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The Collaborative on Fatigue Following Infection (COFFI)

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Abstract

Background: The purpose of COFFI is for investigators of post-infection fatigue (PIF) and other syndromes to collaborate on these enigmatic and poorly understood conditions by studying relatively homogeneous populations with known infectious triggers, and pooling data and stored biosamples to support both epidemiological and laboratory research, to better understand the etiology and risk factors for development and progression of PIF.

Methods: COFFI consists of prospective cohorts from the UK, Netherlands, Norway, USA, New Zealand and Australia, some closed and some open to recruitment. The 9 cohorts closed to recruitment include > 3,000 participants, including nearly 1000 with infectious mononucleosis (IM), > 500 with Q fever, > 800 with giardiasis, > 600 with campylobacter gastroenteritis (CG), 190 with Legionnaires disease and 60 with Ross River virus.

Follow-up has been at least 6 months and up to 10 years. All studies are prospective and use the CDC Fukuda criteria for defining CFS.

Results: Risk factors for nonrecovery included lower physical fitness, female gender, severity of the acute sickness response and autonomic dysfunction.

Conclusions: COFFI is an international collaboration which should be able to answer questions when data are pooled that are not answerable in the individual cohorts, such as do different infectious triggers (e.g., IM vs CG) trigger different PIF syndromes (e.g., chronic fatigue syndrome vs irritable bowel syndrome) or what are predictors of PIF or its severity.

COFFI has a website https://internationalcoffi.wordpress.com/.

Why was the Collaborative set up?

Chronic fatigue syndrome (CFS, also known as myalgic encephalomyelitis or systemic exertion intolerance disorder [SEID]) is a prevalent, but enigmatic and poorly understood condition.[1] CFS is usually defined using use the Fukuda CDC diagnostic criteria.[2] The Oxford criteria also require ≥ 6 months of severe/disabling fatigue that affects physical and mental functioning, and exclude established medical and psychiatric diagnoses.[3] The Canadian Consensus criteria also require ≥ 6 months of fatigue, post-exertional malaise, sleep dysfunction, pain, two or more neurological manifestations and at least one of the following: autonomic, neuroendocrine or immunologic symptoms,[3a] Recently proposed criteria for SEID specify fatigue for 6 months that affects activity and post-exertional malaise and unrefreshing sleep, plus cognitive impairment or orthostatic intolerance, but have no exclusionary criteria.[4] Chronic fatigue (CF) alone is defined as symptomatic fatigue lasting 6 months or more.

Infective illnesses such as infectious mononucleosis (IM) are the only evidence-based triggers of CFS.[5-7] Motivation for a collaborative of investigators of post-infection cohorts is threefold. First, certain infections including IM caused by Epstein-Barr virus (EBV) have been reliably implicated in triggering CFS and therefore provide a known point of time for illness onset. Second, following a cohort after a known infectious trigger allows for homogeneity of the patient population being studied, improving reproducibility of findings.[8,9] Third, a research collaborative offers greatly increased power to support both epidemiological and laboratory research, to better understand the etiology and risk factors for development and progression of PIF..

Despite the fact that the fatigue being studied is post-infection, no evidence exists for persistence of the triggering microbe (e.g., EBV) in patients with CFS.[10,11] Instead, the underlying hypothesis of the collaborative is that prolonged fatigue after infection is a consequence of biologic, behavioral and/or environmental effects, in which susceptible individuals develop alterations in neurobehavioural, cardiovascular and/or immunological systems. In addition, the Collaborative seeks to determine whether different triggers (e.g., IM vs giardiasis) lead to different post infectious consequences (e.g., CFS vs. irritable bowel syndrome [IBS][12]). The overall aim of the collaborative is to characterize and identify risk factors for post-infection fatigue. The specific research questions that COFFI aims to answer are listed in Table 1.

(Table 1 here)

Who is in the Collaborative?

The Collaborative on Fatigue Following Infection (COFFI) was established following a meeting at the Royal Society of Medicine June 2015 in London attended by principle investigators following post-infection cohorts in the UK, Netherlands, Norway, USA, New Zealand and Australia.

