Self-efficacy and pain catastrophizing in systemic lupus erythematosus: relationship to pain, stiffness, fatigue, and psychological distress

**Authors:** Somers T et al

**Summary:** This cross-sectional study examined how self-efficacy for pain control and pain catastrophizing are related to pain, stiffness, fatigue, and psychological distress in patients with systemic lupus erythematosus (SLE). Patients with SLE who completed measures of pain coping cognitions (i.e. self-efficacy for pain control, pain catastrophising), symptom ratings (for pain, stiffness and fatigue) and psychological distress were included. Self-efficacy for pain control and pain catastrophising were associated with physical symptom reports and psychological distress. Patients with lower levels of self-efficacy for pain control reported higher levels of pain, stiffness, and fatigue, and those with higher levels of pain catastrophising had lower positive mood. SLE activity was not associated with physical symptoms, psychological distress, self-efficacy for pain control, or pain catastrophising. In conclusion, pain coping cognitions are significantly related to physical symptoms and psychological distress in patients with SLE.

**Comment:** This is a significant paper, reflecting the senior author’s track record. Not only pain but reported stiffness and fatigue correlate with the coping mechanisms of self-efficacy and catastrophic thinking. Disease activity was independent of the symptoms and coping strategies. The correlations observed in this study allow for further study of the efficacy of psychological management techniques in this condition.

**Reference:** Arthritis Care Res 2012;64(9):1334-1340

Clinical characteristics of a novel subgroup of chronic fatigue syndrome patients with postural orthostatic tachycardia syndrome.

Lewis I, Pairman J, Spickett G, Newton JL., Institute for Ageing & Health, Newcastle University, Newcastle, UK.

Abstract

OBJECTIVES: A significant proportion of patients with chronic fatigue syndrome (CFS) also have postural orthostatic tachycardia syndrome (POTS). We aimed to characterise these patients and differentiate them from CFS patients without POTS in terms of clinical and autonomic features.

METHODS: A total of 179 patients with CFS (1994 Centers for Disease Control and Prevention criteria) attending one of the largest Department of Health-funded CFS clinical services were included in the study.

Outcome measures were: (i) symptom assessment tools including the fatigue impact scale, Chalder fatigue scale, Epworth sleepiness scale (ESS), orthostatic grading scale (OGS) and hospital anxiety and depression scale (HADS-A and -D, respectively), (ii) autonomic function analysis including heart rate variability and (iii) haemodynamic responses including left ventricular ejection time and systolic blood pressure drop upon standing.

RESULTS: CFS patients with POTS (13%, n=24) were younger (29±12 vs. 42±13 years, P<0.0001), less fatigued (Chalder fatigue scale, 8±4 vs. 10±2, P=0.002), less depressed (HADS-D, 6±4 vs. 9±4, P=0.01) and had reduced daytime hypersomnolence (ESS, 7±6 vs. 10±5, P=0.02), compared with patients without POTS.

In addition, they exhibited greater orthostatic intolerance (OGS, 11±5; P<0.0001) and autonomic dysfunction.

A combined clinical assessment tool of ESS ≤9 and OGS ≥9 identifies accurately CFS patients with POTS with 100% positive and negative predictive values.

CONCLUSIONS: The presence of POTS marks a distinct clinical group of CFS patients, with phenotypic features differentiating them from those without POTS.

A combination of validated clinical assessment tools can determine which CFS patients have POTS with a high degree of accuracy, and thus potentially identify those who require further investigation and consideration for therapy to control heart rate.

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Fatigue and exercise intolerance in mitochondrial diseases.

Literature revision and experience of the Italian Network of mitochondrial diseases Open Access Article

M. Mancuso et al The Nation-wide Italian Collaborative Network of Mitochondrial Diseases


Abstract

Fatigue and exercise intolerance are common symptoms of mitochondrial diseases, but difficult to be clinically assessed.

New methods to quantify these rather common complaints are strongly needed in the clinical practice. Coenzyme Q10 administration and aerobic exercise may improve exercise intolerance, but more definite studies are still pending.

Herein, we have revised “how to measure” and “how to treat” these symptoms of mitochondrial patients. Subsequently, we reviewed the clinical data of the 1164 confirmed mitochondrial patients present in the Italian nation-wide database of mitochondrial disease, with special regard to exercise intolerance.

We observed that more of 20% of mitochondrial patients complain of exercise intolerance. This symptom seems to be frequently associated with specific patient groups and/or genotypes. Ragged red fibers and COX-negative fibers are more often present in subjects with exercise intolerance, whereas lactate levels could not predict this symptom.

Multicenter efforts are strongly needed for rare disorders such as mitochondrial diseases, and may represent the basis for more rigorous longitudinal studies.
The relationship between muscle pain and fatigue.

Mastaglia FL., Australian Neuro-Muscular Research Institute and Centre for Neuromuscular and Neurological Disorders, University of Western Australia, Queen Elizabeth II Medical Centre, Perth, WA, Australia.

Abstract

Pain and fatigue may occur together during sustained exhausting muscle contractions, particularly as the limit of endurance is approached, and both can restrict muscle performance. Patients with neuromuscular disorders may have chronic myofascial pain (e.g. fibromyalgia) or contraction-induced pain (e.g. in metabolic myopathies). In some patients these two types of pain may coexist and both may inhibit central motor drive during exercise.

Little is known about the central motor adaptations that occur in patients with neuromuscular disorders and how the effects of pain are mediated.

Transcranial magnetic brain stimulation has made it possible to investigate the changes in excitability of the central motor pathway during fatiguing muscle activity and have thrown light on the mechanisms of fatigue in normal subjects and individuals with chronic fatigue syndrome and multiple sclerosis, but there have been few studies in patients with neuromuscular disorders.

Repetitive magnetic brain stimulation protocols can now be used to modulate the excitability of the motor system during exercise to delay the onset of peripheral fatigue, and to reduce chronic pain.

The possible application of these techniques in patients with neuromuscular disorders warrants further investigation.
Altered functional B-cell subset populations in patients with chronic fatigue syndrome compared to Healthy Controls

A.S. Bradley, B. Ford, A.S. Bansal,

DOI: 10.1111/cei.12043

Abstract

Chronic Fatigue Syndrome (CFS) is a heterogeneous disorder of unknown aetiology characterised by disabling fatigue, headaches, sleep disturbance and several other symptoms. The onset of CFS may follow a viral infection or period of stress.

Patients with CFS do no have hypogammaglobulinaemia, predisposition to recurrent bacterial infections or symptoms of autoimmunity. To date, defects in B-cell numbers or function have not been shown in the literature. However, treatment with anti-B-cell therapy using Rituximab has recently shown benefit to CFS patients.

We therefore postulated that patients with CFS had a subtle humoral immune dysfunction, and performed extended B-cell immunophenotyping.

We undertook a detailed characterisation of the proportions of the different B-cell subsets in 33 patients with CFS fulfilling the Canadian and Fukada criteria for CFS and compared these with 24 age and gender matched healthy controls (HC). CFS patients had greater numbers of naïve B-cells as a % lymphocytes - 6.3 % versus 3.9 % in HC (P=0.034), greater numbers of naïve B-cells as a % of B-cells - 65 % versus 47 % in controls (P=0.003), greater numbers of transitional B-cells - 1.8 % versus 0.8 % in controls (P=0.025) and reduced numbers of plasmablasts - 0.5 % versus 0.9 % in controls (P=0.013).

While the cause of these changes is unclear, we speculate whether they may suggest a subtle tendency to autoimmunity.
Altered Immune Pathway Activity under Exercise Challenge in Gulf War Illness: An Exploratory Analysis

Broderick G, Hamo RB, Vashistha S, Efroni S, Nathanson L, Barnes Z, Fletcher MA, Klimas N., Department of Medicine, University of Alberta, Edmonton, Canada.

Abstract

Though potentially linked to the basic physiology of stress response we still have no clear understanding of Gulf War Illness (GWI), a debilitating illness presenting with a complex constellation of immune, endocrine and neurological symptoms.

Here we compared male GWI (n=20) with healthy veterans (n=22) and subjects with chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME) (n=7). Blood was drawn during a Graded eXercise Test (GXT) prior to exercise, at peak effort (VO2 max) and 4-hours post exercise.

Affymetrix HG U133 plus 2.0 microarray gene expression profiling in peripheral blood mononuclear cells (PBMCs) was used to estimate activation of over 500 documented pathways. This was cast against ELISA-based measurement of 16 cytokines in plasma and flow cytometric assessment of lymphocyte populations and cytotoxicity. A 2-way ANOVA corrected for multiple comparisons (q statistic <0.05) indicated significant increases in neuroendocrine-immune signaling and inflammatory activity in GWI, with decreased apoptotic signaling.

Conversely, cell cycle progression and immune signaling were broadly subdued in CFS. Partial correlation networks linking pathways with symptom severity via changes in immune cell abundance, function and signaling were constructed. Central to these were changes in IL-10 and CD2+ cell abundance and their link to two pathway clusters.

The first consisted of pathways supporting neuronal development and migration whereas the second was related to androgen-mediated activation of NF-κB. These exploratory results suggest an over-expression of known exercise response mechanisms as well as illness-specific changes that may involve an overlapping stress-potentiated neuro-inflammatory response.

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Abnormal muscle membrane function in fibromyalgia patients and its relationship to the number of tender points.

Klaver-Król EG, Zwarts MJ, Ten Klooster PM, Rasker JJ, Department of Neurology and Clinical Neurophysiology, Functie Afdeling, Hospital Group Twente ZGT, Hengelo, The Netherlands.

Abstract

OBJECTIVES: Fibromyalgia (FM) is a disorder characterised by chronic widespread pain in soft tissues, especially in muscles. Previous research has demonstrated a higher muscle fibre conduction velocity (CV) in painful muscles of FM patients. The primary goal of this study was to investigate whether there is also a difference in CV in non-painful, non-tender point (TP) related muscles between FM patients and controls. The secondary goal was to explore associations between the CV, the number of TPs and the complaints in FM.

METHODS: Surface electromyography (sEMG) was performed on the biceps brachii muscle of female FM patients (13) and matched healthy controls (13). Short static contractions were applied with the arm unloaded and loaded at 5% and 10% of maximum voluntary force. The CV was derived by cross-correlation method (CV-cc) and inter-peak latency method (CV-ipl). TP score and Fibromyalgia Impact Questionnaire (FIQ) were performed in all participants. Correlations were calculated between the CVs, TP score and items of the FIQ.

RESULTS: In FM patients, the CV was higher than in the controls (CV-cc p=0.005; CV-ipl p=0.022). The CV was correlated with the number of TPs in FM patients (r=0.642 and 0.672 for CV-cc and CV-ipl, respectively). No correlations were found between the CV and any aspect of health status on the FIQ.

CONCLUSIONS: The results demonstrate abnormally high muscle membrane conduction velocity in FM, even in non-TP muscles. In addition, a relationship has been found between the high membrane velocity and the number of TPs.
Panel rejects experimental chronic fatigue syndrome drug Ampligen

A drug for chronic fatigue syndrome that spent decades in clinical development and won fervent patient support has been turned down for approval by a committee of advisers to the US Food and Drug Administration (FDA) who voted 9–4 against it. The drug, named Ampligen (rintatolimod), has not been shown to be effective or safe, the committee determined on 20 December.

Ampligen is a double-stranded RNA molecule (called poly I:poly C) which is thought to stimulate the immune system. The FDA does not have to follow the recommendations of its advisers, but briefing documents (http://1.usa.gov/WBj9cd) released by the agency strongly suggest that it will. The FDA’s list of deficiencies in the drug application submitted by Hemispherx Biopharma (http://bit.ly/WBjt9b) is stunning and encompasses nearly every aspect of clinical testing.

"Key deficiencies included inadequate evidence of effectiveness or safety, inadequacy of drug–drug interaction studies, lack of carcinogenicity assessment, lack of anti-drug antibody determination, and inadequate analytical methods and drug product specifications," the agency wrote in one of several sections listing problems associated with the application.

FDA representatives also expressed concern over inconsistencies in the data and statistical analyses. An agency representative says of the data: "It raises our eyebrows and makes us wonder what else is in the database that we're not seeing."

Despite these weighty caveats and the drug’s middling performance in the clinic when averaged across all patients, several people with chronic fatigue syndrome (CFS; also called myalgic encephalomyelitis) testified that Ampligen yielded dramatic improvements in their symptoms. Some moved to Reno, Nevada, to be near the clinical-testing site and to receive infusions of the drug.

Alaine Perry, who served as a patient representative on the advisory committee, acknowledged that the Ampligen data are slim, but noted that CFS symptoms can be so severe that some patients would willingly take on a significant mortality risk for the promise of even minor relief of their symptoms. "A very small improvement in a disease like this is life altering," she said. There are no other approved treatments specifically for CFS.

Accelerated approvals are sometimes used in cases of serious unmet medical need, and there was speculation ahead of Thursday’s meeting that recent legislation charging the FDA with expanding its use of accelerated approvals may come to bear on Hemispherx’s application. Ultimately, however, the FDA is bound by requirements that drug-makers convincingly demonstrate efficacy before approval, representatives said.

In fact, according to the FDA briefing documents, the agency made it clear to Hemispherx in June that its application would be unlikely to win approval without additional clinical trials. That revelation probably came as a surprise to many Hemispherx investors, noted The Street’s, Adam Feuerstein (http://bit.ly/WBl6oh).
Men with fibromyalgia often go undiagnosed, Mayo Clinic study suggests

December, 2012 in Arthritis & Rheumatism

Fibromyalgia is a complex illness to diagnose and to treat. There is not yet a diagnostic test to establish that someone has it, there is no cure and many fibromyalgia symptoms—pain, fatigue, problems sleeping and memory and mood issues—can overlap with or get mistaken for other conditions.

A new Mayo Clinic study suggests that many people who have fibromyalgia, especially men, are going undiagnosed. The findings appear in the online edition of the journal Arthritis Care & Research. More research is needed, particularly on why men who reported fibromyalgia symptoms were less likely than women to receive a fibromyalgia diagnosis, says lead author Ann Vincent, M.D., medical director of Mayo Clinic's Fibromyalgia and Chronic Fatigue Clinic.

"Health care providers may not think of this diagnosis when face to face with a male patient with musculoskeletal pain and fatigue," Dr. Vincent says. "These findings need to be explored further."

Researchers focused on Olmsted County, Minn., home to a comprehensive medical records pool known as the Rochester Epidemiology Project, and used multiple methods to try to get at the number of people over age 21 with fibromyalgia. They used the epidemiology project to identify just over 3,000 patients who looked like they might have fibromyalgia.

Roughly a third had a documented fibromyalgia diagnosis. That amounted to 1.1 percent of the county's population 21 and older. In the second method, researchers randomly surveyed Olmsted County adults using the American College of Rheumatology's fibromyalgia research survey criteria. The criteria include the hallmarks of fibromyalgia: widespread pain and tenderness, fatigue, feeling unrested after waking, problems with memory or thinking clearly and depression or anxiety, among other symptoms.

Of the 830 who responded to the survey, 44, or 5.3 percent, met those criteria, but only a dozen had been diagnosed with fibromyalgia. Based on the study's findings, the researchers estimate that 6.4 percent of people 21 and older in Olmsted County have fibromyalgia—far more than have been officially diagnosed with it. Fibromyalgia is more common in women, but men can get it too.

The discrepancy between the number of people reporting fibromyalgia symptoms and the number actually diagnosed with the condition was greatest among men, the study found. Twenty times more men appeared to have fibromyalgia based on their survey response than had been diagnosed, while three times more women reported fibromyalgia symptoms than were diagnosed.

"It is important to diagnose fibromyalgia because we have effective treatments for the disorder," says co-author Daniel Clauw, M.D., director of the University of Michigan Health System Chronic Pain & Fatigue Research Center. Studies also show that properly diagnosing people with fibromyalgia reduces health care costs, because they often need far less diagnostic testing and fewer referrals looking for the cause of their pain.

Read more at: http://medicalxpress.com/news/2012-12-men-fibromyalgia-undiagnosed-...
Association of monoamine-synthesizing genes with the depression tendency in chronic fatigue syndrome patients.

Fukuda S, Horiguchi M, Yamaguti K, Nakatomi Y, Kuratsune H, Ichinose H, Watanabe Y., Department of Medical Science on Fatigue, Osaka City University, Graduate School of Medicine, Osaka, Japan; Center for Molecular Imaging Science, RIKEN, Kobe, Hyogo, Japan.

Abstract

Aims Tyrosine hydroxylase (TH) and GTP cyclohydrolase I (GCH) are the rate-limiting enzymes for the biosynthesis of catecholamines and tetrahydrobiopterin (BH4), respectively.

Since catecholamines and BH4 are thought to be involved in the pathophysiology of CFS, we explored the genetic factors that influence CFS development and examined the possible association between the SNPs of the TH and GCH genes and the various characteristics of CFS patients.

Main methods After drawing venous blood from CFS patients and controls, genomic DNA was then extracted from whole blood in accordance with standard procedures.

Digestion patterns of the PCR products were used for genotyping the SNPs of GCH (rs841; C+243T) and TH (rs10770141; C-824T).

We also performed questionnaires consisting of fatigue-scale and temperament and character inventory scale (TCI) to CFS patients.

Key findings Our results demonstrated that the allele differences for the GCH and TH SNPs were not associated with CFS patients.

We did find that the GCH gene with the C+243T polymorphism affected harm avoidance, while the TH gene with the C-824T polymorphism affected persistence in the CFS patients.

Significance Our results suggest that the biosynthetic pathways of the monoamine neurotransmitters that are mediated by TH and GCH might be associated with the CFS clinical findings, because persistence is the one of the typical personality traits observed in CFS and patients with major depressive disorder exhibit a higher harm avoidance score.
Evidence for overlap between urological and nonurological unexplained clinical conditions.

