, and may be further elevated two days after exercise or activity.
• The relationships between predisposing and perpetuating factors in these changes have yet to be established, but prior genetic and environmental factors are both likely to influence immune responses to infections.

• The recent XMRV retrovirus study had produced interesting results. However the involvement of XMRV remained unproven and the study would need to be replicated using fresh biological samples, different methodologies, other cohorts and disease controls. It would be premature to use tests for this agent in diagnosis, or to initiate treatment studies, until such replication had been achieved.

2.9 Professor Paul Moss discussed the possible role of virology in CFS/ME and presented a review of the current research in this area. The key points raised were as follows:

• Many studies have shown that infection is a strong candidate for triggering CFS/ME.

• Chronic infection was often linked to mood changes.

• CFS/ME had been associated with multiple viruses e.g. herpes viruses (CMV, EBV, HHV-6, HHV-7) as well as parvoviruses, enteroviruses and retroviruses such as XMRV.

• An imbalance between memory and naïve circulating and lymph node T cells has been shown in some studies.

• Small studies had been undertaken to investigate possible novel therapeutic interventions using antiviral approaches, e.g. acyclovir, monoclonal antibodies.

• A model was proposed by which a chronic response to infection might lead to fatigue and lack of exercise which could potentially escalate to a self-reinforcing cycle.

2.9 During the open session, the recent findings implicating a role for the XMRV retrovirus in CFS/ME were discussed. Attendees agreed that it would be important that the XMRV findings were replicated before treatment options could be considered, as well as extending the study to other CFS/ME patient groups in other countries. A consensus should be reached regarding the methodologies to be utilised between different research laboratories while research should be undertaken in well characterised cohorts. Studies in patients that have been recently diagnosed with CFS/ME should also be considered in order to minimise the number of patients with co-morbidities which could produce confounding results.

2.10 During the group discussion Sir Peter Spencer and Dr Charles Shepherd outlined a feasibility study for setting up CFS/ME post mortem and in vivo tissue banks which was being funded jointly by Action for ME and the ME Association. Sir Peter emphasised that the charities in this area were very small compared to other disease-related charities and therefore obtaining funding for large studies was challenging.

2.11 Attendees highlighted that there were potentially many opportunities that could open up research into CFS/ME. For example, little was known about fatigue mechanisms and investigating fatigue in healthy individuals could provide useful clues in understanding the aetiology of CFS/ME.
Since anxiety and depression comprised a large part of the symptoms of CFS/ME alongside other symptoms such as pain, the interaction between biological and psychological mechanisms should be explored, particularly as there was scope to investigate anxiety from the perspective of autonomic nervous dysfunction.

Another cross-cutting area that could prove fruitful to explore was that of mitochondrial function and energy metabolism.

2.12 In summing up the day’s discussions, Professor Holgate noted the many potential interesting avenues for research. Going forward, the right infrastructure needed to be in place, aided by the adoption of a collaborative approach.

3. Day 2 - Working group discussions

3.1 Participants were divided into three mixed groups for discussions at the beginning of the second day, before reporting back in a plenary session. Each group was asked to identify the research priorities and raise any other issues that they felt had not been addressed thus far during the workshop, as well as the following areas:

- group 1 - current UK strengths and resources
- group 2 - partnership models
- group 3 - new technologies and technological platforms

3.2 The reports from each group highlighted the following points:

**Group 1 – Research priorities and UK strengths**

**UK Strengths**
- Existing research cohorts of CFS/ME patients – there were several well characterised cohorts already established including trial cohorts such as PACE.
- Birth cohorts (e.g. “1958” and ALSPAC cohorts which had genetic information) for hypothesis generation. Whilst these were less well characterised it would still be possible to generate results in research studies.
- CFS/ME National Outcomes Database.
- Strong research teams particularly in epidemiology, imaging, gene sequencing, health psychology and non-pharmacological intervention. This was further enhanced by a general willingness to work in multi-disciplinary teams.

**Research priorities**
- To establish a large cohort with broad case definition identified early in primary care before CFS/ME became established e.g. first presentation following viral illness with fatigue and interference with normal activities. This could be followed up with more intensive phenotyping and obtaining biological samples (including samples for sequencing, metabolomics etc) to identify variables/predictors associated with developing confirmed CFS/ME.
In addition to identifying priority groups for intervention studies this would also allow the exploration of the implications of different definitions/cut off points in defining established CFS/ME.

- To identify possible ‘early win’ interventions for phase 2 and early phase 3 clinical trials - e.g. targeted use of cytokines; melatonin for those with sleep problems.
- To undertake genome-wide association studies (GWAS) to identify the genetic components of CFS/ME and possible new targets for intervention. This would be dependent on the availability of well characterised cohorts.
- To develop more comprehensive outcome measures.
- To encourage work across the different existing cohorts (including trial cohorts), e.g. for assessing predictive markers of disease and confirming hypotheses generated in other data sets.

3.3 **Group 2 – Research priorities and partnership models**

**Partnership models**

- A co-ordinated, structured, strategic and collaborative research approach would be needed in moving the field forward.
- Exploring the use of other fatigue-related diseases (such as multiple sclerosis and cancer-related fatigue) as control models for CFS/ME, and utilising existing expertise from these areas in the CFS/ME field.
- Establishing a multi-disciplinary group involving not only scientists (e.g. immunologists, fatigue experts, neuroscientists, psychologists and psychiatrists, neurologists and geneticists) but also the clinical networks and health professionals.
- Pharmaceutical industry involvement would be beneficial, perhaps at a later stage.

**Research priorities**

- Databases of patients with CFS/ME characterised according to agreed criteria. Phenotype identification could only progress if linked to good infrastructure with all groups using the same criteria. This could provide benefit not only in replication of studies but also of increasing ‘n’ numbers. It was also essential to collect biological samples from early-stage disease which would have no or minimal confounding factors which occurred with long-term disease.
  
  Good clinical diagnosis and standardised measurements and assessments were essential to enable comparisons across data sets. Therefore a collaborative approach with researchers working closely with clinicians and other health professionals would be important.
- Patient reported outcomes and quality of life measures.
- The establishment of tissue banks with samples from well characterised patients and controls.
- Improved definition of fatigue and improved understanding of fatigue mechanisms.
Virology and infection triggers – there was potential for virology to be studied in CFS/ME as part of the complex disease pathogenesis. In addition to continued research in this area it would be important for the XMRV study to be replicated before pursuing this avenue of investigation through to clinical trials.

3.4 **Group 3 – Research priorities and new technologies and technological platforms.**

**New technologies/technological platforms**

- Imaging technologies such as fMRI, EEG and MRS and pathological studies using tissue could be utilised for neuroanatomical studies and neurophysiological studies of fatigue.
- Better animal models were needed both of the whole disease and aspects of the disease physiology.
- Genetic studies (GWAS) – needed to be nationally and internationally standardised using well phenotyped samples.
- Improved data collection tools were needed.