At its inception, COFFI comprised the cohorts listed in Tables 2 and 3, of which some are closed (Table 2) and some still open (Table 3) to recruitment. All studies were approved by the appropriate Institutional Review Boards, with consents being obtained as required. The nine cohorts closed to recruitment included > 3,000 participants who had an infectious event, comprising nearly 1000 with IM/glandular fever (4 cohorts), > 500 with Q fever (2 cohorts), > 800 with giardiasis (1 cohort), > 600 with campylobacter gastroenteritis (CG; 1 cohort), 190 with Legionnaires disease (1 cohort) and 60 with Ross River virus (RRV; 1 cohort). Some

of the studies had comparison groups of healthy controls or patients with an upper respiratory tract infection. All studies were prospective. For more details, see Table 2.

(Table 2 here)

Regarding the open studies (Table 3), one is following a well population who may then develop IM, in an attempt to isolate pre-illness risk factors, and two are following patients with various infective triggers. See Table 3 for more details.

(Table 3 here)

How often have they been followed up?

Generally follow-up is at least 6 months, with many studies following participants out to 12 and 24 months, and some for up to 10 years. See Tables 2 and 3 for further details.

What has been measured?

The two main outcomes of interest to COFFI are CF and CFS. Most of the studies collect other questionnaire-derived data and/or biosamples. These, and the measures of fatigue and the diagnostic criteria used are summarized in Tables 2 and 3. Some studies followed cohorts with gastrointestinal tract infectious triggers, and measured development of CFS, IBS and/or functional dyspepsia.

Biosamples have also been collected and are banked by most of the studies. A range of assay data are available, or will be available. For further details, see Tables 2 and 3.

What has been found?

Epidemiology

The prevalence of CFS following IM varied from 8 – 22 % at 6 months (although most studies showed a 9 – 13% prevalence) and 7-9% at 12 months (see Table 4). Following other infectious diseases, the rates of post-infectious fatigue and other sequelae were higher, but so were the rates of fatigue and other symptoms in the control subjects. This may reflect the differing propensity of different pathogens to trigger CFS; however, less rigid definitions of CF, CFS or IBS will also result in higher rates of diagnoses of CF, CFS or IBS both in controls and study subjects.

A previous meta-analysis indicated a prevalence of CFS of 0.76% (95% CI 0.23% to 1.29%).[13] Milder infections such as upper respiratory tract infections did not to lead to CF or CFS at the same rate as more serious infections such as IM.[5,14,15]

(Table 4 here)

Bergen Giardiasis Cohort

The Bergen giardiasis cohort was initiated following an outbreak of giardiasis in 2004: >48,000 people were exposed, 2,500 became ill, and there were 1,252 verified giardiasis cases.[16] Follow-up for fatigue has been as long as 10 years. At 3 years' post-infection, 1,252 cases and 3,598 matched controls were contacted, with response rates of 65% (n=817) and 31% (n=1128), respectively.[14] Relative risks for CF (46% among cases, 12% among controls), severe CF (CF plus an elevated fatigue score; 15% among cases, 2% among controls), and consistent CF (CF present at least 85% of the time; 18% among cases, 5% among controls) were, respectively: 4.0 (3.5 to 4.5); 7.4 (4.9 to 10.9); and 3.6 (2.6 to 4.7). Of 366 fatigued participants at 3 years, 253 were invited to a 5-year fatigue assessment. Of the 53 who

responded, 22 met criteria for CFS, 7 had idiopathic CF, 13 had CF due to other causes, and 11 had recovered.[17] Similarly, risk ratios for IBS 3 years after giardiasis were 46% in cases and 14% in controls; for severe IBS (defined as limiting or restricting daily activity at least "often") 14% of cases and 3% of controls, and for frequent IBS (defined as pain or discomfort at least 1 day per week) 22% of cases and 4% of controls; thus the calculated relative risk for developing IBS, severe IBS or frequent IBS following giardiasis was, respectively, 3.4 (2.9 to 3.8), 5.1 (3.6 to 7.2) and 6.2 (4.5 to 8.3). At 6 years post-infection, the relative risk for IBS was unchanged at 3.4 (2.9 – 3.9), whereas the relative risk for CF was lower at 2.9 (2.3 – 3.4). The incidence of CF or IBS following giardiasis seemed to be about the same after 3 years, but IBS persisted more often than CF after 6 years.[18]