Rodríguez MÁ, Afari N, Buchwald DS; National Institute of Diabetes and Digestive and Kidney Diseases Working Group on Urological Chronic Pelvic Pain. Department of Psychology, University Rey Juan Carlos, Madrid, Spain.

Abstract

PURPOSE: Unexplained clinical conditions share common features such as pain, fatigue, disability out of proportion to physical examination findings, inconsistent laboratory abnormalities, and an association with stress and psychosocial factors.

We examined the extent of the overlap among urological and nonurological unexplained clinical conditions characterized by pain. We describe the limitations of previous research and suggest several possible explanatory models.

MATERIALS AND METHODS: Using hallmark symptoms and syndromes as search terms a search of 12 databases identified a total of 1,037 full-length published articles in 8 languages from 1966 to April 2008.

The search focused on the overlap of chronic pelvic pain, interstitial cystitis, painful bladder syndrome, chronic prostatitis/chronic pelvic pain syndrome or vulvodynia with fibromyalgia, chronic fatigue syndrome, temporomandibular joint and muscle disorders or irritable bowel syndrome.

We abstracted information on authorship, type of case and control groups, eligibility criteria, case definitions, study methods and major findings.

RESULTS: The literature suggests considerable comorbidity between urological and nonurological unexplained clinical conditions. The most robust evidence for overlap was for irritable bowel syndrome and urological unexplained syndromes with some estimates of up to 79% comorbidity between chronic pelvic pain and symptoms of irritable bowel syndrome. However, most studies were limited by methodological problems, such as varying case definitions and selection of controls.

CONCLUSIONS: The overlap between urological and selected nonurological unexplained clinical conditions is substantial. Future research should focus on using standardized definitions, and rigorously designed, well controlled studies to further assess comorbidity, clarify the magnitude of the association and examine common pathophysiological mechanisms.

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**Amitriptyline for neuropathic pain and fibromyalgia in adults.**


**Abstract**

**BACKGROUND:** Amitriptyline is a tricyclic antidepressant that is widely used to treat chronic neuropathic pain (pain due to nerve damage) and fibromyalgia, and is recommended in many guidelines. These types of pain can be treated with antidepressant drugs in doses below those at which the drugs act as antidepressants.

**OBJECTIVES:** To assess the analgesic efficacy of amitriptyline for chronic neuropathic pain and fibromyalgia. To assess the adverse events associated with the clinical use of amitriptyline for chronic neuropathic pain and fibromyalgia.

**SEARCH METHODS:** We searched CENTRAL, MEDLINE, and EMBASE to September 2012, together with reference lists of retrieved papers, previous systematic reviews, and other reviews; we also used our own handsearched database for older studies.

**SELECTION CRITERIA:** We included randomised, double-blind studies of at least four weeks' duration comparing amitriptyline with placebo or another active treatment in chronic neuropathic pain or fibromyalgia.

**DATA COLLECTION AND ANALYSIS:** We extracted efficacy and adverse event data, and two study authors examined issues of study quality independently. We performed analysis using two tiers of evidence. The first tier used data meeting current best standards, where studies reported the outcome of at least 50% pain intensity reduction over baseline (or its equivalent), without the use of last observation carried forward (LOCF) or other imputation method for dropouts, reported an intention-to-treat (ITT) analysis, lasted 8 to 12 weeks or longer, had a parallel-group design, and where there were at least 200 participants in the comparison. The second tier used data that failed to meet this standard and were therefore subject to potential bias.

**RESULTS:** Twenty-one studies (1437 participants) were included; they individually involved between 15 and 235 participants, only four involved over 100 participants, and the median study size was 44 participants. The median duration was six weeks. Ten studies had a cross-over design. Doses of amitriptyline were generally between 25 mg and 125 mg, and dose escalation was common. There was no top-tier evidence for amitriptyline in treating neuropathic pain or fibromyalgia. Second-tier evidence indicated no evidence of effect in cancer-related neuropathic pain or HIV-related neuropathic pain, but some evidence of effect in painful diabetic neuropathy (PDN), mixed neuropathic pain, and fibromyalgia. Combining the classic neuropathic pain conditions of PDN, postherpetic neuralgia (PHN) and post-stroke pain with fibromyalgia for second-tier evidence, in eight studies and 687 participants, there was a statistically significant benefit (risk ratio (RR) 2.3, 95% confidence interval (CI) 1.8 to 3.1) with a number needed to treat (NNT) of 4.6 (3.6 to 6.6).

The analysis showed that even using this potentially biased data, only about 38% of participants benefited with amitriptyline and 16% with placebo; most participants did not get adequate pain relief. Potential benefits of amitriptyline were supported by a lower rate of lack of efficacy withdrawals; 8/153 (5%) withdrew because of lack of efficacy with amitriptyline and 14/119 (12%) with placebo. More participants experienced at least one adverse event; 64% of participants taking amitriptyline and 40% taking placebo. The RR was 1.5 (95% CI 1.4 to 1.7) and the number needed to treat to harm was 4.1 (95% CI 3.2 to 5.7). Adverse event and all-cause withdrawals were not different.

**CONCLUSIONS:** Amitriptyline has been a first-line treatment for neuropathic pain for many years. The fact that there is no supportive unbiased evidence for a beneficial effect is disappointing, but has to be balanced against decades of successful treatment in many patients with neuropathic pain or fibromyalgia.

There is no good evidence of a lack of effect; rather our concern should be of overestimation of treatment effect. Amitriptyline should continue to be used as part of the treatment of neuropathic pain or fibromyalgia, but only a minority of patients will achieve satisfactory pain relief.
Limited information suggests that failure with one antidepressant does not mean failure with all. It is unlikely that any large randomised trials of amitriptyline will be conducted in specific neuropathic pain conditions or in fibromyalgia to prove efficacy.
Reduction of \([(11)C](+)^3\)-MPB Binding in Brain of Chronic Fatigue Syndrome with Serum Autoantibody against Muscarinic Cholinergic Receptor.

Yamamoto S, Ouchi Y, Nakatsuka D, Tahara T, Mizuno K, Tajima S, Onoe H, Yoshikawa E, Tsukada H, Iwase M, Yamaguti K, Kuratsune H, Watanabe Y., Department of Physiology, Osaka City University Graduate School of Medicine, Abeno-ku, Osaka, Japan ; Central Research Laboratory, Hamamatsu Photonics KK, Hamakita, Shizuoka, Japan.

Abstract

BACKGROUND: Numerous associations between brain-reactive antibodies and neurological or psychiatric symptoms have been proposed.

Serum autoantibody against the muscarinic cholinergic receptor (mAChR) was increased in some patients with chronic fatigue syndrome (CFS) or psychiatric disease.

We examined whether serum autoantibody against mAChR affected the central cholinergic system by measuring brain mAChR binding and acetylcholinesterase activity using positron emission tomography (PET) in CFS patients with positive [CFS(+)] and negative [CFS(-)] autoantibodies.

METHODOLOGY: Five CFS(+) and six CFS(-) patients, as well as 11 normal control subjects underwent a series of PET measurements with N-[(11)C]methyl-3-piperidyl benzilate [(11)C](+)^3-MPB for the mAChR binding and N-[(11)C]methyl-4-piperidyl acetate [(11)C]MP4A for acetylcholinesterase activity.

Cognitive function of all subjects was assessed by neuropsychological tests.

Although the brain [(11)C](+)^3-MPB binding in CFS(-) patients did not differ from normal controls, CFS(+) patients showed significantly lower [(11)C](+)^3-MPB binding than CFS(-) patients and normal controls.

In contrast, the [(11)C]MP4A index showed no significant differences among these three groups. Neuropsychological measures were similar among groups.

Summary Our results demonstrate the usefulness of PET as a tool for detecting a reduction of neurotransmitter receptor binding in the brains of patients with high levels of serum autoantibody. Further follow up studies on a number of CFS patients are required in order to more thoroughly investigate alterations in cholinergic and neuronal functions with regard to levels of mAChR autoantibody and clinical symptoms.

CONCLUSION: The present results demonstrate that serum autoantibody against the mAChR can affect the brain mAChR without altering acetylcholinesterase activity and cognitive functions in CFS patients.

http://www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone....

IACFS/ME Newsletter ● April 2013 ● Attachment 4


PLOS one RESEARCH ARTICLE

Reduced Cardiac Vagal Modulation Impacts on Cognitive Performance in Chronic Fatigue Syndrome

Alison Beaumont1, Alexander R. Burton1, Jim Lemon1, Barbara K. Bennett2,3, Andrew Lloyd4, Ute Vollmer-Conna1*

1 School of Psychiatry, University of New South Wales, Sydney, New South Wales, Australia, 2 School of Medical Sciences, University of New South Wales, Sydney, New South Wales, Australia, 3 Department of Medical Oncology, Prince of Wales Hospital, Sydney, New South Wales, Australia, 4 Inflammation and Infection Research Centre, School of Medical Sciences, University of New South Wales, Sydney, New South Wales, Australia

Abstract

Background Cognitive difficulties and autonomic dysfunction have been reported separately in patients with chronic fatigue syndrome (CFS).

A role for heart rate variability (HRV) in cognitive flexibility has been demonstrated in healthy individuals, but this relationship has not as yet been examined in CFS.

The objective of this study was to examine the relationship between HRV and cognitive performance in patients with CFS.

Methods Participants were 30 patients with CFS and 40 healthy controls; the groups were matched for age, sex, education, body mass index, and hours of moderate exercise/week.

Questionnaires were used to obtain relevant medical and demographic information, and assess current symptoms and functional impairment.

Electrocardiograms, perceived fatigue/effort and performance data were recorded during cognitive tasks.

Between–group differences in autonomic reactivity and associations with cognitive performance were analysed.

Results Patients with CFS showed no deficits in performance accuracy, but were significantly slower than healthy controls.

CFS was further characterized by low and unresponsive HRV; greater heart rate (HR) reactivity and prolonged HR-recovery after cognitive challenge.

Fatigue levels, perceived effort and distress did not affect cognitive performance.

HRV was consistently associated with performance indices and significantly predicted variance in cognitive outcomes.

Conclusions These findings reveal for the first time an association between reduced cardiac vagal tone and cognitive impairment in CFS and confirm previous reports of diminished vagal activity.
Gulf War Illness: Symptomatology Among Veterans 10 Years After Deployment.

Smith BN, Wang JM, Vogt D, Vickers K, King DW, King LA.

From the Women’s Health Sciences Division (Drs Smith, Vogt, and King), and Behavioral Science Division (Dr King), National Center for PTSD, VA Boston Healthcare System, Boston, Massachusetts; Department of Psychiatry (Drs Smith and Vogt), Boston University School of Medicine, Boston, Massachusetts; Department of Psychology (Dr Vickers), Ryerson University, Toronto, Ontario, Canada; and Departments of Psychology and Psychiatry, Boston University (Drs King and King), Boston, Massachusetts.

Abstract

OBJECTIVE:: To further elucidate the nature of illness in veterans of the 1990 to 1991 Gulf War (GW) by examining the GW Illness (GWI) definition advanced by the Centers for Disease Control and Prevention, which specified caseness as having at least one symptom from two of the three factors: fatigue, mood-cognition, and musculoskeletal.

METHODS:: A total of 311 male and female GW veterans drawn from across the nation were assessed in a survey-based study approximately 10 years after deployment.

RESULTS:: A total of 33.8% of the probability-weighted sample met GWI criteria. Multiple symptom profiles were found, with more than half of GWI cases endorsing a symptom on all the three factors, and almost all cases endorsing at least one mood-cognition symptom.

CONCLUSION:: Although the Centers for Disease Control and Prevention definition has some limitations that should be considered, it remains a useful tool for assessing the presence of illness in GW veterans.
Back to School and Chronic Fatigue Syndrome

Chronic Viral Diseases Branch, Division of High-Consequence Pathogens and Pathology

With the new school year under way, it is important for school nurses, other clinicians who treat children, and educators to be aware of a poorly recognized debilitating illness that can affect adolescents and children and have an impact on their academic and social functioning.

This illness is chronic fatigue syndrome (CFS), a complex illness that severely affects functioning and quality of life. CFS is often thought of as a problem in adults, but it also affects adolescents and, less frequently, children. CFS remains poorly understood by healthcare professionals, and the symptoms in children and adolescents may be misinterpreted as depression or school avoidance.

In adolescents, CFS is more likely to develop after an acute, flu-like illness or injury, but gradual onset of illness may occur.

Symptoms of CFS in adolescents are similar to those in adults: debilitating mental and physical fatigue resulting in a significant reduction in activity, sleep problems (such as unrefreshing sleep and a need to sleep more during the day), marked worsening of symptoms after physical or mental exertion, muscle and/or joint pain without redness or swelling, headaches, and impaired memory or concentration.

Postural orthostatic tachycardia syndrome (POTS) or orthostatic instability is frequently experienced by children and adolescents with CFS. Sore throat and tender cervical or axillary lymph nodes are also common symptoms in pediatric CFS.

Diagnosing CFS requires ruling out other treatable conditions that could be causing the symptoms. In adolescents, diagnosis is also compounded by the process of puberty, a time of hormonal fluctuation and social transition from childhood to adulthood that can contribute to problems with sleep and social adjustment. Children may have difficulty describing their symptoms.

It is most important to diagnose CFS in adolescents and children to prevent or mitigate the effects of missed school and missed opportunities for socialization. When school nurses recognize and understand the impact of CFS, they can serve as effective advocates to mobilize resources to support the child or adolescent to maximize the student's academic and social development. School absence as a result of illness is best addressed with the school, parents, and physicians as partners.

Adolescence is a critical time in human development that influences the individual's adult life, and friends and socialization are particularly important during this life period. Fortunately, recovery from CFS is more common in adolescents than in adults; however, this does not occur in everyone, and long-term follow-up and adjustments are often needed.
Small fiber neuropathy detected among patients with fibromyalgia

December 6, 2012

WASHINGTON — A majority of patients with fibromyalgia and neuropathic pain were diagnosed with small fiber neuropathy based on reduced epidermal nerve fiber, according to research presented at the American College of Rheumatology Annual Meeting.

Researchers retrospectively examined 56 patients who met either the ACR criteria or the 2010 revised fibromyalgia criteria. Punch biopsies were performed at proximal and distal sites on patients' lower limbs. Epidermal nerve fiber density was counted on 50 micron sections, and PGP 9.5 immunolabeling was performed.

“A significant percentage of patients with fibromyalgia will often have neuropathic complaints, so in addition to the kind of dull muscle, flu-like symptoms, they will get burning, stabbing, tingling [and] allodynia,”

researcher *Todd D. Levine, MD**, assistant professor at the University of Arizona, told *Healio.com*. “Some of them will have autonomic systems. All of that is suggestive that there might be a neuropathic component to their disorder.

“Despite that, if you do traditional EMG/nerve conduction studies, those are normal. One of the reasons we think that it is normal is that the pain fibers … are very small fibers. They're too small to be detected by the standard tests. So, this technique, which involves a small 3-mm punch biopsy, allows us to study these small unmyelinated nerve fibers in patients.”

A standard serologic evaluation searched for identifiable causes for neuropathy in patients with reduced epidermal nerve fiber density, resulting in 61% of patients being diagnosed with small fiber neuropathy.

Five patients displayed evidence of neuropathy on EMG/nerve conduction studies that was inconclusive for diagnosis.

Of the patients with fibromyalgia and small fiber neuropathy, 71% had serologic evidence of underlying etiology for the neuropathy, which had been undetected previously and most of which was treatable. Identifiable causes of small fiber neuropathy among patients included glucose metabolism (n=11), vitamin D deficiency (n=5), Sjögren’s syndrome (n=2) and elevated erythrocyte sedimentation rate (n=2).

“This would argue that at least in some of the patients, the pain generator may be the small nerves, as opposed to being in the brain, where some people think the pain is,” Levine said. “Probably it's going to be a combination of both, so that fibromyalgia is really, probably a combination of pathophysiology.”

***Disclosure:* Levine and researcher David Saperstein, MD, reported ownership or partnership in Corinthian Reference Labs.

For more information: Levine TD. P969: Presence of Small Fiber Neuropathy in a Cohort of Patients with Fibromyalgia.

Sleep Abnormalities in Chronic Fatigue Syndrome/Myalgic Encephalomyelitis: A Review

http://dx.doi.org/10.5664/jcsm.2276

Melinda L. Jackson, Ph.D.; Dorothy Bruck, Ph.D., School of Social Sciences and Psychology, Victoria University, Victoria, Australia

Chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME) is a chronic, disabling illness that affects approximately 0.2% of the population. Non-restorative sleep despite sufficient or extended total sleep time is one of the major clinical diagnostic criteria; however, the underlying cause of this symptom is unknown. This review aims to provide a comprehensive overview of the literature examining sleep in CFS/ME and the issues surrounding the current research findings.

Polysomnographic and other objective measures of sleep have observed few differences in sleep parameters between CFS/ME patients and healthy controls, although some discrepancies do exist. This lack of significant objective differences contrasts with the common subjective complaints of disturbed and unrefreshed sleep by CFS/ME patients.

The emergence of new, more sensitive techniques that examine the microstructure of sleep are showing promise for detecting differences in sleep between patients and healthy individuals. There is preliminary evidence that alterations in sleep stage transitions and sleep instability, and other physiological mechanisms, such as heart rate variability and altered cortisol profiles, may be evident.

Future research investigating the etiology of non-restorative sleep in CFS/ME may also help us to uncover the causes of non-restorative sleep and fatigue in other medical conditions.
High prevalence of orofacial complaints in patients with fibromyalgia: a case-control study.

da Silva LA, Kazyiama HH, de Siqueira JT, Teixeira MJ, de Siqueira SR., Postgraduate Student, Neurology Department, Medical School, University of São Paulo, São Paulo, Brazil.

Abstract

OBJECTIVE: The aim of this study was to investigate the orofacial complaints and characteristics of patients with fibromyalgia syndrome (FS) compared with controls.