**Research priorities**

- Identification of phenotype and phenotypic subgroups. This would require access by researchers to raw data (not prior filtered) for replication studies and different measurable entities for different studies. It would also be important to extend the minimum clinical data currently collected.
- Psycho-physical studies – it was important to continue to undertake small and focussed pathophysiological studies investigating perception, behavioural and physiological response in patients.
- Establishment of longitudinal population-based studies including natural history cohorts which were well focussed and avoided selection bias. Data generated by these studies could be underpinned by co-ordinated tissue collections and repositories.
- Studies on neuro-immunological interactions.

3.5 During the plenary discussion the following points were highlighted:

- It was agreed to be important not to stigmatise the condition, both in terms of treating and caring for those with CFS/ME, and for attracting researchers to the field. CFS/ME was a complex disease that comprised the interaction of different biological, physical and psychological mechanisms. The interactions between these different mechanistic pathways were important and further mechanistic studies needed to be undertaken. Pathways may differ between individual patients and therefore the characterisation of phenotype(s) was paramount.

Phenotype characterisation would facilitate the identification of biomarkers. However, given the complexity of the disease and the many current unknowns, this objective was likely to be achieved
only in the longer term. The objective for the shorter term should be to increase the current knowledge base of the pathogenesis.

- Clarification of the definition of CFS/ME was important. Without this it would be difficult to encourage new researchers from other fields to undertake research in this area.
- Successful collaborative approaches required each stakeholder to take ownership of a particular area.

3.6 Professor Holgate briefly summarised the workshop outcomes which would be discussed by the CFS/ME Expert Group during the spring of 2010. The Group would prioritise the opportunities that were tractable for both the short and longer term and feed back the outcome to the community.

Professor Holgate thanked all the participants for their valuable contributions and closed the meeting.
CFS/ME phenotyping & epidemiology

Esther Crawley

In 15 minutes

- What are we talking about?
- Is it just fatigue?
- What about other illnesses?
- Prevalence and risk factors
- Phenotypes in CFS/ME
- National Outcomes Database

What are we talking about?

Fatigue or CFS/ME?

- Adults: “tired all the time” 25%
- 10% of primary care consultations
- Young people: 20.5% girls, 6.5% “severe fatigue”

Definitions & Criteria

<table>
<thead>
<tr>
<th></th>
<th>Time</th>
<th>Disability</th>
<th>Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>CDC ’94</td>
<td>6 months</td>
<td>Substantial functional impairment</td>
<td>4</td>
</tr>
<tr>
<td>Australia ’90</td>
<td>6 months</td>
<td>Substantial functional impairment</td>
<td>Cognitive symptoms req. Mental fatigue</td>
</tr>
<tr>
<td>Oxford ’91</td>
<td>6 months</td>
<td>Functional impairment</td>
<td>4 required + 2 cognitive, 1 autonomic, 1 neuroendocrine</td>
</tr>
<tr>
<td>Canadian ’03</td>
<td>6 months</td>
<td>Substantial reduction</td>
<td>1 symptom</td>
</tr>
<tr>
<td>NICE ’07</td>
<td>4 months</td>
<td>Substantial reduction</td>
<td>1 symptom</td>
</tr>
<tr>
<td>NICE ’07 (guidelines)</td>
<td>4 months</td>
<td>Substantial reduction</td>
<td>1 symptom</td>
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</table>

Sullivan 2005, Psychological Medicine 35, 1337 - 1348

Cullen 02; Skapinakis 03; Wolbeek 08
What about other illnesses?

Other illnesses

- Qualitative and quantitative studies – Liver, Arthritis, Cancer
- Other? Overlap illnesses? Frequent co-morbid illnesses?
  - CFS/ME, low back pain, irritable bowel syndrome, chronic tension headache, fibromyalgia, TMJ dysfunction, major depression, panic attacks.

Jones '09; Bennett '07; Schur 2007

Kato '09 31,318 twins

Kato '09 31,318 twins

Is CFS/ME all one illness?
Phenotypes

- Adults:
  - 1998 – 2008: 9 studies - 3 - 6 phenotypes

- Children:
  - Paediatric 3 Phenotypes: musculoskeletal; migraine; sore throat (May 09)

- Hickie '09: 33 population studies (37,724 people)
  - 5 phenotypes: musculoskeletal; neurocognitive; inflammation; sleep disturbance; mood disturbance

Prevalence

- NICE and CMO: "at least" 0.2 to 0.4%

- Adult:
  - Prevalence 2.57% (USA)
  - Similar: Sweden, Brazil, India etc

- Paediatric:
  - Prevalence 3/12 ALPSAC of 4.6% (0.1% housebound)

- Difference in prevalence?
  - Definition (length of time & symptoms); recruitment (diagnosis or population screening)

Risk Factors

- Systematic review: Hempel 2007: none replicated

- Known: Older age; female; lower SE class; heritable component; infection (Eg EBV)

- Trauma: Heim '09: Retrospective case – control

- Ethnicity: Dinos '09: meta analysis - ↑ Native Americans OR 1.5 (CI1.08 – 56.4)

- Infection: Katz '09: EBV 6/12(13%), 1 yr (7%), 2 yrs<4% ; Kerr '08: parvovirus and pre-existing stress (OR 25.7, CI 1.7-121.9)

- Mood: Harvey '08 "Psychiatric illness" in adults

British Association CFS/ME

- DH funded clinical services 2004
  - 13 Centres, 38 adult clinical teams, 11 paediatric teams
  - ~ 6000 adults 600 children p/a

- 2009 merged with CFS/ME network
  - Estimated 7000 – 8000 new patients a year

Specialist services

- Minimum Data Set
  - Aim: Benchmarking & Infra structure
  - At assessment:
    - Demographic data, age, postcode, sex, ethnicity, area of residence, employment status and hours worked/ in education, time to assessment
    - Infections: 11 item Chalder fatigue, SF 36 (physical function), HADS, pain VAS, 12 month goal
  - Follow up - 12 months
  - Audits '07 & '08: 70% teams collecting MDS, majority collecting additional data
National Outcomes Database

- 2006: Regional Database
- 2009: Regional to National Dataset
- Currently:
  - 30 teams contributing data
  - Assessment data >3500 adults and children
  - Estimated 5000 adults and children a year
  - Probable 75% follow up

Next steps

- Phenotypes presenting to NHS services
- Evaluating models of care
- GWAS

Summary

- What are we talking about?
  - Definitions are not empirically derived
  - Other illnesses
  - Prevalence and risk factors
  - Need further work on phenotypes
- National Outcomes Database
- Potential for future research

Thanks to

- Alan Emond & CCAH Bristol
- Slides: Nic Timpson & Simon Collins
- Andrew Haig Ferguson, Lou Morphey, Rodney Saunders
- Peter Shiarly
- Collaborators: Jonathan Sterne, Margaret May, Linda Hunt, Andy Ness, George Davey-Smith, Paul Stallard
- The Clinical team: Heather Hill, Avril Missen, Jackie CC, Bev Knops, Carol Salter
- The children and their families
Autonomic dysfunction

Julia L Newton
Newcastle University
MRC workshop 2009

What is autonomic dysfunction?

The history
Rowe et al.,
Is neurally mediated hypotension an unrecognised cause of chronic fatigue?