Auckland CG and IM cohort

The Auckland (New Zealand) Campylobacter gastroenteritis (CG) and IM cohort study followed patients with CG (as a potential trigger for IBS) and IM (as a potential trigger for CFS).[12] At 6 months: 11% of CG patients and 8% of IM patients had IBS; 5% of CG patients and 8% of IM patients had CFS; 7/118 (6%) of identified cases met self-reported criteria for both CFS and IBS. After controlling for age and gender, there was a trend for IM to be associated with CFS, compared with CG (OR 1.48 [0.62 to 3.55]), and odds of IBS were 2-fold higher post-CG compared with post-IM (OR 2.22 [1.11 to 6.62]).

The role of biopsychosocial factors in post-infection fatigue was also explored in the Auckland CG and IM study, based on a cognitive behavioural explanatory model of predisposing, precipitating and perpetuating factors.[12] In this model, fatigue precipitated by infection and/or stress is perpetuated by cognitive (e.g. "I must not let this get the better of me"), behavioural (all-or-nothing behaviour), mood

(anxiety/depression) and biological (e.g., poor sleep, deconditioning) responses. Specific research questions asked were: 1) Does the nature of the moderate to severe infection determine the specific syndrome?, and 2) Are the predisposing and perpetuating psychological factors common across the syndromes?[20,21] The study collected self-reported measures of anxiety, depression, perfectionism, perceived stress, behavioural response to illness, activity, rest, all-or-nothing behaviour, and illness perception. Several self-reported factors emerged as predictors of IBS and CFS which were consistent with a cognitive behavioural model for both syndromes, namely: somatisation, anxiety, negative illness/symptom beliefs, and all-or-nothing behaviour.[20,21] Depression was a risk factor for CFS but not IBS.

Barts IM Cohort

Predictors of post-infectious fatigue in the Barts IM cohort (see Table 2) at 6 months included: a positive monospot test at onset and lower physical fitness at one month follow-up.[19] Cervical lymphadenopathy and duration of initial bed rest predicted a fatigue syndrome at 2 but not 6 months. Neither past mood disorders nor life events predicted a fatigue syndrome at 6 months, in the absence of a comorbid mood disorder.

Prospective Study of IM (Seattle)

The 'Prospective Study of the Natural History of IM Caused by EBV' study (Seattle) reported three factors associated with failure to recover from IM: female gender (OR 3.3 [1.0 to 12]); a greater number of traumatic life events more than 6 months before the disease began (OR 1.7 [1.1 to 2.5], per each additional life event); and greater family support (OR 1.9 [1.1 to 4.2]).[6] No objective measures distinguished patients who failed to recover from those who recovered. Baseline psychiatric

disorders and psychological distress were not associated with failure to recover. Older age, higher temperature, and greater impairments in physical functioning at baseline (shortly after illness onset) were associated with self-reported failure to recover at 2 months, but not at 6 months. That this disparity may indicate that the subacute, 2-month predictors were determined primarily by biological factors, whereas the chronic, 6-month predictors represented a more complex mix of psychologic and social factors.