STUDY DESIGN: We evaluated 25 patients diagnosed with FS compared with 25 gender- and age-matched controls by using a detailed clinical protocol for orofacial pain diagnosis and dental examination.

RESULTS: FS patients had a higher frequency of temporomandibular disorders (TMD), masticatory complaints, pain with mandibular movements, and pain upon palpation of the head and neck area. There were no significant differences related to the dental exam.

CONCLUSIONS: Orofacial complaints including TMD may be present either as symptoms of FS or as a comorbidity associated with this condition. A comprehensive evaluation of patients with FS is necessary to identify the need for specific treatments for orofacial complaints. Future studies, especially those with longitudinal design, should clarify whether a cause-effect relationship exists between orofacial complaints and fibromyalgia.

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PMID:22906580[PubMed - in process]
Purine metabolites in fibromyalgia syndrome.

Fais A, Cacace E, Corda M, Era B, Peri M, Utzeri S, Ruggiero V., Dipartimento di Scienze della Vita e dell'Ambiente, Università di Cagliari, 09042 Monserrato, Cagliari, Italy.

Abstract

OBJECTIVE: To evaluate serum purine metabolite concentrations in patients affected by fibromyalgia syndrome (FMS) and the relationships between their levels and FM clinical parameters.

DESIGN AND METHODS: Serum purine levels were quantified using LC/UV-vis in 22 fibromyalgic females (according to the American College of Rheumatology classification criteria) and 22 healthy females.

RESULTS: Significantly higher serum inosine, hypoxanthine and xanthine levels (p<0.001) and significantly lower serum adenosine (p<0.05) were detected in the FMS patients vs healthy controls. Our data show a negative correlation between adenosine and Fibromyalgia Impact Questionnaire (FIQ).

CONCLUSIONS: Study results suggest that purines, in particular adenosine and inosine, may be involved in pain transmission in fibromyalgia.

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PMID:23000315[PubMed - as supplied by publisher]
Fibromyalgia showed greater association with lupus than Sjőgren’s syndrome


Abstract

Fibromyalgia appeared to contribute to symptoms more in patients with systemic lupus erythematosus than in patients with primary Sjőgren’s syndrome, according to study results.

Researchers in Italy studied 50 patients with systemic lupus erythematosus (SLE; mean age, 44.16 years) and 50 patients with primary Sjőgren’s syndrome (pSS; mean age, 54.14 years). A 100-mm visual analog scale and Fibromyalgia Impact Questionnaire were used by patients to rate fatigue, pain and disease activity. Mood disorders were quantified through the Zung depression and anxiety scales. An algometer was used to evaluate tender points. Fibromyalgia (FM) was determined using 1990 American College of Rheumatology classification criteria.

Forty SLE patients (80%) and 44 patients with pSS (88%) reported fatigue, while 40 in the SLE cohort (80%) and 45 in the pSS group (90%) reported pain. Sixteen patients with SLE (33%) and nine patients with pSS (18%) were diagnosed with FM (P=.022). Patients with SLE had a mean of 7.5 positive tender points (TP) compared with 5.7 in patients with pSS. There also was a greater mean number of TP in patients with SLE and FM compared with those with pSS and FM (15.12 vs. 12.88; P=.02).

In either group, no correlation with disease activity was noted.

“The results of our observation suggest that fatigue reported by pSS patients is mostly related to the disease itself, even if no significant correlation between fatigue and disease activity has been observed,” the researchers reported.

“Among the studies designed to compare fibromyalgia symptoms in [connective tissue diseases], the present one is the first to demonstrate a higher prevalence of FM in SLE than in pSS,” the researchers concluded. “FM seems to contribute to constitutional symptoms more in SLE than in pSS, suggesting a different underlying cause of fatigue and widespread pain in these two different connective tissue diseases.”
Chronic Fatigue Syndrome: How Does It Affect Sleep?

Sleep disruptions experienced by the sufferers of Chronic Fatigue Syndrome.

Published on January 9, 2013 by Michael J. Breus, Ph.D. in Sleep Newzzz

For people with chronic fatigue syndrome, sleep problems are common. Sleep disorders, disruptive and non-refreshing sleep are some of the most frequent complaints from people suffering from chronic fatigue. Chronic fatigue syndrome is a debilitating medical condition. It’s also a mysterious—and historically controversial—illness.

The basic characteristics of chronic fatigue syndrome include ongoing fatigue that interferes with daily activities, problems with memory and concentration, muscle pain and headaches, and other physical symptoms such as sore throat and tender lymph nodes. People with chronic fatigue also experience feelings of malaise after periods of mental and physical exertion.

The causes of chronic fatigue are unknown. There is no test to determine the presence of the illness. Physicians make a diagnosis based on the presence of a cluster of symptoms over an extended period of time, at least 6 months, and by ruling out other conditions. For many years chronic fatigue was considered with skepticism by some in the medical community.

There were those who questioned whether chronic fatigue was an illness at all, rather than the consequence of a sleep disorder or a mental health issue. Over the past two decades, chronic fatigue syndrome has won acceptance by the medical establishment. But much about the disorder—its causes, its mechanisms in the body—remain largely unknown.

Disrupted sleep is a hallmark of chronic fatigue syndrome. Chronic fatigue is associated with a range of sleep problems, including:

- Excessive daytime sleepiness
- Non-restorative sleep (waking feeling tired even after sufficient or prolonged periods of rest)
- Difficulty falling asleep and staying asleep
- Sleep disorders such as obstructive sleep apnea, insomnia, and narcolepsy

Despite the frequency with which people with chronic fatigue syndrome experience sleep disturbances, the connection between sleep and chronic fatigue—like so much else about the disorder—is not well understood.

Researchers at Australia’s Victoria University have conducted a review of research related to sleep and chronic fatigue. Their analysis sheds some light on possible reasons for poor sleep among patients with chronic fatigue.

Read the full article here: http://bit.ly/UDDdVH
Kinematics gait disorder in men with fibromyalgia.

J.M. Heredia-Jimenez and V.M. Soto-Hermoso, Department of Physical Education and Sports, Faculty of Education and Human Science, University of Granada, C/El Greco s/n, 51002, Ceuta, Spain

*Abstract:*

The aim of this study was to assess the kinematics [aspects of motion apart from considerations of mass and force] disorder of gait in men with fibromyalgia.

We studied 12 male with fibromyalgia and 14 healthy men. Each participant of the study walked five trials along a 18.6-m walkway. Fibromyalgia patients completed a Spanish version of Fibromyalgia Impact Questionnaire.

Significant differences between fibromyalgia and control groups were found in velocity, stride length, and cadence. Gait parameters of men affected by fibromyalgia were impaired when compared to those of healthy group due to bradykinesia [abnormal slowness of movement].

According to previous studies to assess gait variables in female patients, the male with fibromyalgia also showed lower values of velocity, cadence, and stride length than healthy group but not reported significant differences in swing, stance, single, or double support phase.
Evaluation of the efficacy of memantine in the treatment of fibromyalgia: study protocol for a doubled-blind randomized controlled trial with six-month follow-up.


ABSTRACT:

BACKGROUND: Fibromyalgia is a prevalent chronic rheumatic disease of great clinical importance. Recent studies have found raised levels of glutamate in the insula, hippocampus and posterior cingulate cortex regions of the brains of fibromyalgia (FM) patients.

This finding has led researchers to speculate about the usefulness of glutamate-blocking drugs such as memantine in the treatment of fibromyalgia.

The hypothesis of this study is that the administration of memantine will reduce the glutamate levels, and furthermore, will decrease the perceived pain.

The aim of this study is to evaluate the efficacy of memantine in the treatment of pain (pain perception).

A secondary objective is to evaluate the efficacy of memantine in the treatment of other clinical symptoms of FM, and to evaluate the efficacy of memantine in reducing brain levels of glutamate, and its effects on the central nervous system as a whole.

Design. A double-blind parallel randomized controlled trial. Participants, Seventy patients diagnosed with FM will be recruited from primary health care centers in Zaragoza, Spain. Intervention. The subjects will be randomized in two groups: A) A treatment group (n = 35), which will receive 20 mg of memantine daily; B) A control group (n = 35), to which will be administered a placebo. There will be a six-month follow-up period (including a titration period of one month).

Outcomes. The main efficacy variable of this study is pain (pain perception). The secondary efficacy variables are clinical symptoms (pain threshold, cognitive function, health status, anxiety, depression, clinical impression and quality of life) and glutamate levels in different regions of the brain, which will be assessed by magnetic resonance spectroscopy.

Randomization and blinding. Randomization has been computer-generated, and the random allocation sequence will be implemented by telephone. Subjects of the study and the research assistants will be blinded to group assignment.

DISCUSSION: There is a need for the development of innovative and more effective treatments for fibromyalgia. This clinical trial will determine whether memantine can be an effective pharmacological treatment for fibromyalgia patients.

Trial registration: Current Controlled Trials ISRCTN45127327EUDRACT 2011-006244-73.
High prevalence of fibromyalgia symptoms among healthy full-term pregnant women.

Saa’d S, Many A, Jacob G, Ablin JN., Internal Medicine 6, Tel Aviv Sourasky Medical Center, Tel Aviv, Israel.

Abstract

The impact of fibromyalgia on the course of pregnancy is not clearly defined. We evaluate the frequency of FMS symptoms among full-term healthy pregnant women and the impact on the course of delivery.

The 2011 modification of the ACR 2010 criteria for FMS diagnosis was used as well as the FIQ, SF-36 and AIMS questionnaires. The 1990 ACR classification criteria were documented.

Data were collected relating to course of the delivery, induction, length of stage 1, 2 and 3 of delivery, epidural anesthesia, artificial rupture of membranes, instrumental delivery and cesarean section. A VAS recording pain intensity during delivery was documented.

Out of 100 women recruited, 27 (27 %) fulfilled Modified FMS criteria. Only one of these women fulfilled ACR 1990 criteria. Women who fulfilled the ACR criteria differed significantly from women who did not fulfill these criteria on a broad range of parameters including widespread pain and fatigue, social functioning, emotional well-being, role limitation and physical functioning.

A significant correlation was found between length of stage 2 and results of the FIQ as well as with components of the SF-36. The intensity of pain during birth however was not correlated with the presence of FMS criteria.

FMS symptoms were highly prevalent among healthy pregnant women at term.

The presence of such symptoms may impact on the course of delivery and the need for anesthesia.

Evaluating for features of centrally mediated pain may be of clinical relevance for physicians involved in the treatment of pregnant women.

PMID: 23263499 [PubMed - as supplied by publisher]
Unique immunologic patterns in fibromyalgia

Frederick G Behm, Igor M Gavin, Oleksiy Karpenko, Valerie Lindgren, Sujata Gaitonde, Peter A Gashkoff and Bruce S Gillis


Abstract

Background

Fibromyalgia (FM) is a clinical syndrome characterized by chronic pain and alldynia. The diagnosis of FM has been one of exclusion as a test to confirm the diagnosis is lacking. Recent data highlight the role of the immune system in FM. Aberrant expressions of immune mediators, such as cytokines, have been linked to the pathogenesis and traits of FM. We therefore determined whether cytokine production by immune cells is altered in FM patients by comparing the cellular responses to mitogenic activators of stimulated blood mononuclear cells of a large number of patients with FM to those of healthy matched individuals.

Methods

Plasma and peripheral blood mononuclear cells (PBMC) were collected from 110 patients with the clinical diagnosis of FM and 91 healthy donors. Parallel samples of PBMC were cultured overnight in medium alone or in the presence of mitogenic activators; PHA or PMA in combination with ionomycin. The cytokine concentrations of IFN-γ, IL-5, IL-6, IL-8, IL-10, MIP-1β, MCP-1, and MIP1-α in plasma as well as in cultured supernatants were determined using a multiplex immunoassay using bead array technology.

Results

Cytokine levels of stimulated PBMC cultures of healthy control subjects were significantly increased as compared to matched non-stimulated PBMC cultures. In contrast, the concentrations of most cytokines were lower in stimulated samples from patients with FM compared to controls. The decreases of cytokine concentrations in patients samples ranged from 1.5-fold for MIP-1β to 10.2-fold for IL-6 in PHA challenges. In PMA challenges, we observed 1.8 to 4-fold decreases in the concentrations of cytokines in patient samples.

Conclusion

The cytokine responses to mitogenic activators of PBMC isolated from patients with FM were significantly lower than those of healthy individuals, implying that cell-mediated immunity is impaired in FM patients. This novel cytokine assay reveals unique and valuable immunologic traits, which, when combined with clinical patterns, can offer a diagnostic methodology in FM.
Perceived Triggers May Not Actually Provoke Migraine

Sue Hughes  Jan 24, 2013

Trying to provoke an attack of migraine with aura in a laboratory setting by using patients' self-reported triggers was successful in very few cases, a new study shows, leading the study authors to conclude that migraine triggers may not be as strong as patients believe.

The study was conducted by a group led by Anders Hougaard, MD, from the Danish Headache Center, Copenhagen.

Dr. Hougaard suggested that these new results could have implications for advice given to patients about triggers.

"Migraine patients are usually advised to identify triggers and try and avoid them," he told Medscape Medical News. "But our research suggests that this may be limiting people's lives and causing unnecessary stress in trying to avoid a wide range of factors which may turn out not to be triggers after all."

"Of course patients need to try to identify triggers but they need to establish that they are true triggers before cutting them out of their lives. So I would advise that they allow several exposures before defining a trigger. Many people avoid a whole array of factors such as red wine, chocolate, cheese, coffee, exercise, and sunlight. This can make life very difficult and it might not be necessary." Dr. Hougaard also pointed out that migraine trigger is not a simple "yes or no" issue. "It is much more complicated than that. The threshold for a migraine attack probably varies according to many other factors including stress, tiredness, hormone levels etc. Patients are more vulnerable to attacks at certain times," he said. "The lab setting is artificial. We can't replicate the stress of everyday life. It would be better to test in an everyday life setting but that's hard for a scientific study."

Trigger or Premonitory Symptom?

Dr. Hougaard also raised the possibility of triggers being confused with cravings or certain behaviors that are actually part of the start of the migraine, or a premonitory symptom. "Migraines are often preceded by certain feelings such as tiredness, excitement or depression or cravings for certain foods. It might be that a craving for chocolate which is a premonitory symptom could be misinterpreted as a migraine trigger." For the study, the researchers recruited 27 patients with migraine aura who reported that bright or flickering light or strenuous exercise would trigger their migraine attacks. They underwent provocation with different types of photo stimulation, strenuous exercise, or a combination of these 2 factors. This resulted in attacks of migraine with aura in only 3 (11%) patients. An additional 3 patients reported migraine without aura. Exercise was a stronger trigger than photo stimulation.

Dr. Hougaard told Medscape Medical News that bright light and physical activity are 2 of the most common triggers for migraine with aura, the other two being stress and emotional influences, which are more difficult to simulate in a laboratory environment. "While we can't extrapolate our results for sure to other triggers and to migraine without aura, I would think there is a strong possibly that the results would also apply to these too," he added.

In an accompanying editorial, Peter J. Goadsby, MD, from the University of California, San Francisco, and Stephen D. Silberstein, MD, Thomas Jefferson University, Philadelphia, Pennsylvania, agree with Dr. Hougaard that the classic advice of avoiding triggers may be wrong. "If migraine is a disorder of habituation of the brain to ordinary sensory signals, should we try to train the brain to habituate rather than avoid the trigger?" they ask. "Many questions are unresolved and require continued careful, bedside approaches to studying this common, disabling brain disorder."

The study was supported by the University of Copenhagen, the Lundbeck Foundation Center for Neurovascular Signalling (LUCENS), the Danish Council for Independent Research-Medical Sciences (FSS), the Novo Nordisk Foundation, and the Research Foundation of the Capital Region of Denmark. Dr. Hougaard, Dr. Goadsby, and Dr. Silberstein have disclosed no relevant financial relationships.

Evidence Grows for Narcolepsy Link to Swine Flu Shot

Jan 22, 2013
By Kate Kelland

STOCKHOLM (Reuters) Jan 22 - Emelie Olsson is plagued by hallucinations and nightmares. When she wakes up, she's often paralyzed, unable to breathe properly or call for help. During the day she can barely stay awake, and often misses school or having fun with friends. She is only 14, but at times she has wondered if her life is worth living.

Emelie is one of around 800 children in Sweden and elsewhere in Europe who developed narcolepsy after being immunized with the Pandemrix H1N1 swine flu vaccine made by British drugmaker GlaxoSmithKline in 2009.

Finland, Norway, Ireland and France have seen spikes in narcolepsy cases, too, and people familiar with the results of a soon-to-be-published study in Britain have told Reuters it will show a similar pattern in children there.

Europe's drugs regulator has ruled Pandemrix should no longer be used in people younger than age 20. The chief medical officer at GSK's vaccines division, Norman Begg, says his firm views the issue extremely seriously and is "absolutely committed to getting to the bottom of this", but adds there is not yet enough data or evidence to suggest a causal link.

Others - including Emmanuel Mignot, a leading expert on narcolepsy, who is being funded by GSK to investigate further - agree more research is needed but say the evidence is already clearly pointing in one direction.

"There's no doubt in my mind whatsoever that Pandemrix increased the occurrence of narcolepsy onset in children in some countries - and probably in most countries," says Mignot, from Stanford University in Palo Alto, California.

Acupuncture for irritable bowel syndrome: primary care based pragmatic randomised controlled trial

**Authors:** MacPherson H et al

**Summary:** This UK study assessed the effectiveness of acupuncture for irritable bowel syndrome (IBS) in primary care when provided as an adjunct to usual care. The 233 participants had IBS with an average duration of 13 years and score of ≥100 on the IBS Symptom Severity Score (SSS). Interventions consisted of 10 weekly individualised acupuncture sessions plus usual care (n=116) or usual care alone (n=117). At 3 months, the IBS SSS was reduced by a significantly greater amount in the acupuncture group (-27.43; p=0.012). The number needed to treat for successful treatment (≥50 point reduction in the IBS SSS) was 6, based on 49% success in the acupuncture group vs 31% in the control group. This between-group benefit largely persisted at 6, 9 and 12 months.