Since then…. >200 publications looking at vascular function in CFS

Why are we still speculating about the role that AD plays in CFS?
- Diagnosis of CFS
- Reproducibility
- Non-specific autonomic testing in inexperienced hands
- In sensitive equipment (underplaying the role of blood pressure regulation)
- Diagnosis of autonomic dysfunction

What is happening now?
• Better objective and subjective assessment tools
• Dynamic testing with real time heart rate and blood pressure
• Increased sensitivity
What is happening now?

• Better objective and subjective assessment tools
• Dynamic testing with real time heart rate and blood pressure
• Increased sensitivity
• Associations don’t disappear

What might the mechanisms be?

• Upstream
• Downstream

Dysautonomia-Associated Fatigue (DAF)

Newton et al., QJM 2007

Muscle MR spectroscopy – 2 mins exercise

Jones & Newton JIM (in press)
Loss of regulation by autonomic nervous system

Hollingsworth et al., AJM (submitted)

Cardiac function by impedance cardiography

Left ventricular work index – marker of myocardial contractility
Left ventricular work index – marker of myocardial contractility

Hearts of those in the CFS group working harder in response to the stress of standing compared to the control group.

Fatigue Severity in Chronic Disease Cohorts in Newcastle

Perceived fatigue is comparable across chronic disease groups

Central Processes

Treatment opportunities ..
In summary

- Significant historical data
- Modern techniques
- Improved diagnostic criteria
- Emerging data to suggest mechanisms

Fatigue Work is Supported by

Liver North
Northern CFS/ME Clinical Network
JRRG
ME Association

Questions?

Julia.newton@nuth.nhs.uk
CFS/ME & SLEEP
Jim Horne

CFS/ME = Heterogenous Disorder

eg: Vollmer-Conna U et al 2006
51 sufferers with mixtures of: obesity, sleep hypopnoea, depression, stress, sleep disturbance, psychosomaticism

CFS & Psychological Status: any bearing on sleep?
- Courjaret et al 2009: no obvious personality factors
- Prins et al 2005: psychiatric status not affect outcome from CBT treatment

‘Non Restorative Sleep’: Non-specific - seen with chronic insomnia
- Persistent dissatisfaction with sleep
- ‘Tossing & turning’ in sleep
- Difficulty getting started in the morning
- Stressful lifestyle
- Anxiety, Irritability, Depressive symptoms
- Mental and physical fatigue: ‘Tiredness’
- No EDS unless other sleep disorder (e.g. OSA PLMS)
- Fibromyalgia
- ‘Inhibited/Repressed’
- Repeated consultations with physician
- Likely to seek ‘alternative medicine’

CFS
Sleepiness vs Fatigue/Tiredness

- Watson et al 2004
  20 discordant monozyg. twins – No diffs in objective sleepiness. Those with CFS mistake fatigue for sleepiness.
- Unger et al 2004
  “while fatigued, CFS subjects not sleepy”
- Randall et al 2005
  Modafinil – mixed effects – largely ineffective.
  Thus, CFS not sleepiness

Sleep EEG in CFS

- Armitage et al 2009
  Sleep EEG itself - ‘normal’
  CFS higher ‘fatigue’ but lower subjective & objective ‘sleepiness’
- Van Hoof et al 2007
  Delayed SO, low sleep efficiency and ‘alpha-delta sleep associated with anxiety’
- Neu et al 2007; Maier et al 2007
  ‘unrefreshing sleep’ - sleep quality ok but misperceived
- Armitage et al 2007
  ‘blunted SWA response’
Sleep may not seem disturbed

Rumination’ in sleep – alpha delta sleep (cf. fibromyalgia)

The Mind in Sleep

Worn Out Syndrome - Post Sleep Inertia

IT’S NOT SLEEPINESS!

Easily produced in healthy adults

Symptoms (last up to 4 – 5 h):
- tiredness, “sleepiness”, lethargy, confusion, heavy limbs, difficulty getting going, feeling “down”

Causes:
- morning oversleeping, sleeping more than 1h at unusual time of day, jetlag

Similarities with/Aggravates CFS?
- Excess sleep at ‘wrong time of day’?
- Worsens CFS?

CFS - ‘fatigued but not sleepy’

Aggravated by WOS – Sleep Inertia?

- Excess daytime dozing
  - sleep at wrong time of day–
  - sleep fragmentation at night?
- Sleep/circadian uncoupling
- Treat:
  - fixed wake up time
  - plenty of real or artificial daylight
  - 3-5mg Melatonin @ dusk/3h before bed

CFS:

Sleep out of Synch with Body Clock?

Too much daytime dozing?

Van Heukelom et al 2006
- phase delay of sleep in CFS – those with with DLMO later than 22.00h – treat with 5mg Melatonin 3h before DLMO
Other Hidden Sleep Disorders?

Sleep may not seem very disturbed compared with controls – but is differently disturbed in CFS

- Apnoea-hypopnoea
- Restless legs /Periodic limb movements

Sleep Apnoea/Hypopnoea or RLS/PLMD?

Reeves et al 2007
18% had sleep disorder (vs 7% controls). Rest: sig more apnoeas – ‘not clinically meaningful’

Guilleminault et al 2006
NonREM instability ‘related to subtle, undiagnosed sleep-disordered breathing’

Ball et al 2004
CFS twins higher AHIs, ‘can’t alone account for sleep complaints’

Fossey et al 2004
58% undiagnosed SA/H or RLS/PLMD. ‘Psychol. disturbances caused by chronic sleep disturb.’

Togo et al 2008
Sleep more disturbed – ‘no sleep disorders’ - but why disturbances?

Hypoventilation in Sleep (Hypopnoea)

‘INSUFFICIENT BREATHING’
- More likely reasons
  - weakness in breathing muscles?
  - Poor central responses to blood levels of: oxygen (hypoxia) and carbon dioxide (hypercapnia)
  - Obese

Central Sleep Apnoea?

- No airway collapse/gagging – respiratory drive stops – nil respiratory movements
- Hypoxia etc causes brief awakening – gasping for breath - little snoring
- Sleep returns – awakening too brief to remember
- Frequent episodes severely disrupt sleep, and excessive daytime sleepiness (EDS)

Periodic Limb (usually leg) Movements in Sleep

TWO RELATED DISORDERS:

RESTLESS LEGS
- “Crawling” sensation usually in thighs causing need to move legs

NOCTURNAL MYOCLONUS
- Kicking of lower leg

Periodic Limb (leg) Movements in Sleep

- Disturb sleep
- Patient usually not aware of extent of PLMS
- More common in: older people, pregnancy, iron deficiency, renal failure
- Treatment –
  - Dopamine receptor agonists (e.g. Mirapexin, Requip)
Overnight Actimetry?