Dubbo Infection Outcomes Study

The Dubbo Infection Outcomes Study (DIOS) showed that the type of infectious trigger was less important than the severity of the acute infectious illness, and found no differences in immune responses or leucocyte transcriptome profiles beyond the acute phase between post-infectious fatigue cases and matched recovered controls.[22-26] These investigators found substantial individual variation in the overall severity of the acute sickness response and in specific symptom manifestations among people infected with the same pathogen. These endophenotypes, or individual symptom profiles were stable over time within subjects with ongoing CFS. In the acute phase, serum levels of the pro-inflammatory cytokines interleukin (IL)-1 and IL-6 were correlated with symptoms, functional polymorphisms in cytokine genes (interferon-γ, IL-6 and IL-10) and the severity of the acute sickness response.[25,27] However, longitudinal analysis of cytokine production found no differences between levels of these cytokines in patients with/without persistent symptoms up to 12 months post-infection.[24] This is consistent with a recent systematic review which found no differences in levels of circulating cytokines, with the possible exception of higher levels of transforming growth factor-ß, among CFS cases compared with controls.[28]

Dutch Q-fever Cohorts

The Dutch Q-fever cohort studies were initiated after approximately 4,000 patients with Q-fever were identified in the Netherlands between 2007 and 2010.[29] These studies included cohorts comprising approximately 336 Q-fever patients who experienced onset of illness between 2010 and 2011. Patients with Q-fever were compared with: a) (at 12 months) patients with Legionnaires' disease (N=190)[30,31]; b) (at 24 months) healthy controls (N=130)[32]. Q-fever cases improved over 24 months, but many still reported poor health. Several risk factors were identified: female gender, younger adults, having pre-existing health problems, consuming no alcohol, using medication, being hospitalised in the previous 3 months, and receiving additional treatment for Q-fever.

Ongoing and recently completed studies

CFS Following IM in College Students (Chicago)

The three ongoing cohort studies within COFFI are continuing to enrol participants and/or collect data. The first is an NIH-funded study in Chicago, which builds upon the lead investigators' findings from an earlier cohort study which followed 301 adolescents with monospot-positive IM in the greater Chicago area.[7] In the earlier study, 39 (13%) participants met criteria for CFS at 6 months, 22 (7%) met criteria at 12 months, and 13 (4%) met criteria at 24 months. Exercise tolerance testing at 6 months found no difference in peak work capacity, but adolescents with CFS had a lower degree of fitness and exercised less efficiently than recovered controls.[34] Morning cortisol was reduced in 3/9 cases *versus* 1/9 controls[35], and some differences were found in network cytokine expression profiles as well[36], somewhat different from findings in DIOS,[24] although not all cytokines studied were the same and the participants in the Chicago study were younger. Finally, cases and recovered controls completed an Autonomic Symptom Checklist at baseline (~2 months post-IM) and at 6, 12 and 24 months post-IM, with substantial

differences evident at each time point.[37] Several biologically plausible hypotheses can be addressed: Is there an autonomic predisposition to non-recovery from IM, or does (severe) IM lead to CFS? These hypotheses can only be addressed by prospective studies beginning when subjects are well (see Table 3, and if a single study does not have the power to resolve the issue, pooling data from > 1 study very well might.

Chronic Fatigue Following Acute EBV Infections in Adolescents (Norway)

The CEBA study[39] (see Table 2) recruited 200 adolescents (age 12-19 years) with serologically-confirmed EBV+ IM and 70 healthy controls. This study had a 6-month follow-up period, followed by a randomised controlled intervention for 60 subjects with EBV infections and persistent fatigue, to test cognitive behavioural therapy (CBT) and music therapy against routine care, with follow-up to 15 months. Perpetuating factors to be studied include: cognitive, endocrinologic, autonomic and immune function. Participants will undergo functional MRI and semi-structured interviews. The first part of the study concluded in June 2017; data are currently being analysed (see Table 2).

Sydney Infectious Outcomes Study

The Sydney Infectious Outcomes Study (SIOS; see Table 3) builds upon the DIOS study. SIOS has been recruiting subjects with any acute febrile (presumed viral) illness (≥38°C) with systemic features (e.g. myalgia), for enrolment within 48 hours of onset and characterisation of the acute sickness response. An initial finding in SIOS has been a reduction in heart rate variability (HRV; indicative of autonomic disturbance) among subjects with post-infectious fatigue, and that low HRV was strongly associated with unrefreshed sleep[40]. Subjects with a greater increase in

HRV also had a shorter duration of illness, and this increase in HRV also had an inverse correlation with the serum inflammatory marker C-reactive protein.