**Comment:** IBS is widely studied in the alternative medical arena. This study attempted to deal the condition a blow by treating patients with weekly acupuncture sessions. With the treatment group coming out head first (though not by much), acupuncture for IBS may well be worth a stab.

**Reference:** BMC Gastroenterology 2012;12:150
http://www.biomedcentral.com/1471-230X/12/150/abstract
BMC Family Practice 2013, 14:12

Cost-effectiveness of supported self-management for CFS/ME patients in primary care.

Gerry Richardson, David Epstein, Carolyn Chew-Graham, Christopher Dowrick, Richard P Bentall, Richard K Morriss, Sarah Peters, Lisa Riste, Karina Lovell, Graham Dunn, Alison J Wearden

Nurse led self-help treatments for people with chronic fatigue syndrome/myalgic encephalitis (CFS/ME) have been shown to be effective in reducing fatigue but their cost-effectiveness is unknown.

Methods: Cost-effectiveness analysis conducted alongside a single blind randomised controlled trial comparing pragmatic rehabilitation (PR) and supportive listening (SL) delivered by primary care nurses, and treatment as usual (TAU) delivered by the general practitioner (GP) in North West England. A within trial analysis was conducted comparing the costs and quality adjusted life years (QALYs) measured within the time frame of the trial.

296 patients aged 18 and over with CFS/ME diagnosed using the Oxford criteria were included in the cost-effectiveness analysis.

Results: Treatment as usual is less expensive and leads to better patient outcomes compared with Supportive Listening. Treatment as usual is also less expensive than Pragmatic Rehabilitation.

PR was effective at reducing fatigue in the short term, but the impact of the intervention on QALYs was uncertain. However, based on the results of this trial, PR is unlikely to be cost-effective in this patient population.

Conclusions: This analysis does not support the introduction of SL.

Any benefits generated by PR are unlikely to be of sufficient magnitude to warrant recommending PR for this patient group on cost-effectiveness grounds alone. However, dissatisfaction with current treatment options means simply continuing with 'treatment as usual' in primary care is unlikely to be acceptable to patients and practitioners.

Trial registration: The trial registration number is IRCTN74156610

http://www.biomedcentral.com/content/pdf/1471-2296-14-12.pdf
Psychosom Med. 2013 Jan 16. [Epub ahead of print]

Life Course Study of the Etiology of Self-Reported Irritable Bowel Syndrome in the 1958 British Birth Cohort.

Goodwin L, White PD, Hotopf M, Stansfeld SA, Clark C., Barts and The London School of Medicine and Dentistry, Queen Mary University of London; and Department of Psychological Medicine, Institute of Psychiatry, King's College London, London, UK.

Abstract

Objective: Irritable bowel syndrome (IBS) is a common gastrointestinal disorder with unknown etiology. This is the first study to use a life course approach to examine premorbid risk markers for self-reported IBS in a UK birth cohort.

Methods: Cohort study using the 1958 British birth cohort, which included 98.7% of births in 1 week in England, Wales, and Scotland. The outcome was self-reported IBS by the age of 42 years, classified with onset after 24 years and onset after 34 years. Childhood psychopathology was assessed by the Rutter scales, and adulthood psychopathology was assessed by the Malaise Inventory.

Results: The prevalence of self-reported IBS in this cohort was 8.4% by 42 years (95% confidence interval [CI] = 8.2-8.6). In multivariate analyses, being female (odds ratio [OR] = 2.00, 95% CI = 1.67-2.36), reporting 1 week to 1 month of school absence for ill health at 16 years (OR = 1.27, 95% CI = 1.03-1.56) and psychopathology at 23 years (OR = 1.25, 95% CI = 1.01-1.54) and 33 years (OR = 2.20, 95% CI = 1.74-2.76) were associated with an increased odds for IBS. Prospectively measured childhood adversity showed no significant association.

Conclusions: This is the first study to show a long-term prospective link between premorbid psychopathology and later self-reported IBS, in agreement with previous findings on chronic fatigue syndrome http://bjp.rcpsych.org/content/199/4/323.long.

There is no evidence that prospective measures of childhood adversity are risk markers for IBS, and there is weak evidence that prospective measures of childhood illness at 16 years are risk markers for IBS, differing to results from the same cohort for psychopathology, chronic fatigue syndrome, and chronic widespread pain.

This study also does not replicate the findings of retrospective studies examining the etiology of IBS.

PMID: 23324872 [PubMed - as supplied by publisher]
Investigation of Hemispherx Biopharma, Inc.(makers of Ampligen)

By Business Wire via The Motley, Posted under: Investing a

WASHINGTON--(BUSINESS WIRE via The Motley, Posted under: Investing)-- Cohen Milstein Sellers & Toll PLLC is conducting an investigation to determine whether Hemispherx Biopharma, Inc. ("Hemispherx" or the "Company") and certain of its officers and directors made false and misleading statements and/or omissions in violation of Sections 10(b) and 20(a) of the Securities Exchange Act of 1934.

A class action lawsuit was filed in the U.S. District Court Eastern District of Pennsylvania by another law firm on behalf of purchasers of the common stock of Hemispherx Biopharma, Inc. (NYS: HEB) between March 19, 2012 and December 17, 2012, inclusive (the "Class Period").

Hemispherx is a pharmaceutical company engaged in the clinical development and manufacture of new drug therapies, including Ampligen, an experimental drug to be used in the treatment of viral and immune-based chronic disorders such as Chronic Fatigue Syndrome ("CFS"). The complaint alleges that Hemispherx and certain of its officers and directors ("Defendants") made false and misleading statements regarding the safety and efficacy of Ampligen, and also misrepresented and/or failed to disclose that Hemispherx could not demonstrate the requisite safety and efficacy of Ampligen because its clinical trials were not properly designed.

The Company submitted a New Drug Application ("NDA") to the U.S. Food and Drug Administration ("FDA") for Ampligen in 2007. In 2009, the FDA rejected the application, stating that the clinical studies for the drug "did not provide credible evidence of efficacy of Ampligen" in patients with CFS and recommending that the Company conduct additional studies of the drug.

On October 22, 2012, the Company announced that the FDA had scheduled a meeting with an advisory committee to review the Ampligen NDA for the treatment of CFS. On December 18, 2012, the FDA posted on its website briefing documents for the December 20 advisory committee meeting that were described as "sharply critical" of the Company and Ampligen. In addition to citing "multiple concerns" with the efficacy and safety of Ampligen, the briefing documents criticized Hemispherx for submitting post-hoc analyses from a deficient Phase III study of Ampligen rather than starting a new one as requested. The briefing documents also revealed the FDA had warned Hemispherx in a meeting on June 8, 2012 that, "[i]t would be unusual for this type of data to provide adequate evidence of efficacy."

Read the full story here: http://aol.it/101BI5U
Chronic fatigue syndrome following infections in adolescents.

Katz BZ, Jason LA.

Source
aDivision of Infectious Diseases, Ann and Robert H. Lurie Children's Hospital of Chicago, Northwestern University Feinberg School of Medicine bCenter for Community Research, DePaul University, Chicago, Illinois, USA.

Abstract

PURPOSE OF REVIEW:
To review the recent epidemiology, pathophysiology, and treatment of postinfectious chronic fatigue syndrome (CFS) in adolescents.

RECENT FINDINGS:
Thirteen percent of adolescents (mainly women) met the criteria for CFS 6 months following infectious mononucleosis; the figure was 7% at 12 months and 4% at 24 months. Peak work capacity, activity level, orthostatic intolerance, salivary cortisol, and natural killer cell number and function were similar between adolescents with CFS following infectious mononucleosis and recovered controls. Autonomic system, oxygen consumption, peak oxygen pulse, psychological and cytokine network differences were documented between those who recovered and those who did not.

SUMMARY:
The prognosis of CFS is better in adolescents than in adults. Activity level, exercise tolerance, and orthostatic testing could not distinguish patients with CFS from adolescents who have recovered from infectious mononucleosis (controls), while certain cytokine network analyses, life stress factors, and autonomic symptoms could.

PMID:
23263024
[PubMed - in process]
Cerebral vascular control is associated with skeletal muscle pH in chronic fatigue syndrome patients both at rest and during dynamic stimulation.

Jiabao Hea, Kieren G. Hollingswortha, Julia L. Newtont, Andrew M. Blamirea, Institute of Cellular Medicine & Newcastle Magnetic Resonance Centre, Newcastle University, Newcastle upon Tyne, United Kingdom b Institute for Ageing and Health, Newcastle University, Newcastle upon Tyne, United Kingdom Corresponding author at: Newcastle Magnetic Resonance Centre, Newcastle University, Newcastle upon Tyne, NE4 5PL, United Kingdom.

http://dx.doi.org/10.1016/j.nicl.2012.12.006

Abstract

Cerebral blood flow (CBF) is maintained despite changing systemic blood pressure through cerebral vascular control, with such tight regulation believed to be under local tissue control. Chronic fatigue syndrome (CFS) associates with a wide range of symptoms, including orthostatic intolerance, skeletal muscle pH abnormalities and cognitive impairment. CFS patients are known to have reduced CBF and orthostatic intolerance associates with abnormal vascular regulation, while skeletal muscle pH abnormalities associate with autonomic dysfunction. These findings point to autonomic dysfunction as the central feature of CFS, and cerebral vascular control being influenced by factors outside of the brain, a macroscopic force affecting the stability of regional regulation. We therefore explored whether there was a physiological link between cerebral vascular control and skeletal muscle pH management in CFS.

Seventeen consecutive CFS patients fulfilling the Fukuda criteria were recruited from our local CFS clinical service. To probe the static scenario, CBF and skeletal muscle pH were measured at rest using MRI and 31P magnetic resonance spectroscopy (31P-MRS).

To examine dynamic control, brain functional MRI was performed concurrently with Valsalva manoeuvre (VM), a standard autonomic function challenge, while 31P-MRS was performed during plantar flexion exercise.

Significant inverse correlation was seen between CBF and skeletal muscle pH at rest (r = -0.67, p < 0.01). Prolonged cerebral vascular constriction during the sympathetic phase of VM was associated with higher pH in skeletal muscle after plantar flexion exercise (r = 0.69, p < 0.008).

In conclusion, cerebral vascular control is closely related to skeletal muscle pH both at rest and after dynamic stimulation in CFS.


Yoga for Functional Ability, Pain and Psychosocial Outcomes in Musculoskeletal Conditions: A Systematic Review and Meta-Analysis.

Ward L, Stebbings S, Cherkin D, Baxter GD., Centre for Physiotherapy Research, School of Physiotherapy, University of Otago, Dunedin, New Zealand.

Abstract

OBJECTIVES: Musculoskeletal conditions (MSCs) are the leading cause of disability and chronic pain in the developed world, impacting both functional ability and psychosocial health. The current review investigates the effectiveness of yoga on primary outcomes of functional ability, pain and psychosocial outcomes across a range of MSCs.

METHODS: A comprehensive search of 20 databases was conducted for full-text, randomized controlled trials of yoga in clinically diagnosed MSCs.

RESULT: Seventeen studies met the inclusion criteria, involving 1,626 participants with low back pain (LBP), osteoarthritis (OA), rheumatoid arthritis (RA), kyphosis or fibromyalgia. Studies were quality rated, and analysed for the effect of yoga on primary outcomes, immediately post-intervention. Twelve studies were rated as good quality.

Yoga interventions resulted in a clinically significant improvement in functional outcomes in mild-to-moderate LBP and fibromyalgia, and showed a trend to improvement in kyphosis (excessive outward curvature of the spine, causing hunching of the back).

Yoga significantly improved pain in OA, RA and mild-to-severe LBP.

Psychosocial outcomes were significantly improved in mild-to-moderate LBP and OA.

Meta-analysis of good-quality studies showed a moderate treatment effect for yoga of -0.64 (95%CI -0.89 to -0.39) for functional outcomes and -0.61 (95%CI -0.97 to -0.26) for pain outcomes.

CONCLUSIONS: Evidence suggests that yoga is an acceptable and safe intervention, which may result in clinically relevant improvements in pain and functional outcomes associated with a range of MSCs. Future analysis of outcomes which take into account the amount of yoga received by participants may provide insight into any putative duration or dosage effects of yoga interventions for MSCs.

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**Unique immunologic patterns in fibromyalgia**

Frederick G Behm¹, Igor M Gavin², Oleksiy Karpenko², Valerie Lindgren¹, Sujata Gaitonde¹, Peter A Gashkoff¹ and Bruce S Gillis¹*

**•• Corresponding author: Bruce S Gillis bsgmd@hotmail.com**

**Author Affiliations**

¹ Department of Pathology, University of Illinois at Chicago (UIC), Chicago, IL, USA

² Research Resource Center, University of Illinois at Chicago, Chicago, IL, USA


The electronic version of this article is the complete one and can be found online at: [http://www.biomedcentral.com/1472-6890/12/25](http://www.biomedcentral.com/1472-6890/12/25)

**Abstract**

**Background**

Fibromyalgia (FM) is a clinical syndrome characterized by chronic pain and allodynia. The diagnosis of FM has been one of exclusion as a test to confirm the diagnosis is lacking. Recent data highlight the role of the immune system in FM. Aberrant expressions of immune mediators, such as cytokines, have been linked to the pathogenesis and traits of FM. We therefore determined whether cytokine production by immune cells is altered in FM patients by comparing the cellular responses to mitogenic activators of stimulated blood mononuclear cells of a large number of patients with FM to those of healthy matched individuals.

**Methods**

Plasma and peripheral blood mononuclear cells (PBMC) were collected from 110 patients with the clinical diagnosis of FM and 91 healthy donors. Parallel samples of PBMC were cultured overnight in medium alone or in the presence of mitogenic activators; PHA or PMA in combination with ionomycin. The cytokine concentrations of IFN-γ, IL-5, IL-6, IL-8, IL-10, MIP-1β, MCP-1, and MIP1-α in plasma as well as in cultured supernatants were determined using a multiplex immunoassay using bead array technology.

**Results**

Cytokine levels of stimulated PBMC cultures of healthy control subjects were significantly increased as compared to matched non-stimulated PBMC cultures. In contrast, the concentrations of most cytokines were lower in stimulated samples from patients with FM compared to controls. The decreases of cytokine concentrations in patients samples ranged from 1.5-fold for MIP-1β to 10.2-fold for IL-6 in PHA challenges. In PMA challenges, we observed 1.8 to 4-fold decreases in the concentrations of cytokines in patient samples.

**Conclusion**
The cytokine responses to mitogenic activators of PBMC isolated from patients with FM were significantly lower than those of healthy individuals, implying that cell-mediated immunity is impaired in FM patients. This novel cytokine assay reveals unique and valuable immunologic traits, which, when combined with clinical patterns, can offer a diagnostic methodology in FM.
Chronic Fatigue and Personality: A Twin Study of Causal Pathways and Shared Liabilities.

Poeschla B, Strachan E, Dansie E, Buchwald DS, Afari N., Department of Psychiatry and Behavioral Sciences, School of Medicine, University of Washington, Box 359911, Seattle, WA, 98104-2499, USA,

Abstract

BACKGROUND: The etiology of chronic fatigue syndrome (CFS) remains unknown. Personality traits influence well-being and may play a role in CFS and unexplained chronic fatigue.

PURPOSE: This study aimed to examine the association of emotional instability and extraversion with chronic fatigue and CFS in a genetically informative sample.

METHODS: We evaluated 245 twin pairs for two definitions of chronic fatigue. They completed the Neuroticism and Extraversion subscales of the NEO Five Factor Inventory. Using a co-twin control design, we examined the association between personality and chronic fatigue.

RESULTS: Higher emotional instability was associated with both definitions of chronic fatigue and was confounded by shared genetics. Lower extraversion was also associated with both definitions of fatigue, but was not confounded by familial factors.

CONCLUSIONS: Both emotional instability and extraversion are related to chronic fatigue and CFS. Whereas emotional instability and chronic fatigue are linked by shared genetic mechanisms, the relationship with extraversion may be causal and bidirectional.

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**Fibromyalgia patients reported more sensory, nonsensory symptoms than RA, OA patients**


**Abstract**

Patients with fibromyalgia reported more sensory and nonsensory symptoms compared with patients with rheumatoid arthritis or osteoarthritis, according to study results.

Researchers studied 11,288 patients; 1,199 had fibromyalgia (mean age, 57.8 years; 95.8% women), 8,533 had rheumatoid arthritis (RA; mean age, 62.3 years; 80.6% women), and 1,556 had osteoarthritis (OA; mean age, 66.5 years; 81.7% women).

Patients with fibromyalgia also were more likely to smoke and to be obese.

Somatic symptoms were divided into sensory, including hearing difficulties, and evaluative nonsensory symptoms, including easy bruising and hair loss.

Also included was influenza vaccination, a nonsymptom that was neutral for psychological content or meaning. Logistic regression was used to adjust data for age and sex.

Fibromyalgia patients had greater hearing difficulties (36.2%) compared with RA and OA patients (21.4% and 24.1%, respectively), hair loss (23.4% vs. 18.1% and 15.8%) and easy bruising (47.6% vs. 41.5% and 38.5%).

Influenza vaccination was less common in fibromyalgia patients (57.1%) compared with RA (63.6%) and OA (60.9%) patients.

The probability of sensory and nonsensory symptoms was similar across all rheumatic diseases when controlled for fibromyalgianess (fibromyalgia intensity). Fibromyalgianess was not associated with influenza vaccine between all groups.

“The associations between fibromyalgia/fibromyalgianess and evaluative [nonsensory] symptoms must occur through mechanisms other than central sensitization and augmentation, and are consistent with over-reporting that has a psychological basis,” the researchers concluded. “However, augmentation of sensory symptoms does not preclude simultaneous over-reporting. … Symptoms linked to fibromyalgia are identified across the entire spectrum of fibromyalgia, and do not require a diagnosis of fibromyalgia.”