Body Movements in Normal Sleep

Validation of Actigraphy vs Sleep EEG

THANKS

Work & Interests of Sleep Research Centre

- FUNDAMENTAL
  - Sleep function – for brain rather than body
  - How much sleep do we really need – and what type?
  - Cortical activity in sleep – neuroimaging with EEG
  - Sleep loss and frontal lobe (‘executive’) functions – including similarities with natural ageing
  - Sleep, thermoregulation, obesity (BMI) & metabolic syndrome
- APPLIED
  - Sleep-related road crashes: epidemiology, mechanisms, countermeasures, potentiation by alcohol and medicines, medico-legal issues
  - Sleep loss, sleepiness at work, shiftwork
  - Sleep loss and social interaction/cognition
  - Radio frequency radiation (mobile phones) - brain effects
  - Children’s sleep
  - Sleep apnoea
- CLINICAL
  - Sleep in old age
  - Insomnia
  - Chronic fatigue syndrome

‘Non Restorative Sleep’:

Specific Causes

- chronic pain
- chronic infection (e.g. lyme disease)
- circadian rhythm disorder
- depression and/or anxiety
- endocrine dysfunction (e.g. hypothyroidism)
- evident sleep disorders (OSA, PLMS),
- poor sleep environment (hot, cold noisy)
- disturbing bed partner
- other sleep fragmentation
Pain and chronic fatigue syndrome

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The purpose of pain

- Caused by actual or potential injury or tissue damage
- Defence mechanism
- Warning, protection
- Escape
- Rest, healing
- Learning

Can be maladaptive

- Poorly related to an actual injury: back pain, fibromyalgia, migraine
- Too late to be a warning: cancer pain
- Neuropathic or generated by damage to the nervous system itself: post-surgical, postviral pain
- Causes suffering, depression, anxiety, lack of mobility
- Huge economic burden, loss of working days, income support

Physiological & pathological pain

- Nociceptive
- Persistent
  - Inflammatory
  - Neuropathic
  - Can become chronic

Inflammatory versus neuropathic pain

Damage to the peripheral nerves or central sensory pathways

Tissue damage - build up of inflammatory agents in the damaged area

Complex nature of pain

- Sensory component – but different from other sensations
- Motor and autonomic component
- Affective component – unpleasant, threatening and aversive
- Can alter brain function – anxiety, insomnia, etc
- Context, attention
- Individual differences
- Culture, gender, age
**Multiple sites of pain processing**

- **Cortical sensory processing**
- **Limbic system, affective component**
- **Brainstem control systems**
- **Spinal sensory component**

**Peripheral component to pain in CFS?**

- Plasticity in primary afferent nociceptive nerve fibres by which an acute inflammatory insult or environmental stressor can trigger long-lasting hypersensitivity of nociceptors to inflammatory cytokines.
- This "hyperalgesic priming," depends on PKCε and a switch in intracellular signaling pathways that mediate cytokine-induced nociceptor hyperexcitability.

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**Altered CNS processing in CFS?**

- Psychophysical evidence abnormal processing of experimental pain
- Temporal summation of pain (wind-up) assessed, using repetitive thermal stimulation.
- Fibromyalgia patients perceived
  - greater intensity of the first stimulus within a series
  - greater temporal summation within a series.
  - after-sensations that were greater in magnitude, lasted longer and were more frequently painful.

**Altered endogenous pain control in CFS?**

- Descending inhibition of pain from endogenous brainstem opioid networks operating at spinal cord level. Mediates effects of attention, expectation etc.
- Typically demonstrated experimentally by 'diffuse noxious inhibitory control' (DNIC), where noxious stimulation of one region of the body decreases pain from another region.
- Fibromyalgia patients lack DNIC effects on experimental pain, compared to normal control subjects.

**Altered cortical pain processing in CFS?**

- Numerous areas of the cortex are involved in pain perception. Not one exclusive area - a ‘pain matrix’.
- To test difference in cortical processing, need to keep perceived pain intensity the same in each group.

**Do some people have a genetic predisposition to feel more pain?**

- Single nucleotide polymorphism (SNP)-based genetic association studies suggest following genes related to pain sensitivity
  - **COMT** (encoding catechol-O-methyltransferase),
  - **GCH1** (encoding GTP cyclohydrolase 1)
  - **OPRM1** (encoding the µ-opioid receptor)
- Recent suggestion that DRD3 Ser9Gly polymorphism is related to pain in fibromyalgia.
- Story is more complicated than the original studies suggested.
- Plans to incorporate genotyping information into clinical pain practice is premature.
Does early life experience affect pain perception in adult life?

- Generalised reduction of skin sensitivity all over the body
- Localised increase in pain sensitivity on repeat injury in the area of early damage


The need for animal models of pain in CFS

- New model that depletes biogenic amines (serotonin, noradrenaline and dopamine) with reserpine, throughout the body including peripheral and CNS.
- Muscle and cutaneous mechanical hyperalgesia, loss of the biogenic amines in the CNS, and accompanying depression.
- Hyperalgesia is reversed by antidepressants and anticonvulsants, but not non-steroidal anti-inflammatory drugs.
- Not known if animals treated with reserpine have other symptoms associated with FMS such as fatigue, anxiety, and sleep disturbance


Potential causes of pain in CFS

- Decreased endogenous descending control
- Enhanced windup
- Nociceptor sensitization
- Genetic determinants?
- Early life experience?
Possible directions of future studies in chronic fatigue syndrome, learning from current state

Professor Gijs Bleijenberg
Expert Centre Chronic Fatigue
Radboud University Nijmegen Medical Centre
The Netherlands

Scientific research
- cfs
- cancer related fatigue
- chronic fatigue in chronic diseases
- chronic fatigue in Cambodia veterans

Patient care
Education

Possible directions of future studies in Chronic Fatigue Syndrome

- Population based studies to increase insight in the development of CFS
- Cohort studies of groups at high risk for developing CFS with an emphasis on the development of the maintaining factors
- Process research and mediation analyses of treatment studies; experimental studies to discover mechanisms
- Studies investigating neurobiological or physiological markers of CFS in relation to treatment effect
- Action research: early detecting of CFS by physicians and promoting healthcare seeking by patients

The multi-factorial etiology of CFS

- Predisposing factors ➢ Patient characteristics or circumstances present long before onset
- Precipitating factors ➢ Triggers of CFS, also during period before fatigue becomes chronic (6 months)
- Perpetuating factors ➢ Maintaining factors

Model of CFS

Precipitating factors ➢ FATIGUE ➢ Perpetuating factors

Predisposing factors

Time
**Predisposing factors**

Findings from cohort & case control studies

- No replication of a predisposing factor in more than two studies (Hempel et al, 2007)
- Most factors only tested in one study

Examples
- Female sex
- Older age
- Low physical activity in childhood
- High physical activity later life
- Childhood trauma
- Neuroendocrine dysfunction
- Psychiatric illness

**Directions of future studies in Chronic Fatigue Syndrome**

1. Population based studies to increase insight in the development of CFS are needed

**Precipitating factors**

Findings from cohort studies

- Cohort studies looked at groups where a potential trigger (virus, absence of work) already occurred
- Not only the trigger, but also factors during the period until fatigue becomes chronic (6 months) are considered as precipitating

Examples:
- Fatigue (severity) in several studies
- Pain symptoms
- Physical inactivity
- Days spent in bed at onset of infection
- Number of visits to GP
- Low physical functioning
- Sick certification

**Precipitating factors**

- Same problem: seldom replication

**Perpetuating factors**

- Cognitions and behaviours in response to fatigue are found to perpetuate symptoms
- Little is known about the process from precipitating factors to perpetuating factors. Especially, how and when certain factors become perpetuating.