In combination with the findings from the Chicago IM study, these SIOS data support a potential role for the autonomic nervous system in the development of CFS.[37,40] Studies in SIOS are focusing also on disturbances in circadian rhythm and biological correlates of fatigue when exacerbated by physical exercise or cognitive challenge.[41]

Bergen Giardiasis Study

The Bergen giardiasis study has completed follow up of participants at 10 years' post-infection: 1,176 cases and 2,330 matched controls have been contacted, with response rates of 50% (n=590) and 30% (n=696), respectively. Cases and controls were assessed for IBS, CF and fibromyalgia, and DNA samples are being analysed by the Genes in Irritable Bowel Syndrome Research Network Europe (GENIEUR) study.

Qure Study

Another recently completed study is the Qure study (Table 2), a 3-arm randomized controlled trial (N=154) of treatment of Q-fever fatigue syndrome with CBT *vs* doxycycline *vs* placebo at 6 months.[42] These recently published results showed that doxycycline treatment had no effect on fatigue 6 months after Q fever diagnosis compared to placebo (3.0 percentage points fewer with placebo vs doxycycline), unlike CBT which reduced fatigue 6.2 percentage points more than placebo (p=0.03). Finally there is the FAME study (see Table 3) from the University of Southampton.[43]

What are the main strengths and weaknesses?

The strongest elements of COFFI are new (and future) cohort studies. The older cohorts are limited to provision of biosamples, and data for meta-analyses of prevalence and risk factors. Additional infectious disease outbreaks are potential avenues for further research and collaboration within the COFFI network. The main limitation is the relatively small number of cases of post-infection CFS, but again, pooling of data will increase the power of future meta-analyses. Also, in the past, different cohorts did not always use the same measures. As the COFFI Network progresses, we hope to be able to standardize the methods used across studies.

Uniform classification of CFS across studies

All the COFFI studies which had CFS as an outcome use the Oxford or Fukuda CDC diagnostic criteria for CFS.[2,3] Other studies that have used CF [30,32,44] usually also report on individuals meeting the Fukuda criteria for CFS, again allowing for pooling of data.

Standardization of other patient-reported and clinical measurements may be problematic, given the wide range of instruments used (see Tables 2 and 3). The current NIH effort to standardize Common Data Elements with which to study CFS will be crucial to facilitate future data pooling. Similarly, standardization of measurement of key predictive factors (e.g., the severity of the acute infection) and indicators of social adversity across studies will be needed if data are to be successfully pooled.

Homogeneity of the patient populations studied

COFFI circumvents the key issue of patient heterogeneity in studies of the prevalence of CFS [44,45] in that all CFS cases in COFFI follow a documented infectious event. Pooled analyses may still need to consider CFS endophenotypes

such as those which can be defined by different symptom profiles or those that result from different infectious triggers (e.g., IM or Q fever vs Campylobacter or Giardia infection).[46, 47]

Can I get hold of the data?/Where can I find out more?

COFFI is modelled on the successful InC[3] International Collaboration of Incident HIV and Hepatitis C in Injecting Cohorts,[48] and will encourage the participation of interested investigators. As COFFI evolves, it is anticipated that new cohorts will be invited to participate, to expand the geographic and population representation in the collaboration. Readers who wish to find out more should visit the COFFI website at www.internationalcoffi.wordpress.com or contact the corresponding author.

COFFI will be governed by an Executive Committee, comprising the COFFI lead investigator (Chair), project coordinator, data leader and specimen leader. A COFFI Steering Committee will comprise the above persons, plus the Principal Investigator(s) from each of the participating studies. Standard Operating Procedures will be developed to define COFFI policy on data and sample sharing, authorship, admission of new cohorts, and consideration of research proposals, e.g. requests for patient specimens. COFFI will invite the participation of subject matter experts in, e.g. statistics, virology, genetics, etc. where such expertise is not found among COFFI members.

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