**Disclosure:** Researcher Winfried Häuser, MD, reports receiving a consultancy honorarium for study design from Daiichi Sankyo.
The therapeutic value of yoga in neurological disorders.

Mishra SK, Singh P, Bunch SJ, Zhang R., Department of Neurology, Keck School of Medicine, USC, Neurology Department, GLA and Olive-View UCLA Medical Center, CA, USA.

Abstract

BACKGROUND: The ancient mind and body healing methods of yoga recently sparked fervor in the scientific community as an alternative and complementary means of therapy. Since the World Health Organization officially began promoting yoga in developing countries in 1978, yoga has been cited for its therapeutic potential and has been widely recognized in Western culture.

However, as an increasing number of people practice yoga for remedial purposes, researchers raise two important questions: 1) Is yoga a valid complementary management and rehabilitation treatment modality? 2) What conditions show promise of treatment with this intervention?.

OBJECTIVE: This review article uses comprehensive scientific, evidence-based studies to analyze the efficacy of various basic and applied aspects of yoga in disease prevention and health promotion. It specifically intends to expose the effects of yoga in neurological disorders, particularly epilepsy, stroke, multiple sclerosis, Alzheimer’s disease, peripheral nervous system disease, and fibromyalgia.

MATERIALS AND METHODS: Information was gathered from various resources including PubMed, Ovid, MD-Consult, USC, and U.C.L.A. libraries. Studies were selected and reviewed on the basis of sample size, control, randomization, double-blinding, and statistical analysis of results.

RESULTS: The practice of yoga and meditation demonstrates statistically encouraging physiological and psychological improvements in the aforementioned neurological disorders. However, there were certain flaws and inadequacies in the study designs employed to evaluate the same. A critical analysis of these studies is presented.

CONCLUSIONS: With the aim to focus attention on this widespread yet largely unexamined treatment modality, this paper seeks to provide direction and support for further research necessary to validate yoga as an integrative, alternative, and complementary therapy.


A Chronic Fatigue Syndrome (CFS) severity score based on case designation criteria


Division of Rheumatology, Immunology and Allergy, Georgetown University, Washington, DC, USA; School of Medicine, University of Pennsylvania, Philadelphia, PA, USA; Internal Medicine Residency Program, 1415 Woodland Ave, Suite 140, Des Moines, IA 50309, USA; Department of Internal Medicine, Norwalk Hospital, Norwalk, CT, USA; School of Medicine, Georgetown University, Washington, DC, USA; School of Medicine University of South Florida, Tampa, FL, USA

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Abstract:

Background: Chronic Fatigue Syndrome case designation criteria are scored as physicians’ subjective, nominal interpretations of patient fatigue, pain (headaches, myalgia, arthralgia, sore throat and lymph nodes), cognitive dysfunction, sleep and exertional exhaustion.

Methods: Subjects self-reported symptoms using an anchored ordinal scale of 0 (no symptom), 1 (trivial complaints), 2 (mild), 3 (moderate), and 4 (severe). Fatigue of 3 or 4 distinguished “Fatigued” from “Not Fatigued” subjects.

The sum of the 8(Sum8) ancillary criteria was tested as a proxy for fatigue. All subjects had history and physical examinations to exclude medical fatigue, and ensure categorization as healthy or CFS subjects.

Results: Fatigued subjects were divided into CFS with ≥4 symptoms or Chronic Idiopathic Fatigue (CIF) with ≤3 symptoms. ROC of Sum8 for CFS and Not Fatigued subjects generated a threshold of 14 (specificity=0.934; sensitivity=0.928).

CFS (n=256) and CIF (n=55) criteria were refined to include Sum8≥14 and ≤13, respectively.

Not Fatigued subjects had highly skewed Sum8 responses. Healthy Controls (HC; n=269) were defined by fatigue=2 and Sum8≤13. Those with Sum8≥14 were defined as CFS–Like With Insufficient Fatigue Syndrome (CFSLWIFS; n=20).

Sum8 and Fatigue were highly correlated (R2=0.977; Cronbach’s alpha=0.924) indicating an intimate relationship between symptom constructs. Cluster analysis suggested 4 clades each in CFS and HC. Translational utility was inferred from the clustering of proteomics from cerebrospinal fluid.

Conclusions: Plotting Fatigue severity versus Sum8 produced an internally consistent classifying system. This is a necessary step for translating symptom profiles into fatigue phenotypes and their pathophysiological mechanisms.
Postural orthostatic tachycardia syndrome as a clinically important subgroup of chronic fatigue syndrome: further evidence for central nervous system dysfunctioning

Jo Nijs1,2,*, Kelly Ickmans1,2

In this issue of the *Journal of Internal Medicine*, Lewis and colleagues [1] provide compelling data for a novel subgroup within the chronic fatigue syndrome (CFS) population. They show that approximately 13% (24/179) of CFS patients have postural orthostatic tachycardia syndrome (POTS), a form of dysautonomia implying that when patients change their body position from supine to upright, their heart rate will increase abnormally (tachycardia).

POTS is associated with several symptoms often seen in CFS patients: fatigue, lightheadedness, dizziness, neurocognitive deficits and exercise intolerance.

Importantly, this was a confirmatory study of a previously published pilot study that found a prevalence rate for POTS of 29% in a smaller sample (n=63) of CFS patients [2].

Another significant finding is the differences in fatigue severity, depressive thoughts, and daytime hypersomnolence between CFS patients with and without POTS, providing evidence for the clinical importance of POTS in CFS.
Low-dose naltrexone for the treatment of fibromyalgia: Findings of a small, randomized, double-blind, placebo-controlled, counterbalanced, crossover trial assessing daily pain levels

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Author Information

1. Stanford University School of Medicine, Palo Alto, California

Email: Jarred Younger (jarred.younger@stanford.edu)

*Department of Anesthesia, Stanford University School of Medicine, 780 Welch Road, Suite 207F, Palo Alto, CA 94304-1573

Abstract

Objective

To determine whether low dosages (4.5 mg/day) of naltrexone reduce fibromyalgia severity as compared with the nonspecific effects of placebo. In this replication and extension study of a previous clinical trial, we tested the impact of low-dose naltrexone on daily self-reported pain. Secondary outcomes included general satisfaction with life, positive mood, sleep quality, and fatigue.

Methods

Thirty-one women with fibromyalgia participated in the randomized, double-blind, placebo-controlled, counterbalanced, crossover study. During the active drug phase, participants received 4.5 mg of oral naltrexone daily. An intensive longitudinal design was used to measure daily levels of pain.

Results

When contrasting the condition end points, we observed a significantly greater reduction of baseline pain in those taking low-dose naltrexone than in those taking placebo (28.8% reduction versus 18.0% reduction; \( P = 0.016 \)). Low-dose naltrexone was also associated with improved general satisfaction with life (\( P = 0.045 \)) and with improved mood (\( P = 0.039 \)), but not improved fatigue or sleep. Thirty-two percent of participants met the criteria for response (defined as a significant reduction in pain plus a significant reduction in either fatigue or sleep problems) during low-dose naltrexone therapy, as contrasted with an 11% response rate during placebo therapy (\( P = 0.05 \)). Low-dose naltrexone was rated equally tolerable as placebo, and no serious side effects were reported.

Conclusion
The preliminary evidence continues to show that low-dose naltrexone has a specific and clinically beneficial impact on fibromyalgia pain. The medication is widely available, inexpensive, safe, and well-tolerated. Parallel-group randomized controlled trials are needed to fully determine the efficacy of the medication.

Plasmacytoid Dendritic Cells in the Duodenum of Individuals Diagnosed with Myalgic Encephalomyelitis Are Uniquely Immunoreactive to Antibodies to Human Endogenous Retroviral Proteins

KENNY L. DE MEIRLEIR1,*,
Svetlana F. KHAIBOULLINA1,*,
MARC FRÉMONT4,
JAN HULSTAERT3,
ALBERT A. RIZVANOV6,
ANDRÁS PALOTÁS7 and
VINCENT C. LOMBARDI1,2

Author Affiliations

1. Whittemore Peterson Institute for Neuro-Immune Disease, Reno, NV, U.S.A.
2. Department of Pathology, University of Nevada, Reno, NV, U.S.A.
3. Department of Human Physiology and Medicine, Vrije University of Brussels, Brussels, Belgium
4. R.E.D. Laboratories, Zellik, Belgium
5. Department of Gastroenterology, General Hospital Jan Portaels, Vilvoorde, Belgium
6. Department of Genetics, Kazan Federal University, Kazan, Russia
7. Asklepios-Med (private medical practice and research center), Szeged, Hungary

Correspondence to: Vincent C. Lombardi, Ph.D., Director of Research, Whittemore Peterson Institute for Neuro-Immune Disease, University of Nevada, Reno 1664 N Virginia Street MS 0552, Reno, NV 89557 U.S.A. Tel: +1 7756828278, Fax: +1 7756828258, e-mail: vclombardi@wpinstitute.org

Abstract

Myalgic encephalomyelitis (ME) is a debilitating illness of unknown etiology characterized by neurocognitive dysfunction, inflammation, immune abnormalities and gastrointestinal distress. An increasing body of evidence suggests that disruptions in the gut may contribute to the induction of neuroinflammation. Therefore, reports of human endogenous retroviral (HERV) expression in association with neuroinflammatory diseases prompted us to investigate the gut of individuals with ME for the presence of HERV proteins. In eight out of 12 individuals with ME, immunoreactivity to HERV proteins was observed in duodenal biopsies. In contrast, no immunoreactivity was detected in any of the eight controls. Immune reactivity to HERV Gag and Env proteins was uniquely co-localized in hematopoietic cells expressing the C-type lectin receptor CLEC4C (CD303/BDC2A), the co-stimulatory marker CD86 and the class II major histocompatibility complex HLA-DR, consistent with plasmacytoid dendritic cells (pDCs). Although the significance of HERVs present in the pDCs of individuals with ME has yet to be determined, these data raise the possibility of an involvement of pDCs and HERVs in ME pathology. To our knowledge, this report describes the first direct association between pDCs and HERVs in human disease.
Myalgic encephalomyelitis (ME) is a debilitating disorder characterized by multi-systemic neuropathology, gastrointestinal (GI) dysfunction, inflammation, and innate immune dysregulation (1). Immunological symptoms often include viral reactivation, cytokine and chemokine irregularities, and decreased natural killer (NK) cell function (2-7). Additionally, reports of individuals with ME–expressing autoantibodies (8, 9), and the successful treatment of ME with the B-cell-depleting drug rituximab (10, 11), suggest that a subset of these individuals may suffer from an uncharacterized antibody–mediated autoimmunity.

Little is known regarding the pathophysiology of ME; therefore, diseases with similar or overlapping symptoms often serve as useful guides when exploring new experimental concepts. For instance, autoimmune diseases such as multiple sclerosis (MS) and systemic lupus erythematosus (SLE) have many symptoms that overlap with those of ME. Neurological manifestations often associated with ME (12), are analogous to the neuroinflammation and cognitive abnormalities associated with MS and SLE (13, 14). Additionally, GI aberrations, which are common to individuals with MS and SLE (15-17), are among the most frequent symptoms reported by those with ME (18, 19).

The gut–associated lymphoid tissue represents the largest immune compartment in the body. In fact, it has been estimated that more than 60% of all T–cells may reside within the small intestine (20), emphasizing the potential contribution of the gut to systemic immunity. Indeed, increases in serum bacterial by-products, particularly lipopolysaccharides resulting from bacterial translocation in the gut, are found to be associated with systemic immune activation in many diseases such as HIV/AIDS, inflammatory bowel disease (IBD), and acute graft–versus–host disease (21-23). Extraintestinal immune dysregulation originating within the gut is described in such diseases as HIV/AIDS and idiopathic lymphocytopenia (24, 21). Although, its contribution to neuroimmune disease in humans is largely unknown, recent studies using animal models support a connection between GI immunity and neuroinflammation. Lee and colleagues reported intestinal microbiota to significantly influence the balance between pro–inflammatory and anti–inflammatory immune responses during the induction of experimental autoimmune encephalomyelitis, an animal model for MS (25). While limitations always exist when using animal models to study human disease, these data clearly support the concept of neuroinflammation associated with alterations in the gut.

Emerging evidence supports a role for human endogenous retroviruses (HERVs) in the etiopathology of autoimmune diseases such as MS and SLE (26). HERVs are remnants of ancient retroviral infections that integrated into the germ line and are now transmitted vertically (27). Not including the long interspersed elements (LINE) and other retrotransposons, HERVs constitute approximately 8% of the human genome (28). Although HERV proteins are self–antigens and should not induce an immune response, HERV proteins and serum antibodies against HERVs have been associated with a number of autoimmune diseases, including MS and SLE (29-32). These associations have motivated researchers to search for a role of HERV proteins in human pathology. Although associations are often difficult to render into definitive causation, it is widely believed that the humoral immune response against HERV proteins leads to autoimmunity through a process of molecular mimicry (33). HERV proteins are also known to act as superantigens, which have the ability to cause polyclonal T–cell activation and massive cytokine production (34). In 2001, Perron and colleagues reported the potential immunopathogenic properties of the HERV–W envelope protein, as a major proinflammatory and superantigenic determinant associated with MS (35).

In summary, individuals with ME have a significant number of symptoms that are similar to those described in autoimmune diseases such as MS and SLE. Additionally, the expression of HERV proteins has been observed in the lymphoid tissue of individuals with autoimmune disease. Finally, the gut represents the largest lymphoid compartment and is a significant site of ME–related pathology. For these reasons, we sought to determine if endogenous retroviral proteins could be detected in GI tissue of those with ME.

Human Endogenous Retrovirus-K18 Superantigen Expression and Human Herpesvirus-6 and Human Herpesvirus-7 Viral Loads in Chronic Fatigue Patients.

Oakes B, Hoagland-Henefield M, Komaroff AL, Erickson JL, Huber BT., Graduate Program in Pharmacology and Experimental Therapeutics, Sackler School of Graduate Biomedical Sciences, Tufts University.

Abstract

Background. Chronic Fatigue Syndrome (CFS) is a complex, heterogeneous disease characterized by debilitating fatigue that is not improved with bed rest and worsens after physical activity or mental exertion. Despite extensive research into a cause of CFS, no definitive etiology has been determined; however, a large percentage of CFS patients note an acute infectious event that triggers their fatigue.

Methods. Blood and saliva were collected from 39 CFS cases and 9 healthy control subjects. Peripheral blood mononuclear cells (PBMCs) were tested for human endogenous retrovirus-K18 (HERV-K18) env transcripts using a TaqMan qPCR. In addition, viral copy number of human herpesvirus-6 (HHV-6) and human herpesvirus-7 (HHV-7) were measured in both saliva and PBMCs using TaqMan qPCRs. Transcript levels and viral copy number were compared to patient CFS symptom severity.

Results. HERV-K18 env transcripts were not significantly different between healthy control subjects and CFS patients.

Also, HERV-K18 env transcripts did not correlate with HHV-6 viral copy number or HHV-7 viral copy number in either PBMCs or saliva. HHV-6 viral copy number and HHV-7 viral copy number in both PBMCs and saliva were not significantly different between healthy control subjects and CFS patients.

HERV-K18 env transcripts, HHV-6 viral copy number, and HHV-7 viral copy number did not correlate with CFS symptom severity.

Conclusions. We fail to demonstrate a difference in HERV-K18 env transcripts, HHV-6 viral copy number, and HHV-7 viral copy number between CFS patients and healthy controls. Our data do not support the hypothesis of reactivation of HHV-6 or HHV-7 in CFS.
Pesticides and Human Chronic Diseases; Evidences, Mechanisms, and Perspectives.

Mostafalou S, Abdollahi M., Department of Toxicology and Pharmacology, Faculty of Pharmacy and Pharmaceutical Sciences Research Center, Tehran University of Medical Sciences, Tehran, Iran.

Abstract

Along with the wide use of pesticides in the world, the concerns over their health impacts are rapidly growing.

There is a huge body of evidence on the relation between exposure to pesticides and elevated rate of chronic diseases such as different types of cancers, diabetes, neurodegenerative disorders like Parkinson, Alzheimer, and amyotrophic lateral sclerosis (ALS), birth defects, and reproductive disorders.

There is also circumstantial evidence on the association of exposure to pesticides with some other chronic diseases like respiratory problems, particularly asthma and chronic obstructive pulmonary disease (COPD), cardiovascular disease such as atherosclerosis and coronary artery disease, chronic nephropathies, autoimmune diseases like systemic lupus erythematosus and rheumatoid arthritis, chronic fatigue syndrome, and aging (aging is not a disease).

The common feature of chronic disorders is a disturbance in cellular homeostasis, which can be induced via pesticides’ primary action like perturbation of ion channels, enzymes, receptors, etc., or can as well be mediated via pathways other than the main mechanism.

In this review, we present the highlighted evidence on the association of pesticide's exposure with the incidence of chronic diseases and introduce genetic damages, epigenetic modifications, endocrine disruption, mitochondrial dysfunction, oxidative stress, endoplasmic reticulum stress and unfolded protein response (UPR), impairment of ubiquitin proteasome system, and defective autophagy as the effective mechanisms of action.

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Chronic fatigue syndrome 5 years after giardiasis: differential diagnoses, characteristics and natural course


Kristine Mørch, Kurt Hanevik, Ann C Rivenes, Jørn E Bødtker, Halvor Næss, Bjarte Stubhaug, Knut-Arne Wensaaas, Guri Rortveit, Geir E Eide, Trygve Hausken and Nina Langeland

Abstract (provisional)

Background: A high prevalence of chronic fatigue has previously been reported following giardiasis after a large waterborne outbreak in Bergen, Norway in 2004. The aim of this study was to describe and evaluate differential diagnoses and natural course of fatigue five years after giardiasis among patients who reported chronic fatigue three years after the infection.