**Directions of future studies in Chronic Fatigue Syndrome**

2. Cohort studies of groups at high risk for developing CFS with an emphasis on the development of the perpetuating factors are needed
A model of perpetuating factors
(Vercoulen et al, 1998)

- Low self-efficacy
- Somatic attributions
- Decreased physical activity
- Focussing on bodily symptoms
- Fatigue

Common factors in models of perpetuating factors
(based on cohort studies)

- Fatigue related cognitions (e.g. focus on bodily sensations or somatic attributions)
- Lack of physical activity

Interventions aimed at perpetuating factors

- Graded exercise therapy
- Cognitive Behaviour Therapy specific for CFS (graded activity + fatigue related cognitions)

Efficacy of Graded Exercise for CFS

- Both GET and CBT reduce fatigue and disabilities
- What are possible mechanisms of change?
- Knowledge of mechanisms of change can improve treatments and enhances insight in what is central to the disorder

Efficacy of CBT for CFS
The mediating role of physical activity

Assessment of physical activity

Increase in physical activity measured by actigraphy

Mediation analysis of three RCT’s

Moss-Morris et al, 2005, GET

Experimental studies on maintaining factors of CFS

The mediating role of physical activity

Chronic Fatigue Expert Centre

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Moss-Morris et al, 2005, GET

Experimental studies on maintaining factors of CFS

Chronic Fatigue Expert Centre

12 weeks of graded exercise

- 25 patients in GET and 24 in CG
- GET: heart rate monitor, daily exercises
- Significant more reduction in fatigue in GET

Possible mechanism:
- Increase in fitness was not related to reduction of fatigue, but decrease in symptom focussing was

All trials showed a significant decrease of fatigue after CBT compared to control condition

- In none of the trials the effect of CBT on fatigue was mediated by a change in physical activity
- Patients can recover without an increase of their physical activity

Experimental studies on CFS maintaining factors can help to better understand the mechanisms

Some examples:
- VR experiments; disentangling exercise and perception of exercise
- Laboratory experiments on attentional bias; studying attention focussing and symptoms/disability
Directions of future studies in Chronic Fatigue Syndrome

3. Process research and mediation analyses of treatment studies as well as experimental studies in order to better understand mechanisms of change and maintaining mechanisms are needed.

Neurobiology and CFS

The symptoms in CFS (a.o. concentration and sleep problems) suggest a Central Nervous System dysfunction.

Neurobiological abnormalities

- Altered pattern of cerebral activity (fMRI)
- Reduced grey matter volume
- Changes in functioning of HPA-axis
- Different pattern of central neurophysiological activity during movement

The problem is:
What do these abnormalities mean?
Are they central to the condition? A consequence? An epiphenomenon?

Do neurobiological abnormalities change after treatment of CFS?

- Increase in grey matter volume after CBT
- Hypocortisolism partially reversible, also associated with a poorer response to CBT. Hypocortisolism might be a perpetuating factor.
- By looking at neurobiological abnormalities in relation to fatigue change, the place and meaning of these abnormalities can be better understood.
Directions of future studies in Chronic Fatigue Syndrome

4. Studies investigating neurobiological or physiological markers of CFS in relation to treatment effect are needed. Combining experimental and mediation studies with change in neurobiological parameters is still a better direction.

5. Action research: early detecting of CFS by physicians and promoting healthcare seeking by patients is needed.

Possible directions of future studies

- Action research: early detecting of CFS by physicians and promoting healthcare seeking by patients
- Process research and mediation analyses of treatment studies; experimental studies to discover mechanisms
- Studies investigating neurobiological or physiological markers of CFS in relation to treatment effect
- Cohort studies of groups at high risk for developing CFS with an emphasis on the development of the maintaining factors
- Population based studies to increase insight in the development of CFS

Health care

- There are several indications that there are many more CFS patients in the general population than detected or diagnosed:
  - example: 1% CFS in general population; →70% consulted GP; 7% CFS diagnosis
- One factor is probably the attitude, lack of knowledge and/or approach of the GP (and specialist)
- Another factor might be the lack of health care seeking of the patient

Possible directions of future studies

1. Development of CFS
2. Development of maintaining factors
3. Neurobiological and physiological factors in relation to change in fatigue
4. Mechanism of change in treatment of fatigue; experimental studies
5. Early detecting of CFS and promoting healthcare
Imaging in Chronic Fatigue Syndrome

**Imaging Modalities**
- PET/SPET Cerebral Blood Flow/Metabolism/ Ligand PET neurochemistry
- MRI Structural Imaging (Inc DTI)
- MRS Neurochemistry/Energy Metabolism
- fMRI- Functional neural activity. Cerebral perfusion

Radiotracers for affective disorders

- **123I-IBZM**
- **11C-MDL 100907**
- **11C-Raclopride**
- **11C-FLB 457**
- **11C-WAY 100635**
- **11C-DASB**

5-HT1A Receptor Binding in Chronic Fatigue Syndrome (N= 10)

Reductions of **11C-WAY 100635** BP in Recovered Patients with Major Depressive Disorder Bhagwagar et al Molecular Psychiatry 2004.

Voxel Morphometry in CFS

De Lange et al, 2005
Global Decrease in Grey Matter Volume in CFS (28 patients and 28 controls)

Use of fMRI to Identify Abnormal Brain Circuitry in Mood Disorder

Altered Brain Activity in Fibromyalgia Following a pain Stimulus

Neural Correlates of Imagined Fatigue in CFS Patients (n= 12) and Controls (n= 11)

fMRI and Working Memory

Increased Activity in STG in FH+ Participants

In Major Depression, relative to controls, the same performance elicits greater activation of working memory circuitry
Auditory Working Memory IN CFS (n=19) and Controls (N=18)

Magnetic Resonance Spectroscopy

- Proton MRS
  NAA, Choline Creatinine, Aspartate, Glutamate, GABA, Lactate

- Phosphorus MRS
  ATP, Phosphocreatinine, Phosphate Esters, Intracellular PH

Conclusions

- Brain imaging offers a means of exploring pathophysiology in CFS
- Investigations are complicated by lack of understanding of neural correlates of fatigue and co-morbidity of many CFS patients
- Generally sample sizes are too small and methodology too disparate to yield reliable findings at present
If this study is replicated, and if a causal link to CFS/ME is established, it will be important to determine the genetic factors governing the susceptibility of individuals to XMRV.

Method of choice: Genome-wide association (GWA) studies.
‘Missing heritability’

- Genetic factors determining human height using data from approximately 63,000 individuals.
- More than 40 important genes were identified.
- Nevertheless, these account for just over 5% of normal height variation.

Pathway and Gene Identification

- What is unusual about genes in these intervals?

- Gene Ontology
- Gene expression
- Gene pathways
- cis-eQTLs
- Mouse Phenotypes

Human Genome

- The majority of risk alleles in GWA studies lie outside of protein-coding sequence.
  - So changes in ncRNA loci or aberrant regulation of gene expression could often underlie disease.
- Approximately 10% of the genome is functional.
  - So ~ 300Mb of human sequence, if mutated, could lead to disease.

Review of MRC strategy in Genomics and Genetics

- “HTP sequencing will significantly change the way in which biological research is done. As for all paradigm changes (e.g. the development of computers), at this early stage it is impossible to predict how far this technology will extend biomedical research, but it is clear to everyone involved in this field that HTP sequencing is a revolutionary development. Any assay where the readout is (or could be made to be) DNA can use this technology.”

Plummending sequencing costs

- 30X-coverage
- Short reads (~90% of genome)
- $48,000

www.everygenome.com
Single-molecule sequencing of an individual human genome

$48,000; 4 weeks

Others

- Pacific Biosciences – $5k per genome in 2010?
- Life Technologies
- 454 Life Sciences
- Oxford Nanopore
- Ion Torrent

Common variants from the 1000 Genomes Project

SNPs, CNVs, inversions etc

The challenges of having so much data

The storage, analysis, and interpretation of genetic data is becoming more complex. This is leading to a need for better tools and techniques to handle the increasing volume of data. Some of the challenges include:

- **Data Storage:** With the increasing amount of genetic data being generated, there is a need for more efficient storage solutions.
- **Data Analysis:** The analysis of genetic data requires sophisticated computational tools and algorithms.
- **Data Interpretation:** Interpreting genetic data requires a deep understanding of genetics and biology.

These challenges are not only technical but also ethical, as they raise questions about privacy and confidentiality.
Chronic Fatigue Syndrome (CFS/ME)

Possible Mechanisms

- Chronic Infection?
- Chronic Immune Activation?

Clinical Clues

- Infective triggers common
- Timing in relation to triggering infection
- Pattern of triggering infections
- Character of symptoms
- Severity of triggering illness and outcome
- Altered infection pattern with illness/recovery
- Increased clinical expression of atopy
- Autoimmunity association – High reactors?
- Changed symptoms in intercurrent infection
- Changes during chemotherapy, immune Rx

Infections and CFS

- EBV, CMV, HSV, HHV-6
- HBV, HCV, HAV
- Enteroviruses
- Parvovirus
- HIV
- Ross River Virus
- Coxiella burnetii
- Toxoplasma
- Salmonella (typhi and non typhi)
- Brucella
- Borrelia
- M Tuberculosis

Laboratory Clues

- Reduced Natural Killer cell function
- Reduced NK cell perforin
- CD8 Lymphocyte activation markers up
- CD38; HLA-DR; CD26
- Th1-Th2 imbalance
- Pro-inflammatory cytokines elevated
- IL1-beta; TNF-alpha; IL-6
- Anti-inflammatory cytokines elevated
- TGF-beta; IL-10
- Cytokine Polymorphisms
  - IFN-gamma; IL-10; IL-17
- Exercise/Activity and cytokines

Pathogenetic Factors

- Predisposing
  - Nature; Nurture
- Precipitating
  - Infective; Non-Infective
- Perpetuating
  - Internal; External
Hypothesis

- Persistent Immune Dysregulation after infection or other trigger
- Central and peripheral neural dysfunction resulting from effects of immune mediators
- Everything else is down-stream – secondary or adaptive

XMRV?

- DNA in 68/101 stored CFS patient PBMCs
  - cf 8/218 controls. *But ? 20 with lymphoma …*
- XMRV is actively expressed, can pass from cell to cell, leads to a detectable immune response
- Need independent and substantive confirmation
  - Fresh samples, different methods,
  - Different cohorts, disease controls
- XMRV: cause, effect, passenger, contaminant?
- Premature to apply clinical tests or treatments
Viral Infection and Chronic Fatigue Syndrome

Paul Moss
University of Birmingham

Summary

- Role of infection on psychological and physical function
- Evidence for role of infection in CFS
  - Herpes viruses
  - Parvoviruses
  - Retroviruses
  - Other agents
- Potential for therapeutic intervention

Infection

- Physical and psychological effects of acute infection are well known
- Effects mediated by release of inflammatory mediators such as interferon and chemokines
- Many of these can gain access to CNS
- Do these effects have any evolutionary advantage?
- Not unreasonable that chronic infection could lead to similar problems

Temperature

Chronic infection

- Viral
  - Herpes viruses
  - Parvovirus
  - Retroviruses
  - Enteroviruses
- Parasites
- Bacteria

Does it matter which virus is the trigger for CFS?
Prospective study of chronic fatigue syndromes precipitated by pathogens

- **Objective:** To delineate the risk factors, symptoms and longitudinal course of prolonged illnesses after a variety of acute infections.
- **Design:** Prospective cohort study following patients from the time of acute infection with Epstein-Barr virus (glandular fever), Coxiella burnetii (Q fever), or Ross River virus (epidemic polyarthritis).
- **Participants:** 253 patients enrolled and followed at regular intervals over 12 months by self report, structured interview, and clinical assessment.
- **Outcome measures:** Detailed medical, psychiatric, and laboratory evaluations at six months to apply diagnostic criteria for chronic fatigue syndrome. Premorbid and intercurrent illness characteristics recorded to define risk factors for chronic fatigue syndrome.

Results:
- Prolonged illness characterised by disabling fatigue, musculoskeletal pain, neurocognitive difficulties, and mood disturbance was evident in 29 (12%) of 253 participants at six months, of whom 28 (11%) met the diagnostic criteria for chronic fatigue syndrome.
- This post-infective fatigue syndrome phenotype was stereotyped and occurred at a similar incidence after each infection.
- The syndrome was predicted largely by the severity of the acute illness rather than by demographic, psychological, or microbiological factors.
- Conclusions: A relatively uniform post-infective fatigue syndrome persists in a significant minority of patients for six months or more after clinical infection with several different viral and non-viral micro-organisms.

Fig 1 Survival curves of post-infective fatigue syndrome by infective agent after onset of acute infection. Kaplan-Meier analyses of proportion of participants within each infective subcohort who remained as cases. Test of equality across groups: (G2)2=3.45, df=3, P=0.19

Fig 2 Patterns of change in individual symptom factors in participants with and without post-infective fatigue syndrome. Median (horizontal bar) and 25th/75th centiles (box extremities) of normalized factor scores for six symptom domains in confirmed cases of post-infective fatigue syndrome cases (orange boxes; n=28) and those who recovered more promptly (white boxes; n=225)

Fig 3 Differential rates of resolution of individual symptom factors after acute infection. Scores on each of six symptom factors for each participant (n=229) over 12 months in three divided time periods, calculated from factor analysis. Mean symptom scores standardised (to ensure comparability) by dividing the mean at each time point for each factor by its mean at baseline.