Methods: Patients who three years after Giardia infection met Chalder's criteria for chronic fatigue (n=347) in a questionnaire study among all patients who had laboratory confirmed giardiasis during the Bergen outbreak (n=1252) were invited to participate in this study five years after the infection (n=253). Structured interviews and clinical examination were performed by specialists in psychiatry, neurology and internal medicine/infectious diseases. Fukuda et al's 1994 criteria were used to diagnose chronic fatigue syndrome (CFS) and idiopathic chronic fatigue (ICF). Self-reported fatigue recorded with Chalder Fatigue Questionnaire three and five years after infection were compared.

Results: 53 patients were included. CFS was diagnosed in 41.5% (22/53) and ICF in 13.2% (7/53). Chronic fatigue caused by other aetiology was diagnosed in 24.5% (13/53); five of these patients had sleep apnoea/hypopnoea syndrome, six had depression and five anxiety disorder, and among these two had more than one diagnosis. Fatigue had resolved in 20.8% (11/53). Self-reported fatigue score in the cohort was significantly reduced at five years compared to three years (p<0.001).

Conclusion: The study shows that Giardia duodenalis may induce CFS persisting as long as five years after the infection. Obstructive sleep apnoea/hypopnoea syndrome, depression and anxiety were important differential diagnoses, or possibly comorbidities, to post-infectious fatigue in this study. Improvement of chronic fatigue in the period from three to five years after giardiasis was found.

The development of an activity pacing questionnaire for chronic pain and/or fatigue: a Delphi technique.

Antcliff D, Keeley P, Campbell M, Oldham J, Woby S., Pennine Acute Hospitals NHS Trust, North Manchester General Hospital, Manchester M8 5RB, UK; School of Nursing, Midwifery and Social Work, University of Manchester, Manchester M13 9PL, UK.

Abstract

OBJECTIVE: Activity pacing is frequently advised as a coping strategy for the management of chronic conditions (such as chronic low back pain, chronic widespread pain and chronic fatigue syndrome/myalgic encephalomyelitis). Despite anecdotal support for activity pacing, there is limited and conflicting research evidence into the efficacy of this strategy. There is no consensus on the interpretation of ‘pacing’ due to diverse descriptions, including strategies that encourage both increasing and decreasing activities. Furthermore, at present, there are few validated scales to measure how patients pace their activities. The aim of this study was to undertake the first stage in the development of a comprehensive tool that assesses the multi-faceted nature of pacing among patients with chronic conditions.

DESIGN: Three-round Delphi technique.

PARTICIPANTS: Expert panel based in the UK including patients and clinicians.

RESULTS: The 42 participants who completed three rounds of Delphi included 4 patients, 3 nurses, 26 physiotherapists and 9 occupational therapists. The 38 questions that reached consensus to be included in the questionnaire encompassed a number of different facets of pacing, for example, breaking down tasks, not overdoing activities, and gradually increasing activities.

CONCLUSIONS: To our knowledge, this is the first study that has engaged both patients and clinicians in a Delphi technique to develop an activity pacing questionnaire. In contrast to existing pacing scales, our questionnaire appears to contain a number of distinct facets of pacing. Further study is being undertaken to engage patients in the exploration of the validity, reliability and acceptability of the questionnaire.

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Fatigue severity of patients with idiopathic chronic fatigue compared to healthy subjects.

Lee NH, Son CG., SourceLiver and Immunology Research Center, Daejeon Oriental Hospital of Daejeon University, 22-5 Daheung-dong, Jung-gu, Daejeon, 302-724, Republic of Korea.

Abstract

OBJECTIVE: To analyze the fatigue severity of patients with idiopathic chronic fatigue (ICF) and to compare the severity of this group with that of healthy subjects.

METHODS: One hundred and nine ICF patients and 98 healthy subjects were enrolled in this study. Fatigue severity was measured using the Korean-translated Chalder fatigue severity questionnaire. All subjects scored each item on a 10-point scale as a self-rating numeric scale (NRS), and additionally rated their feeling of general fatigue by visual analogue scale (VAS).

RESULTS: The total NRS scores of patients with ICF was 53 +/- 15 compared with 25 +/- 14 of healthy subjects (2.4 folds for physical symptoms vs. 1.7 +folds for mental symptoms respectively). The VAS scores of patients with ICF were 2.7 times as high as those of healthy subjects.

CONCLUSION: This report is the first to compare the severity of fatigue between ICF patients and healthy subjects. This study contains reference data applicable for the management of this disorder in field of complementary and alternative medicine.

PMID: 23297555 [PubMed - indexed for MEDLINE]
**Relationship between autonomic cardiovascular control, case definition, clinical symptoms, and functional disability in adolescent chronic fatigue syndrome: An exploratory study**


**Abstract (provisional)**

Chronic Fatigue Syndrome (CFS) is characterized by severe impairment and multiple symptoms. Autonomic dysregulation has been demonstrated in several studies.

We aimed at exploring the relationship between indices of autonomic cardiovascular control, the case definition from Centers for Disease Control and Prevention (CDC criteria), important clinical symptoms, and disability in adolescent chronic fatigue syndrome.

Thirty eight CFS patients aged 12--18 years were recruited according to a wide case definition (i.e., not requiring accompanying symptoms) and subjected to head-up tilt test (HUT) and a questionnaire. The relationships between variables were explored with multiple linear regression analyses.

In the final models, disability was positively associated with symptoms of cognitive impairments (p<0.001), hypersensitivity (p<0.001), fatigue (p=0.003) and age (p=0.007). Symptoms of cognitive impairments were associated with age (p=0.002), heart rate (HR) at baseline (p=0.01), and HR response during HUT (p=0.02).

Hypersensitivity was associated with HR response during HUT (p=0.001), high-frequency variability of heart rate (HF-RRI) at baseline (p=0.05), and adherence to the CDC criteria (p=0.005).

Fatigue was associated with gender (p=0.007) and adherence to the CDC criteria (p=0.04).

**From the discussion**: These results, in concert with other findings suggesting that all chronic fatigue states share a relatively stereotyped set of symptoms [47], add to the concerns about the validity of the CDC definition, in particularly among adolescents...

**In conclusion**, a) The disability of CFS patients is not only related to fatigue but to other symptoms as well; b) Altered cardiovascular autonomic control is associated with certain symptoms; c) The CDC criteria are poorly associated with disability, symptoms, and indices of altered autonomic nervous activity.

The full study can be found here: [http://www.bpsmedicine.com/content/pdf/1751-0759-7-5.pdf](http://www.bpsmedicine.com/content/pdf/1751-0759-7-5.pdf)
**Abstract**

In medically ill patients the term 'somatic symptoms' is used to understand those symptoms which cannot be fully understood in the light of existing medical illness(es). These include a number of physical symptoms and also certain clinical syndromes such as irritable bowel syndrome, fibromyalgia, and chronic fatigue syndrome among others.

However, it is increasingly recognized that such patients have larger degrees of psychological morbidities, especially depressive and anxiety disorders, and have disproportionately elevated rates of medical care utilization, including outpatient visits, hospitalizations and total healthcare costs.

In view of this psychological morbidity, significant distress and functional impairment, the role of the consultation-liaison psychiatrist is prominent in the management of these patients.

A consultation-liaison (CL) psychiatrist is expected to be part of the primary care team to manage patient with unexplained SS, and at the same time is expected to guide colleagues to practice a patient-centred approach to improve the outcome of patients with such symptoms.

The clinical work of a CL psychiatrist involves evaluation of patients with medically unexplained symptoms for probable psychiatric disorders and treatment of psychiatric morbidity and also management of patients without psychiatric morbidity.

Management strategies include reattribution, cognitive behaviour therapy and antidepressants, with each strategy showing varying degrees of success.
Decreased muscle concentrations of ATP and PCR in the quadriceps muscle of fibromyalgia patients - A (31) P-MRS study.

Gerdle B, Forsgren MF, Bengtsson A, Leinhard OD, Sören B, Karlsson A, Brandejsky V, Lund E, Lundberg P., Rehabilitation Medicine, Department of Medicine and Health Sciences (IMH), Faculty of Health Sciences, Linköping University, Sweden; Pain and Rehabilitation Centre, UHL, Linköping, Sweden.

Abstract

BACKGROUND AND METHODS: Fibromyalgia (FMS) has a prevalence of approximately 2% in the population. Central alterations have been described in FMS, but there is not consensus with respect to the role of peripheral factors for the maintenance of FMS. (31) P Magnetic Resonance Spectroscopy ((31) P-MRS) has been used to investigate the metabolism of phosphagens in muscles of FMS patients, but the results in the literature are not in consensus.

The aim was to investigate the quantitative content of phosphagens and pH in resting quadriceps muscle of patients with FMS (n = 19) and in healthy controls (Controls; n = 14) using (31) P-MRS. It was also investigated whether the concentrations of these substances correlated with measures of pain and/or physical capacity.

RESULTS: Significantly lower concentrations of adenosine triphosphate (ATP) and phosphocreatinine (PCr; 28-29% lower) were found in FMS.

No significant group differences existed with respect to inorganic phosphate (Pi), Pi/PCr and pH. The quadriceps muscle fat content was significantly higher in FMS than in Controls [FMS: 9.0 ± 0.5% vs. Controls: 6.6 ± 0.6%; (mean ± standard error); P = 0.005].

FMS had significantly lower hand and leg capacity according to specific physical test, but there were no group differences in body mass index, subjective activity level and in aerobic fitness.

In FMS, the specific physical capacity in the leg and the hand correlated positively with the concentrations of ATP and PCr; no significant correlations were found with pain intensities.

CONCLUSIONS: Alterations in intramuscular ATP, PCr and fat content in FMS probably reflect a combination of inactivity related to pain and dysfunction of muscle mitochondria.

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PMID: 23364928 [PubMed - as supplied by publisher]

Pain Physiology Education Improves Health Status and Endogenous Pain Inhibition in Fibromyalgia: A Double-Blind Randomized Controlled Trial.


Abstract

OBJECTIVES:: There is evidence that education on pain physiology can have positive effects on pain, disability, and catastrophization in patients with chronic musculoskeletal pain disorders.

A double-blind randomized controlled trial (RCT) was performed to examine whether intensive pain physiology education is also effective in fibromyalgia (FM) patients, and whether it is able to influence the impaired endogenous pain inhibition of these patients.

METHODS:: Thirty FM patients were randomly allocated to either the experimental (receiving pain physiology education) or the control group (receiving pacing self-management education). The primary outcome was the efficacy of the pain inhibitory mechanisms, which was evaluated by spatially accumulating thermal nociceptive stimuli.

Secondary outcome measures included pressure pain threshold measurements and questionnaires assessing pain cognitions, behavior, and health status.

Assessments were performed at baseline, 2 weeks, and 3 months follow-up. Repeated measures ANOVAS were used to reveal possible therapy effects and effect sizes were calculated.

RESULTS:: After the intervention the experimental group had improved knowledge of pain neurophysiology (P<0.001). Patients from this group worried less about their pain in the short term (P=0.004). Long-term improvements in physical functioning (P=0.046), vitality (P=0.047), mental health (P<0.001), and general health perceptions (P<0.001) were observed.

In addition, the intervention group reported lower pain scores and showed improved endogenous pain inhibition (P=0.041) compared with the control group.

DISCUSSION:: These results suggest that FM patients are able to understand and remember the complex material about pain physiology. Pain physiology education seems to be a useful component in the treatment of FM patients as it improves health status and endogenous pain inhibition in the long term.

PMID: 23370076 [PubMed - as supplied by publisher]
Gulf War illness linked to nervous system damage

A UT Southwestern Medical Center-based study proves that Gulf War illness stems from damage to the body’s autonomic nervous system, which controls heart rate, sweating, digestion, sleep, and other bodily processes running in the background.

The study, based on a sample of 97 people selected for detailed neurologic testing from 8,020 representative Gulf War veterans, also confirmed high correlations between the symptoms of sick veterans and abnormalities in the cholinergic autonomic system that’s typically at work during periods of inactivity.

“This really locates the basis for most of the symptoms and the reason the sick veterans have a hard time describing it – because it’s part of the nervous system that you’re not normally aware of,” said lead author Dr. Robert Haley, Professor of Internal Medicine and Chief of Epidemiology.

“The control system for most bodily functions that you are not aware of is malfunctioning.”

The study, appearing online in JAMA Neurology (formerly Archives of Neurology), is the largest thus far among a series of studies attempting to track down autonomic nervous system abnormalities in those with Gulf War illness.

Full story: http://bit.ly/Y0Q59e
Study suggests Fibromyalgia might be an immunologic disorder

The role of immune system dysfunction in Fibromyalgia research has been downplayed in recent years. If this new research into the immune system can be replicated it may very well be that Fibromyalgia is a neuroimmune syndrome.

The researchers used several methods to study the cytokine levels of people with Fibromyalgia to healthy subjects. Cytokines are part of our immune system which are proteins that help manage our immune response.

The study sought to determine whether cytokine production by immune cells is altered in FM patients by comparing the cellular responses to mitogenic activators of stimulated blood mononuclear cells of a large number of patients with FM to those of healthy matched individuals.

Methods: The study was done by the blind method. There were a total of 110 Fibromyalgia subjects and 91 control subjects involved. All the FM subjects had symptoms and a diagnosis of at least one year and underwent two independent examinations to confirm they met criteria. All FM patients were off their fibromyalgia medications two weeks prior to the study being started.

Patients with comorbid conditions were excluded. The study done by BMC Clinical Pathology.

Findings: Essentially Fibromyalgia patients had substantially lower levels that the control group. Cytokine levels “of stimulated PBMC cultures of healthy control subjects were significantly increased as compared to matched non-stimulated PBMC cultures. In contrast, the concentrations of most cytokines were lower in stimulated samples from patients with FM compared to controls. The decreases of cytokine concentrations in patient samples ranged from 1.5-fold for MIP-1β to 10.2-fold for IL-6 in PHA challenges. In PMA challenges, we observed 1.8 to 4-fold decreases in the concentrations of cytokines in patient samples.” BMC Clinical Pathology December 17, 2012

The research concludes “The cytokine responses to mitogenic activators of PBMC isolated from patients with FM were significantly lower than those of healthy individuals, implying that cell-mediated immunity is impaired in FM patients. This novel cytokine assay reveals unique and valuable immunologic traits, which, when combined with clinical patterns, can offer a diagnostic methodology in FM.

Conclusion: The findings uncovered evidence that FM is an immunologic disorder. They prove that the immunologic basis of FM occurs independently of any subjective features. The fact that individual cytokines exhibited similar dynamics in patient samples reveals that the FM patients are uniform in regard to their cellular immunologic responses.”

Based on one study there is not enough evidence to say that Fibromyalgia is an immunologic disorder, but if more studies confirm similar findings across patients with FM it could mean a great deal. It could lead to people being diagnosed early and prevent misdiagnosis if a diagnostic tool can be identified.

http://www.biomedcentral.com/1472-6890/12/25
The prevalence and impact of early childhood trauma in Chronic Fatigue Syndrome.


Abstract

BACKGROUND: Although some studies have found high rates of early childhood trauma in Chronic Fatigue Syndrome (CFS), the role of early trauma in this condition remains controversial.

METHODS: This study examined the prevalence of early childhood trauma and its impact on daily fatigue and pain levels over a 14-day period in a sample of 90 carefully screened CFS patients using a diary method approach. Data were analyzed using multilevel analysis.

RESULTS: More than half of the patients (54.4%) had experienced at least one type of early trauma, with the majority of these patients reporting multiple traumas. Prevalence rates were particularly high for emotional trauma (i.e., emotional abuse and/or emotional neglect) (46.7%). Moreover, total trauma scores and emotional abuse significantly predicted higher levels of daily fatigue and pain over the 14-day period, even when controlling for demographic features and depressed mood.

CONCLUSIONS: This is the first study to demonstrate that early childhood trauma predicts increasing levels of core symptoms of CFS in the daily flow of life.

Moreover, findings of this study suggest that emotional trauma may be particularly important in CFS.

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PMID: 23421962 [PubMed - as supplied by publisher]
Age-of-onset of menopause is associated with enhanced painful and non-painful sensitivity in fibromyalgia.


Research Institute on Health Sciences (IUNICS), University of the Balearic Islands, Cra. de Valldemossa km 7.5, 07122, Palma de Mallorca, Spain.

Abstract

Fibromyalgia (FM) is a chronic pain condition characterized by high prevalence in women. In particular, estrogen deficit has been considered as a potentially promoting factor of FM symptoms.

This study was aimed to examine the relationship between age-of-onset of menopause and pain sensitivity in FM. For this purpose, pain sensitivity was assessed in 74 FM and 32 pain-free control women. All participants were postmenopausal and underwent a detailed semi-structured clinical interview, including data about menopause transition, previous history of hysterectomy or ovariectomy, and menses time.

Participants were divided into two groups depending on age-of-onset of menopause: early menopause [≤49 years] vs. late menopause [>49 years]. Pain and non-pain thresholds were assessed by using cold, heat, mechanical, and electrical stimulation.

FM women showed higher overall pain sensitivity as compared with healthy subjects. FM women with early age-of-onset of menopause displayed greater pain and non-pain sensitivity than FM women with late age-of-onset of menopause, whereas no differences were observed in healthy women due to age-of-onset of menopause.

These results suggest that an early transition to menopause (shortening the time of exposure to estrogens) may influence pain hypersensitivity and could be related to aggravation of FM symptoms.

PMID:23417348 [PubMed - as supplied by publisher]
Evaluating the DePaul Symptom Questionnaire in the ME Research UK cohort: extension study.

Prof. Julia Newton, Institute for Ageing and Health, Newcastle University, UK

Background and aim

Since 2006, the group at Newcastle University has investigated the autonomic nervous system parameters along with muscle, liver and heart function in a large patient cohort.

The researchers have reported that, compared with healthy people, many ME/CFS patients have a) impaired cardiac function, including reduced cardiac mass and blood pool volumes; b) dysfunction of the autonomic nervous system; c) fatigue that is directly related to the burden of autonomic nervous system symptoms; d) an abnormal heart rate response to standing; e) a lower blood pressure, and abnormal blood pressure regulation; and f) substantially slower recovery from standardised exercise of the skeletal muscles.

At present there are several case definitions for ME/CFS, but all are exclusionary and rely on collections of non-specific symptoms shared with other illnesses.

Prof. Leonard Jason at a university in Chicago has developed a standard questionnaire (The DePaul Symptom Questionnaire, DSQ) to assess core symptoms of ME/CFS, with the aim of ensuring that symptoms are assessed in a consistent way across settings to aid in diagnosis.

This questionnaire has now been refined (Jason et al, American Journal of Biochemistry and Biotechnology http://thescipub.com/html/10.3844/ajbbsp.2010.120.135) and is being made available to other research groups for operational testing on existing ME/CFS cohorts.

Importantly, the DSQ now comes in a format which scores symptoms and SF36 data, and produces a “diagnosis” based on several of the more common definitions of ME, CFS and ME/CFS. If this instrument is found to be sufficiently sensitive, it could greatly assist patient diagnosis, saving time (as it can be completed in the patient’s home and brought to the clinic for scoring) and improving confidence in the diagnosis. In the course of the ME Research UK-funded patient cohort study at Newcastle University, the researchers have collected a large volume of clinical, autonomic and symptom data, and they have available full data sets from almost 200 patients who have attended the Newcastle ME/CFS Service and been referred to their research programme.

Each of these patients has been assessed on the basis of the Fukuda 1994 CFS and the Canadian 2003 ME/CFS definitions as part of their clinical examinations, but through the timely development of the DSQ an opportunity has arisen to compare the clinical diagnoses of patients in the Newcastle ME Research UK cohort with those derived from the more structured DSQ instrument.

The results obtained will also be shared with Prof. Jason’s group in Chicago, adding to the data on the usefulness of the DSQ which he hopes to acquire from research groups around the world in different populations of patients. Considering the importance of the ME Research UK cohort and its well-characterised nature, the results could throw valuable light on diagnostic categories and on the utility of the DSQ in practice.

http://www.meresearch.org.uk/research/studies/ongoing/depaulquestio...
The costs associated with sleep symptoms among patients with fibromyalgia.

Wagner JS, Chandran A, Dibonaventura M, Cappelleri JC., Health Outcomes Practice, Kantar Health, New York, NY

Abstract

Aims: To assess the costs associated with sleep symptoms among patients with fibromyalgia (FM).

Patients & methods: Patients reporting physician-diagnosed FM from the National Health and Wellness Survey were categorized into three groups based on the number of sleep symptoms reported: two or more sleep symptoms (n = 1353), one sleep symptom (n = 574) and no sleep symptoms (n = 269).

Annual direct and indirect costs were compared among the groups controlling for relevant confounders.

Results: After adjusting for demographic and health characteristics, patients with FM with one, two or more sleep symptoms had higher annual physician costs (US $12,328 and US $12,261, respectively) and higher annual emergency room visit costs (US $846 and US $729, respectively) than patients with FM without any sleep symptoms (physician visit costs: US $9,845; emergency room visit costs: US $527; all p < 0.05).

Similarly, both patients with one (US $18,100) and two or more sleep symptoms (US $18,428) reported higher total indirect costs compared with those without any sleep symptoms (US $14,711; p < 0.05).

Conclusions: Among the FM population, sleep symptoms were prevalent and associated with higher direct and indirect costs, suggesting improved management may have long-term cost savings.

PMID: 23402453 [PubMed - in process]
Risk of narcolepsy in children and young people receiving AS03 adjuvanted pandemic A/H1N1 2009 influenza vaccine: retrospective analysis

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1. Elizabeth Miller, consultant epidemiologist1.
3. Lesley Stellitano, public health researcher13.
5. Anne Marie Winstone, public health researcher13.
7. Christopher Verity, consultant paediatric neurologist13

Author Affiliations

Correspondence to: E Miller liz.miller@hpa.org.uk
Accepted 30 January 2013

Abstract

Objective To evaluate the risk of narcolepsy in children and adolescents in England targeted for vaccination with AS03 adjuvanted pandemic A/H1N1 2009 vaccine (Pandemrix) from October 2009.

Design Retrospective analysis. Clinical information and results of sleep tests were extracted from hospital notes between August 2011 and February 2012 and reviewed by an expert panel to confirm the diagnosis. Vaccination and clinical histories were obtained from general practitioners.

Setting Sleep centres and paediatric neurology centres in England.

Participants Children and young people aged 4-18 with onset of narcolepsy from January 2008.

Main outcome measures The odds of vaccination in those with narcolepsy compared with the age matched English population after adjustment for clinical conditions that were indications for vaccination. The incidence of narcolepsy within six months of vaccination compared with the incidence outside this period measured with the self controlled cases series method.

Results Case notes for 245 children and young people were reviewed; 75 had narcolepsy (56 with cataplexy) and onset after 1 January 2008. Eleven had been vaccinated before onset; seven within six months. In those with a diagnosis by July 2011 the odds ratio was 14.4 (95% confidence interval 4.3 to 48.5) for vaccination at any time before onset and 16.2 (3.1 to 84.5) for vaccination within six months before onset. The relative incidence from the self controlled cases series analysis in those with a diagnosis by July 2011 with onset from October 2008 to December 2010 was 9.9 (2.1 to 47.9). The attributable risk was estimated as between 1 in 57,500 and 1 in 52,000 doses.

Conclusion The increased risk of narcolepsy after vaccination with AS03 adjuvanted pandemic A/H1N1 2009 vaccine indicates a causal association, consistent with findings from Finland. Because of variable delay in diagnosis, however, the risk might be overestimated by more rapid referral of vaccinated children.
Effect of aquatic exercise training on fatigue and health-related quality of life in patients with multiple sclerosis

Authors: Kargarfard M et al

Summary: This study examined the effectiveness of aquatic exercise training on fatigue and health-related quality of life (HRQOL) in women with multiple sclerosis (MS). 32 women diagnosed with relapsing-remitting MS were randomised to aquatic exercise (3 supervised 60-min sessions per week for 8 weeks) or a control group. Fatigue was assessed using the Modified Fatigue Impact Scale and HRQOL was assessed using the Multiple Sclerosis Quality of Life-54 questionnaire at baseline, 4 weeks and 8 weeks. Data were available for 21 patients (10 from the exercise group and 11 controls). The groups did not differ significantly at baseline but patients in the exercise group showed significant improvements in fatigue and subscores of HRQOL after 4 and 8 weeks compared with the control group. In conclusion, aquatic exercise training appears to improve fatigue and HRQOL in patients with MS and should be considered in the management of this relatively common disease.

Comment: Fatigue is a big problem for people with MS. The exact cause remains obscure, but deconditioning clearly plays a role. Encourage your patients to engage in structured exercise programmes balanced to increase fitness without exacerbating the fatigue.

http://tinyurl.com/aeq2qnm
Validation of the Innsbruck REM sleep behavior disorder inventory

Authors: Frauscher B et al

Summary: This study reported the development of a short REM sleep behaviour disorder screening questionnaire. The questionnaire initially included 7 REM sleep behaviour disorder items and 2 non-REM sleep behaviour disorder items and was validated in 70 patients with REM sleep behaviour disorder and 140 non-REM sleep disorder controls. Response patterns to all 7 REM sleep behaviour disorder-specific items differed between the 2 groups (all p<0.05), whereas the 2 non-REM sleep behaviour disorder-specific control items did not. AUC was >0.700 in 5 of the 7 REM sleep behaviour disorder-specific items so these 5 items were then incorporated into the Innsbruck REM sleep behaviour disorder inventory. In this, a cutoff of 0.25 (number of positive symptoms divided by number of answered questions) had a sensitivity of 0.914 and a specificity of 0.857 for both idiopathic and Parkinson’s-related REM sleep behaviour disorder. In conclusion, the Innsbruck REM sleep behaviour disorder inventory is a promising, easy-to-use, short screening tool for REM sleep behaviour disorder.

Comment: REM sleep behaviour disorder (RBD) is a striking clinical phenomenon. Usually REM sleep is associated with paralysis of voluntary muscles except for respiration. REM is also a sleep phase associated with dreaming of vigorous activity, and the paralysis prevents acting out of those dreams. In RBD, patients, or more often their sleeping partners, report sometimes violent acting out of dreams in the early hours of the morning. The partner is often struck or sometimes semi-purposefully attacked. When awakened, the patient often reports dreaming of a chase or assault. RBD is strongly associated with neurodegenerative disorders particularly Parkinson’s disease, Lewy body dementia and multiple system atrophy. RBD tends to be transient, but if it is troublesome, it can be managed with clonazepam.

Reference: Mov Disord 2012;27(13):1673-1678
Drug-dependence behaviour and outcome of medication-overuse headache after treatment

Authors: Corbelli I et al

Summary: This study examined the causes of failure of various strategies to manage medication-overuse headache (MOH). 120 inpatients with MOH underwent abrupt discontinuation of the overused medication before starting a 6-day in-patient detoxification regimen and prophylactic treatment. The Leeds Dependence Questionnaire (LDQ) was administered at baseline and after 1-year of follow-up to assess substance dependence. 56.7% of patients were successfully detoxified (responder group) and 43.3% were not (nonresponder group). The mean LDQ total score did not differ significantly between groups at baseline, but was significantly higher in the nonresponder group than the responder group at 1 year (12.1 vs 7.8; p<0.001). The pattern of the responses of the patients in the responder group differed from that in the nonresponder group in the items relating to the compulsion to start, compulsion to continue, primacy of effect, constancy of state and cognitive set. In conclusion, nonresponders to MOH management strategies show a drug dependence pattern similar to that previously described in addicts.

Comment: Medication overuse, or rebound, headache is common and severely disabling. The International Headache Society diagnostic criteria defines the disorder as headache on more than 15 days per month associated with intake of complex analgesics (such as codeine) or triptans on more than 10 days per month or simple analgesics (paracetamol or NSAID) on more than 15 days per month. As described in this study, patients with intact psychology who develop the disorder have a high rate of response to withdrawal of the offending medication. For your patients with frequent headaches, take a careful history of the rate of analgesic and triptan intake. For patients with less frequent headache, warn them not to exceed the above frequency of dosing.

Reference: J Headache Pain 2012;13(8):653-660
Dyspnea in Chronic Fatigue Syndrome (CFS): Comparison of Two Prospective Cross-Sectional Studies.

Georgetown University Medical Center.

Abstract

Chronic Fatigue Syndrome (CFS) subjects have many systemic complaints including shortness of breath. Dyspnea was compared in two CFS and control cohorts (Fukuda criteria augumented with severity scales) to characterize pathophysiology.

Cohort 1 of 257 CFS and 456 control subjects were compared using the Medical Research Council chronic Dyspnea Scale (MRC Score; range 0-5).

Cohort 2 of 106 CFS and 90 controls answered a Dyspnea Severity Score (range 0-20) adapted from the MRC Score. Subsets of both cohorts completed CFS Severity Scores, fatigue, and other questionnaires.

A subset had pulmonary function and total lung capacity measurements.

Results show MRC Scores were equivalent between sexes in Cohort 1 CFS (1.92 [1.72-2.16]; mean [95% C.I.]) and controls (0.31 [0.23-0.39]; p<0.0001).

Receiver-operator curves identified 2 as the threshold for positive MRC Scores in Cohort 1.

This indicated 54% of CFS, but only 3% of controls, had significant dyspnea.

In Cohort 2, Dyspnea Score threshold of 4 indicated shortness of breath in 67% of CFS and 23% of controls. Cohort 2 Dyspnea Scores were higher for CFS (7.80 [6.60-9.00]) than controls (2.40 [1.60-3.20]; p<0.0001).

CFS had significantly worse fatigue and other complaints compared to controls. Pulmonary function was normal in CFS, but Borg scores and sensations of chest pain and dizziness were significantly greater during testing than controls.

General linear model of Cohort 2 CFS responses linked Dyspnea with rapid heart rate, chest pain and dizziness.

In conclusion, sensory hypersensitivity without airflow limitation contributed to dyspnea in CFS. Correlates of dyspnea in controls were distinct from CFS suggesting different mechanisms.

PMID: 23445698 [PubMed - in process]

The full study can be found here: http://www.ccsenet.org/journal/index.php/gjhs/article/download/*222...
Fatigue and widespread pain in systemic lupus erythematosus and Sjögren’s syndrome: symptoms of the inflammatory disease or associated fibromyalgia?


Abstract

Fatigue and generalised pain are debilitating symptoms that negatively impact the quality of life in patients with systemic lupus erythematosus (SLE) and primary Sjögren's syndrome (pSS).

Chronic widespread musculoskeletal pain and fatigue are the clinical hallmarks of fibromyalgia (FM), a clinical entity which can be associated to connective tissue disease.

The aim of the present study was to assess the prevalence of FM syndrome, fatigue and widespread pain in SLE and pSS patients and to evaluate the contribution of inflammatory disease and FM on those constitutional symptoms.

Fifty SLE and 50 pSS patients were enrolled in the study. Patients rated fatigue, pain, and disease activity using a 100-mm visual analogue scale and completed the Health Assessment Questionnaire and the Fibromyalgia Impact Questionnaire. Zung depression and anxiety scales were used to quantify mood disorders. Tender points were evaluated using an algometer. Disease activity score as evaluated for each SLE and pSS patient.

Fibromyalgia has been diagnosed in a significantly higher percentage of SLE patients than pSS patients (32% vs. 18%, p=0.022) even if the percentage of patients reporting fatigue and pain was higher among pSS patients.

No correlation with disease activity was observed in either group of patients. FM seems to contribute to constitutional symptoms more in SLE than in pSS, suggesting a different underlying cause of fatigue and widespread pain in these two different connective tissue diseases.

PMID: 23261010 [PubMed - in process]
The neuropsychiatric and neuropsychological features of chronic fatigue syndrome: revisiting the enigma.

Christley Y, Duffy T, Everall IP, Martin CR., School of Health, Nursing and Midwifery, University of the West of Scotland, Ayr Campus, University Avenue, Ayr, KA8 0SX, UK,

Abstract

The aim of this article is to provide a comprehensive and updated review of the key neuropsychiatric and neuropsychological complaints associated with chronic fatigue syndrome (CFS).

Neuropsychiatric and neuropsychological difficulties are common in CFS and are linked primarily to disorders of mood, affect and behaviour. The neuropsychiatric complaint most frequently encountered amongst CFS patients is depression and in particular major depressive disorder (MDD).

Despite decades of research, the precise aetiological relationship between CFS and MDD remains poorly understood. This has resulted in the development of a number of interesting and polarised hypotheses regarding the aetiological nature of CFS. Recent scientific advances have however begun to unravel a number of interesting inflammatory and immunological explanations that suggest CFS and MDD are distinct yet interrelated conditions.

The possibility that the overlap between CFS and MDD might be explained in terms of shared oxidative and nitrosative (IO&NS) pathways is an area of intense research interest and is reviewed in detail in this article. The overlap between CFS and MDD is further differentiated by variations in HPA axis activity between the two disorders.

Important immunological differences between MDD and CFS are also reviewed with particular emphasis on antiviral RNase L pathways in CFS. In addition to the presence of neuropsychiatric complaints, CFS is also associated with neuropsychological symptoms such as impaired attention, memory and reaction time. The key neuropsychological problems reported by CFS patients are also included in the review in an effort to understand the significance of cognitive impairment in CFS.

PMID:23440559[PubMed - in process]
The GI microbiome and its role in Chronic Fatigue Syndrome: A summary of bacteriotherapy

Borody, Thomas J1; Nowak, Anna2; Finlayson, Sarah3

Abstract:

Introduction: Chronic Fatigue Syndrome (CFS) has a complex and multifactorial etiology making treatment and definitive diagnosis, currently made through exclusion, difficult. Current therapies, such as cognitive behaviour therapy and graded exercises, are inadequate and targeted to address symptoms, rather than the underlying disease pathology. Increasing evidence implicates the microbiota of the gut in a number of conditions previously thought distinct from the gastrointestinal system.

Previous work with bacteriotherapy in CFS has suggested a link between the condition and the composition and health of the gut microbiota. Here, we review and further examine a larger cohort of CFS patients who had undergone bacteriotherapy for their CFS.

Method: A total of 60 patients from the Centre for Digestive Diseases presented with CFS. Of these, 52 patients had concurrent IBS and 4 patients additionally had constipation. All underwent initial transcolonoscopic infusion of 13 non-pathogenic enteric bacteria.

52/60 patients undertook an additional rectal infusion a day later and 3/60 undertook an additional 2 rectal infusions.

Results: 35/60 patients who underwent initial bacteriotherapy responded to treatment. 10/15 patients who failed this course were offered a secondary transcolonoscopic infusion followed by a rectal infusion or an oral course of cultured bacteria. Of these 7/10 responded, giving a total of 42/60 (70%) patients who responded to treatment.

Contact was achieved with 12 patients after 15-20 year follow-up. Complete resolution of symptoms was maintained in seven of the twelve patients and 5/12 did not experience recurrence for approximately 1.5-3 years post bacteriotherapy.

Conclusion: Bacteriotherapy achieves initial success rate of 70% in CFS and a 58% sustained response. Given that manipulation of the colonic microbiota improved CFS symptoms, bacteriotherapy for CFS warrants further investigation and may provide further insight into a possible etiology of CFS.
Role of the Toll Like Receptor (TLR) Radical Cycle in Chronic Inflammation: Possible Treatments Targeting the TLR4 Pathway.

Lucas K, Maes M., Sportzenkoppel 54, 22359, Hamburg, Germany.