*Period of non-resolution of individual symptom domain between two time points of assessment (that is, gradient=0)
Herpes viruses

Herpes Viruses such as CMV trigger an enormous immune response in healthy people

People who carry CMV have a totally different pattern of memory and naïve T cells

The CD8+ memory T cell count is stable with age

CMV greatly increases the number of memory T cells

<table>
<thead>
<tr>
<th>20-40</th>
<th>40-60</th>
<th>60+</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total population</td>
<td>700</td>
<td>600</td>
</tr>
<tr>
<td>CMV neg</td>
<td>400</td>
<td>300</td>
</tr>
<tr>
<td>CMV pos</td>
<td>300</td>
<td>200</td>
</tr>
</tbody>
</table>

Principles of herpes virus infection

- Eight herpes viruses
- Primary infection often ‘silent’
- Never cleared from the host after infection
- Suppressed by immune response
- Viral reactivation occurs during periods of ‘stress’
- Clinical problem in immunosuppressed people

People who carry CMV have a totally different pattern of memory and naïve T cells
The CD8+ naïve T cell count declines with age.

CMV reduces the naïve cell count at all ages.

CMV seropositivity at age 50 years accelerates naïve T cell decline by 25 years.

Potential clinical implications of the large CMV-specific immune response.

Primary infection.

Sometimes the initial (primary) infection with CMV can cause clinical problems.

Justine Henin-Hardenne:

“I though it was the end of my tennis. Even as a person I could feel myself changing. I just wanted to stay at home and not see anyone, not even my friends. But slowly I got better. I still have to be careful and I can’t train or work as hard as I once did.”
Case study: patient with glandular fever due to CMV infection

- 38 year old man
- Admitted to hospital with fatigue, fever and lymphocytosis
- Diagnosis of acute CMV-associated infectious mononucleosis
- Recruited into prospective study of immune response to CMV
- Clinical picture dominated by CFS
- 8 years later, never returned to full time employment
- Prone to relapses of low mood and fatigue
- Clearly relates problems to acute infection

CMV association with mood disorders

- Association between antibody titre to CMV infection and depression
  - (Phillips, 2007)
- Can such a common infection be associated with generalised change in performance?
  - Infection with CMV is the norm
  - Probably offers some benefit to human host
  - Modulation of psychological performance is possible

Active CMV infection in patients with chronic fatigue syndrome

- Aims: investigate if antibodies to CMV early antigens are important in CFS
- Methods: 4774 serological tests were performed in 1135 patients with patients using two immunoassays, Copalis and ELISA. The Copalis immunoassay utilised HCMV early gene products of UL44 and UL57 recombinant antigens for detection of HCMV IgM antibody, and viral capsid antigen for detection of HCMV IgG antibody.

Begai et al. 2008 JCP. Nashville

- Results: 45.6% were positive for HCMV IgG by both assays.
- 12% were positive for IgM HCMV serum antibody to early antigens
- Conclusions: Immunoassays are specific in the detection and differentiation of active HCMV infection in a subset of patients with CFS.

Activation of human herpesviruses 6 and 7 in patients with chronic fatigue syndrome

- BACKGROUND: Human herpesvirus 6 (HHV-6) and 7 (HHV-7) have been suggested as possible triggering agents for chronic fatigue syndrome (CFS)
- OBJECTIVES: To determine the possible association of HHV-6 and HHV-7 infections with CFS
- STUDY DESIGN: The prevalence of latent/persistent and active viral infections by nPCR in 17 CFS patients was examined. In addition, 12 patients with unexplained chronic fatigue and 20 blood donors (BD) were studied.

Chapenko et al. JCV 2006. Riga

- RESULTS: Active HHV-6 and dual (HHV-6 + HHV-7) infections were detected in CFS patients only and frequency of HHV-7 reactivation was also significantly higher in these patients.
- CONCLUSIONS: HHV-7 may be involved in the pathogenesis of CFS and reactivation of both viruses may provoke changes in the phenotype of circulating lymphocytes
IgM serum antibodies to Epstein-Barr virus are uniquely present in a subset of patients with the chronic fatigue syndrome

Patients and Methods: Fifty-eight CFS patients and 68 non-CFS matched controls were studied. Serum antibodies to EBV viral capsid antigen (VCA) IgM and EBV Early Antigen, diffuse (EA, D) were identified in 33 CFS patients (Group A subset EBV VCA IgM 62.3 ± 8.3, neg. <20), but were not present in other CFS patients. (Group B subset EBV VCA IgM 6.8 ± 0.7) controls (p<0.0001).

Results: EBV VCA IgM titers remained positive in CFS patients for 24-42 months.

Conclusion: Serum antibody to EBV VCA IgM may be a specific diagnostic test for a second subset of CFS patients.

Lerner et al. 2004 Wayne State

Chronic fatigue syndrome after infectious mononucleosis in adolescents

Objective: To characterize prospectively the course and outcome of chronic fatigue syndrome in adolescents during a 2-year period after infectious mononucleosis.

Methods: 301 adolescents (12-18 years of age) with infectious mononucleosis were identified and screened for non-recovery 6 months after infectious mononucleosis by using a telephone screening interview. Nonrecovered adolescents underwent a medical evaluation, with follow-up screening 12 and 24 months after infectious mononucleosis. After blind review, final diagnoses of chronic fatigue syndrome at 6, 12, and 24 months were made by using established pediatric criteria.

Results: Six, 12, and 24 months after infectious mononucleosis, 13%, 7%, and 4% of adolescents, respectively, met the criteria for chronic fatigue syndrome.

Katz et al. 2009. Chicago

Increased body mass index is associated with excess fatigue in acute infectious mononucleosis - but not increased CFS

Objective: To examine the influence of body mass index (BMI) and weight change on fatigue severity and failure to recover in individuals with acute infectious mononucleosis.

Methods: 148 individuals presenting with a positive monospot test. We obtained measured weights and vitality subscale scores from the Short Form-36 Health Survey (SF-36) at the index visit and at 6 months.

Results: The mean age of the participants was 21 years and 24% were overweight or obese. During acute illness, overweight and obese participants had an adjusted odds ratio for low vitality scores of 2.9 (confidence interval 1.2-7.1) compared to normal weight subjects. Neither index BMI nor 6-month weight gain was significantly associated with prolonged fatigue or failure to recover.

Conclusion: Overweight and obese patients with acute infectious mononucleosis are more likely to experience severe fatigue. In contrast, neither baseline weight nor weight gain appear to impede recovery.

Seattle, 2008 Journal of Chronic Fatigue Syndrome 14 (3); 27 – 36

How can we treat CFS secondary to herpes virus infections?

- Anti-viral drugs
- Accidexor
- Immunostimulants
- Antibodies that deplete B cells e.g. rituximab

Reduce EBV load within the body

Valacyclovir treatment in Epstein-Barr virus subset chronic fatigue syndrome: Thirty-six months follow-up

Background: A blinded-random placebo-controlled trial of valacyclovir in EBV CFS subset was performed and the EBV subset was followed for thirty-six months (Group 2). Patients were given valacyclovir at 14.3 mg/kg every 6 hours.

Results: After six-months, CFS patients receiving valacyclovir experienced an increased mean least square EI point score + 1.12 units (122 kcal/day), while the placebo cohort increased + 0.42 EI units (65 kcal/day). Tachycardias decreased and abnormal cardiac wall motion improved. Serum antibody titers to EBV VCA IgM decreased. Patients resumed normal activities.

Lerner et al, 2007. Nashville
B cell depletion for chronic fatigue syndrome

- **Background:** A patient with CFS had unexpected, marked recovery of CFS symptoms lasting for five months during and after cytotoxic chemotherapy for Hodgkin’s disease. We reasoned that the transient CFS recovery was related to methotrexate treatment, which induces immunomodulation in part through B-cell depletion.
- **Methods:** This patient and two additional CFS patients were B-cell depleted by infusion of the monoclonal anti-CD20 antibody rituximab.
- **Results:** All three had improvement of all CFS symptoms. Patients 1 and 2 had major amelioration from 6 weeks after intervention, patient 3 slight improvement from the same time, but then improved markedly from 26 weeks after intervention. The symptomatic effect lasted until weeks 16, 18 and 44, respectively.

Flage et al, 2009, Norway

Detection of an Infectious Retrovirus, XMRV, in Blood Cells of Patients with Chronic Fatigue Syndrome

- Chronic fatigue syndrome (CFS) is a debilitating disease of unknown etiology that is estimated to affect 17 million people worldwide.
- Studying peripheral blood mononuclear cells (PBMCs) from CFS patients, we identified DNA from a human gammaretrovirus, xenotropic murine leukemia virus–related virus (XMRV), in 68 of 101 patients (67%) as compared to 8 of 218 (3.7%) healthy controls.
- Cell culture experiments revealed that patient-derived XMRV is infectious and that both cell-associated and cell-free transmission of the virus are possible. Secondary viral infections were established in uninfected primary lymphocytes and indicator cell lines after their exposure to activated PBMCs, B cells, T cells, or plasma derived from CFS patients.
- These findings raise the possibility that XMRV may be a contributing factor in the pathogenesis of CFS

Lombardi, 2009 Science

Retroviral DNA can be amplified from patients with CFS

Retroviral proteins are also expressed
Potential contaminant?

- 3 genomes were sequenced and were 99% identical to prostate cancer variant - but sequence polymorphism was present
- Sequences do not cluster with endogenous murine retrovirus

CFS lymphocytes can transfer infection to a prostate cancer cell line

(1) Virus can be transmitted by plasma
(2) There appears to be a serological immune response

Further work

- A highly significant association between the XMRV retrovirus and CFS.
- Is XMRV infection a causal factor in the pathogenesis of CFS or a passenger virus in the immunosuppressed CFS patient population?
- What is the relationship between XMRV infection status and the presence or absence of other viruses that are often associated with CFS (e.g., herpesviruses)?
- Are these viruses cofactors in pathogenesis?
- Does XMRV infection alter the risk of cancer development in CFS?
- XMRV infection status does not correlate with the RNASEL genotype

Preexisting psychological stress predicts acute and chronic fatigue and arthritis following symptomatic parvovirus b19 infection

- Background: Psychological stress is thought to be an important factor in the pathogenesis of chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME). We sought to examine this relationship in the context of parvovirus B19 infection.
- Methods: 39 patients with laboratory documented acute parvovirus B19 infection were asked to complete questionnaires on negative life events, perceived stress, and negative affect relevant to the time of onset of parvovirus infection and during the preceding 12 months.
- Scores were combined into an overall stress index, which was then examined for associations with parvovirus-associated symptoms at acute infection and during the ensuing 1-3 years.

Kerr et al, St Georges 2008
• Results. Stress index was significantly associated with development of fatigue during the acute phase of parvovirus B19 infection and also with chronic fatigue and arthritis occurring 1-3 years following acute parvovirus B19 infection.

• Logistic regression that included all clinical variables indicated that a high stress index at the time of onset of infection was the primary predictor of CFS/ME 1-3 years following acute parvovirus B19 infection (odds ratio, 25.7; 95% confidence interval, 1.7-121.9; P=0.005).

• Conclusions. We report a highly significant association between psychological stress and development of acute and chronic fatigue and arthritis several years following laboratory-documented acute parvovirus B19 infection.

Pathogenesis of parvovirus B19 infection: Host gene variability, and possible means and effects of virus persistence

• follow-up studies of patients with acute symptomatic parvovirus B19 infection showed a significant proportion of patients develop prolonged arthritis and chronic fatigue syndrome (CFS).

• Cases have high levels of pro-inflammatory cytokines in their circulation and that this correlates with the symptoms.

• A single-nucleotide polymorphism (SNP) associated with symptomatic B19 infection occurs in the Ku80 gene which has recently been shown to be a B19 co-receptor.

Enterovirus infection and CFS

Chronic fatigue syndrome is associated with chronic enterovirus infection of the stomach

• Background and Aims: enteroviruses have been implicated as one of the causes of CFS. Since most CFS patients have persistent or intermittent gastrointestinal (GI) symptoms, the presence of viral capsid protein 1 (VP1), enterovirus (EV) RNA and culturable virus in the stomach biopsy specimens of patients with CFS was evaluated.

• Methods: 165 consecutive patients with CFS underwent upper GI endoscopies and antrum biopsies. Immunoperoxidase staining was performed using EV-specific monoclonal antibody (mAb) or a control mAb specific for cytomegalovirus (CMV). RT-PCR ELISA was performed on RNA extracted from paraffin sections or samples preserved in RNA later. Biopsies from normal stomach and other gastric diseases served as controls. 75 samples were cultured for EV.

• Results. 130/165 (82%) biopsies stained positive for VP1 within parietal cells, whereas 7/34 (20%) of the controls stained positive (p < 0.001). CMV mAb failed to stain any of the biopsy specimens. Biopsies taken from six patients at the onset of the CFS/abdominal symptoms, and 2-6 years later showed positive staining in the paired specimens. EV RNA was detected in 20/24 (83%) paraffin sections or samples preserved in RNA later, in 1/21 controls had detectable EV RNA (p<0.01); 13 patients had detectable EV RNA from two samples taken 6 years apart; 5 patient samples showed transient growth of non-cytopathic enteroviruses.

• Conclusion: Enterovirus VP1, RNA and non-cytopathic viruses were detected in the stomach biopsy specimens of CFS patients with chronic abdominal complaints. A significant subset of CFS patients may have a chronic, disseminated, non-cytoplastic form of enteroviral infection, which could be diagnosed by stomach biopsy.
Infection, Immunity and Somatic symptoms

Infection → Immune activation → Malaise → Recovery

Pathophysiology of CFS and Infection

Chronic Infection → Immune activation → CFS

Herpes viruses
Retroviruses
Parvo, Entero

Infection → Immune activation → CFS

Immune modulation

Physical and Psychological impairment

11% at 6 months?

Summary

- Acute viral infection mimics 'acute CFS syndrome' and persistent infection is a strong candidate for driving CFS
- Understanding which viruses, if any, are primary agents is difficult
  - There is the potential for novel clinical interventions
    - Use these in combination with graded exercise therapy and cognitive behaviour therapy?