Abstract

Activation of the Toll-like receptor 4 (TLR4) complex, a receptor of the innate immune system, may underpin the pathophysiology of many human diseases, including asthma, cardiovascular disorder, diabetes, obesity, metabolic syndrome, autoimmune disorders, neuroinflammatory disorders, schizophrenia, bipolar disorder, autism, clinical depression, chronic fatigue syndrome, alcohol abuse, and toluene inhalation.

TLRs are pattern recognition receptors that recognize damage-associated molecular patterns and pathogen-associated molecular patterns, including lipopolysaccharide (LPS) from gram-negative bacteria.

Here we focus on the environmental factors, which are known to trigger TLR4, e.g., ozone, atmosphere particulate matter, long-lived reactive oxygen intermediate, pentachlorophenol, ionizing radiation, and toluene.

Activation of the TLR4 pathways may cause chronic inflammation and increased production of reactive oxygen and nitrogen species (ROS/RNS) and oxidative and nitrosative stress and therefore TLR-related diseases.

This implies that drugs or substances that modify these pathways may prevent or improve the above mentioned diseases.

Here we review some of the most promising drugs and agents that have the potential to attenuate TLR-mediated inflammation, e.g., anti-LPS strategies that aim to neutralize LPS (synthetic anti-LPS peptides and recombinant factor C) and TLR4/MyD88 antagonists, including eritoran, CyP, EM-163, epigallocatechin-3-gallate, 6-shogaol, cinnamon extract, N-acetylcysteine, melatonin, and molecular hydrogen.

The authors posit that activation of the TLR radical (ROS/RNS) cycle is a common pathway underpinning many "civilization" disorders and that targeting the TLR radical cycle may be an effective method to treat many inflammatory disorders.
A narrative review on the similarities and dissimilarities between myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) and sickness behavior

Gerwyn Morris, George Anderson, Piotr Galecki, Michael Berk and Michael Maes

Abstract (provisional)

It is of importance whether myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) is a variant of sickness behavior.

The latter is induced by acute infections/injury being principally mediated through proinflammatory cytokines.

Sickness is a beneficial behavioral response that serves to enhance recovery, conserves energy and plays a role in the resolution of inflammation. There are behavioral/symptomatic similarities (for example, fatigue, malaise, hyperalgesia) and dissimilarities (gastrointestinal symptoms, anorexia and weight loss) between sickness and ME/CFS.

While sickness is an adaptive response induced by proinflammatory cytokines, ME/CFS is a chronic, disabling disorder, where the pathophysiology is related to activation of immunoinflammatory and oxidative pathways and autoimmune responses.

While sickness behavior is a state of energy conservation, which plays a role in combating pathogens, ME/CFS is a chronic disease underpinned by a state of energy depletion.

While sickness is an acute response to infection/injury, the trigger factors in ME/CFS are less well defined and encompass acute and chronic infections, as well as inflammatory or autoimmune diseases. It is concluded that sickness behavior and ME/CFS are two different conditions.

http://www.biomedcentral.com/content/pdf/1741-7015-11-64.pdf
Researchers launch study on dual fibromyalgia treatment

The Fibromyalgia Research Program at the University of Washington is conducting a study to determine if combining two types of treatment can benefit patients who have been diagnosed with fibromyalgia, a chronic pain disorder affecting approximately 4 million Americans.

Patients will be tested over the course of 15 weeks to determine the effectiveness of combining pharmacological and nonpharmacological treatment. They will receive either a placebo or tramadol, an FDA-approved drug used for treatment of moderate to severe pain.

The patients will then be treated with either cognitive behavioral therapy or health education.

Dr. Dennis Turk, University of Washington, one of the researchers working on the study, is confident that combining pharmacological and nonpharmacological treatments will help patients. He said studies have shown that tramadol (Ultram) is an effective treatment for fibromyalgia, though there hasn’t been a study that has compared the dual use of tramadol and a nonpharmacological treatment.

Though the program’s combination theory hasn’t been tested, Turk said one treatment isn’t enough. He added that 40 percent of patients see a 30 percent benefit from each treatment. But this leaves a lot of patients still experiencing symptoms of fibromyalgia.

Turk, who researches other chronic pain conditions, such as back pain and whiplash injuries, has studied fibromyalgia since 1996. He said he wants to do whatever he can to help those with the condition.

“Fibromyalgia is particularly interesting because it has so many co-occurring features,” he said. “It’s so prevalent, and we are so poor at handling it very well that the challenges are great, the opportunities are great, and the ability to potentially improve the function and quality of life of a large number of people makes this a target that I would find very interesting.”

Dr. James Robinson, another researcher involved in the study, is also eager to help improve the lives of people with the disorder.

“These patients are often quite desperate,” Robinson said. “There are many practitioners who will offer all sorts of strange therapies, and the patients — in my mind — are at risk to get inappropriate overtreatment.

It’d be nice to know what we’re doing based on evidence.”

The Fibromyalgia Research Program is still looking for patients to participate in the study.

For more information: http://clinicaltrials.gov/ct2/show/NCT01598753?term=Turk&rank=11
Cholinergic autonomic dysfunction in veterans with gulf war illness: confirmation in a population-based sample.

R. W. Haley RW et al., Clinical and Translational Research Center, University of Texas Southwestern Medical Center, Dallas.

Abstract

Background: The authors of prior small studies raised the hypothesis that symptoms in veterans of the 1991 Gulf War, such as chronic diarrhea, dizziness, fatigue, and sexual dysfunction, are due to cholinergic autonomic dysfunction.

Objective: To perform a confirmatory test of this prestated hypothesis in a larger, representative sample of Gulf War veterans.

Design: Nested case-control study.

Participants: Representative samples of Gulf War veterans meeting a validated case definition of Gulf War illness with 3 variants (called syndromes 1-3) and a control group, all selected randomly from the US Military Health Survey.

Main Outcome Measures: Validated domain scales from the Autonomic Symptom Profile questionnaire, the Composite Autonomic Severity Score, and high-frequency heart rate variability from a 24-hour electrocardiogram.

Results: The Autonomic Symptom Profile scales were significantly elevated in all 3 syndrome groups (P < .001), primarily due to elevation of the orthostatic intolerance, secretomotor, upper gastrointestinal dysmotility, sleep dysfunction, urinary, and autonomic diarrhea symptom domains.

The Composite Autonomic Severity Score was also higher in the 3 syndrome groups (P = .045), especially in syndrome 2, primarily due to a significant reduction in sudomotor function as measured by the Quantitative Sudomotor Axon Reflex Test, most significantly in the foot; the score was intermediate in the ankle and upper leg and was nonsignificant in the arm, indicating a peripheral nerve length-related deficit.

The normal increase in high-frequency heart rate variability at night was absent or blunted in all 3 syndrome groups (P < .001).

Conclusion: Autonomic symptoms are associated with objective, predominantly cholinergic autonomic deficits in the population of Gulf War veterans.


http://www.prohealth.com/library/showarticle.cfm?libid=17908
Specific Interferon-γ detection for the diagnosis of previous Q fever.

Schoffelen T, Joosten LA, Herremans T, de Haan AF, Ammerdorffer A, Rümke HC, Wijkmans CJ, Jan Roest HI, Netea MG, van der Meer JW, Sprong T, van Deuren M., Department of Medicine, Radboud University Nijmegen Medical Centre, and Nijmegen Institute for Infection, Inflammation and Immunity (N4i), Nijmegen, The Netherlands.

Abstract

Background. Current practice for diagnosis of Q fever, caused by the intracellular pathogen Coxiella burnetii, relies mainly on serology and, in pre-vaccination assessment, on skin testing (ST), which both have drawbacks. In this study, C. burnetii-specific interferon-γ (IFN-γ) production was used as a new diagnostic tool for previous Q fever, circumventing most of these drawbacks. Our aim was to compare this test to serology and ST.

Methods. 1,525 individuals from an endemic area with a risk for chronic Q fever were enrolled. IFN-γ production was measured after in vitro stimulation of whole blood with C. burnetii antigens. Various formats using different C. burnetii antigens were tested. Serology and ST were performed in all individuals.

Results. In all assay formats, C. burnetii-specific IFN-γ production was higher (P<0.0001) in seropositive or ST-positive subjects than in seronegative and ST-negative subjects. Whole blood incubated for 24 hours with C.burnetii Nine Mile showed optimal performance. After excluding subjects with equivocal serology and/or borderline ST results, IFN-γ production was 449±82 pg/mL in the positive individuals (n=219) but only 21±3 pg/mL in negative subjects (n=908).

Using Bayesian analysis, sensitivity and specificity (87.0% and 90.2%, respectively) were similar to the combination of serology and ST (83.0% and 95.6%). Agreement with the combination of serology and ST was moderate (84% concordance, κ=0.542).

Conclusions. Specific IFN-γ detection is a novel diagnostic assay for previous C. burnetii infection and shows similar performance and practical advantages over serology and ST. Future studies to investigate the clinical value in practice are warranted.

PMID: 23463641 [PubMed - as supplied by publisher]
Cost-effectiveness of counselling, graded-exercise and usual care for chronic fatigue: evidence from a randomised trial in primary care.


Abstract

Background: Fatigue is common and has been shown to result in high economic costs to society. The aim of this study is to compare the cost-effectiveness of two active therapies, graded-exercise (GET) and counselling (COUN) with usual care plus a self-help booklet (BUC) for people presenting with chronic fatigue.

Methods: A randomised controlled trial was conducted with participants consulting for fatigue of over three months' duration recruited from 31 general practices in South East England and allocated to one of three arms. Outcomes and use of services were assessed at 6-month follow-up. The main outcome measure used in the economic evaluation was clinically significant improvements in fatigue, measured using the Chalder fatigue scale. Cost-effectiveness was assessed using the net-benefit approach and cost-effectiveness acceptability curves.

Results: Full economic and outcome data at six months were available for 163 participants; GET = 51, COUN = 58 and BUC = 54. Those receiving the active therapies (GET and COUN) had more contacts with care professionals and therefore higher costs, these differences being statistically significant. COUN was more expensive and less effective than the other two therapies. The incremental cost-effectiveness ratio of GET compared to BUC was equal to £987 per unit of clinically significant improvement. However, there was much uncertainty around this result.

Conclusion: This study does not provide a clear recommendation about which therapeutic option to adopt, based on efficiency, for patients with chronic fatigue. It suggests that COUN is not cost-effective, but it is unclear whether GET represents value for money compared to BUC.

Clinical Trial Registration number at ISRCTN register: 72136156

fulltext- http://www.biomedcentral.com/1472-6963/12/264
Probable Late Lyme Disease

A Variant Manifestation of Untreated Borrelia burgdorferi Infection

John N Aucott, Ari Seifter, Alison W Rehman

Disclosures
BMC Infect Dis. 2012;12(173)

Abstract

Background Lyme disease, a bacterial infection with the tick-borne spirochete Borrelia burgdorferi, can cause early and late manifestations. The category of probable Lyme disease was recently added to the CDC surveillance case definition to describe patients with serologic evidence of exposure and physician-diagnosed disease in the absence of objective signs. We present a retrospective case series of 13 untreated patients with persistent symptoms of greater than 12 weeks duration who meet these criteria and suggest a label of 'probable late Lyme disease' for this presentation.

Methods The sample for this analysis draws from a retrospective chart review of consecutive, adult patients presenting between August 2002 and August 2007 to the author (JA), an infectious disease specialist. Patients were included in the analysis if their current illness had lasted greater than or equal to 12 weeks duration at the time of evaluation.

Results Probable late Lyme patients with positive IgG serology but no history of previous physician-documented Lyme disease or appropriate Lyme treatment were found to represent 6% of our heterogeneous sample presenting with ≥12 weeks of symptom duration. Patients experienced a range of symptoms including fatigue, widespread pain, and cognitive complaints. Approximately one-third of this subset reported a patient-observed rash at illness onset, with a similar proportion having been exposed to non-recommended antibiotics or glucocorticosteroid treatment for their initial disease. A clinically significant response to antibiotics treatment was noted in the majority of patients with probable late Lyme disease, although post-treatment symptom recurrence was common.

Conclusions We suggest that patients with probable late Lyme disease share features with both confirmed late Lyme disease and post-treatment Lyme disease syndrome. Physicians should consider the recent inclusion of probable Lyme disease in the CDC Lyme disease surveillance criteria when evaluating patients, especially in patients with a history suggestive of misdiagnosed or inadequately treated early Lyme disease. Further studies are warranted to delineate later manifestations of Lyme disease and to quantify treatment benefit in this population.
Altered functional B cell subset populations in patients with chronic fatigue syndrome compared to healthy controls.

Bradley AS, Ford B, Bansal AS., Department of Immunology, St Helier University Hospital NHS Trust, Carshalton, Surrey, UK.

Abstract

Chronic fatigue syndrome (CFS) is a heterogeneous disorder of unknown aetiology characterized by disabling fatigue, headaches, sleep disturbance and several other symptoms. The onset of CFS may follow a viral infection or period of stress.

Patients with CFS do not have hypogammaglobulinaemia, predisposition to recurrent bacterial infections or symptoms of autoimmunity. To date, defects in B cell numbers or function have not been shown in the literature.

However, treatment with anti-B cell therapy using Rituximab has recently shown benefit to CFS patients. We therefore postulated that patients with CFS had a subtle humoral immune dysfunction, and performed extended B cell immunophenotyping.

We undertook a detailed characterization of the proportions of the different B cell subsets in 33 patients with CFS fulfilling the Canadian and Fukada criteria for CFS and compared these with 24 age- and gender-matched healthy controls (HC).

CFS patients had greater numbers of naive B cells as a percentage of lymphocytes: 6·3 versus 3·9% in HC (P = 0·034), greater numbers of naive B cells as a percentage of B cells: 65 versus 47% in controls (P = 0·003), greater numbers of transitional B cells: 1·8 versus 0·8% in controls (P = 0·025) and reduced numbers of plasmablasts: 0·5 versus 0·9% in controls (P = 0·013).

While the cause of these changes is unclear, we speculate whether they may suggest a subtle tendency to autoimmunity.

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Can Coenzyme Q10 improve clinical and molecular parameter in Fibromyalgia?


Source

Abstract
Fibromyalgia (FM) is a complex disorder that affects up to 5% of the general population worldwide. Its pathophysiological mechanisms are difficult to identify and current drug therapies demonstrate limited effectiveness. Both mitochondrial dysfunction and coenzyme Q10 (CoQ10) deficiency have been implicated in FM pathophysiology. We have investigated the effect of CoQ10 supplementation.

We carried out a randomized, double-blind, placebo-controlled trial to evaluate clinical and gene expression effects of forty days of CoQ10 supplementation (300mg/day), in twenty FM patients. This study was registered with controlled-trials.com (ISRCTN 21164124).

An important clinical improvement was shown after CoQ10 vs placebo treatment showing a reduction of FIQ (P<0.001), and a most prominent reduction in pain (P<0.001), fatigue and morning tiredness (P<0.01) subscales from FIQ.

Furthermore, we observed an important reduction in pain visual scale (P<0.01) and a reduction in tender points (P<0.01), including recovery of inflammation, antioxidant enzymes, mitochondrial biogenesis and AMPK gene expression levels, associated with phosphorylation of AMPK activity.

These results lead to the hypothesis that CoQ10 have a potential therapeutic effect in FM, and indicate new potential molecular targets for the therapy of this disease. AMPK could be implicated in the pathophysiology of FM.

PMID: 23458405[PubMed - as supplied by publisher]
Small fibre pathology in patients with fibromyalgia syndrome

Nurcan Üçeyler, Daniel Zeller, Ann-Kathrin Kahn, Susanne Kewenig, Sarah Kittel-Schneider, Annina Schmid, Jordi Casanova-Molla, Karlheinz Reiners, Claudia Sommer

Department of Neurology, University of Würzburg & Department of Psychiatry, University of Würzburg, 97080 Würzburg, Germany

Summary

Fibromyalgia syndrome is a clinically well-characterized chronic pain condition of high socio-economic impact. Although the pathophysiology is still unclear, there is increasing evidence for nervous system dysfunction in patients with fibromyalgia syndrome.

In this case-control study we investigated function and morphology of small nerve fibres in 25 patients with fibromyalgia syndrome.

Patients underwent comprehensive neurological and neurophysiological assessment. We examined small fibre function by quantitative sensory testing and pain-related evoked potentials, and quantified intraepidermal nerve fibre density and regenerating intraepidermal nerve fibres in skin punch biopsies of the lower leg and upper thigh.

The results were compared with data from 10 patients with monopolar depression without pain and with healthy control subjects matched for age and gender.

Neurological and standard neurophysiological examination was normal in all patients, excluding large fibre polyneuropathy. Patients with fibromyalgia syndrome had increased scores in neuropathic pain questionnaires compared with patients with depression and with control subjects (P < 0.001 each).

Compared with control subjects, patients with fibromyalgia syndrome but not patients with depression had impaired small fibre function with increased cold and warm detection thresholds in quantitative sensory testing (P < 0.001).

Investigation of pain-related evoked potentials revealed increased N1 latencies upon stimulation at the feet (P < 0.001) and reduced amplitudes of pain-related evoked potentials upon stimulation of face, hands and feet (P < 0.001) in patients with fibromyalgia syndrome compared to patients with depression and to control subjects, indicating abnormalities of small fibres or their central afferents.

In skin biopsies total (P < 0.001) and regenerating intraepidermal nerve fibres (P < 0.01) at the lower leg and upper thigh were reduced in patients with fibromyalgia syndrome compared with control subjects.

Accordingly, a reduction in dermal unmyelinated nerve fibre bundles was found in skin samples of patients with fibromyalgia syndrome compared with patients with depression and with healthy control subjects, whereas myelinated nerve fibres were spared.

All three methods used support the concept of impaired small fibre function in patients with fibromyalgia syndrome, pointing towards a neuropathic nature of pain in fibromyalgia syndrome.

http://brain.oxfordjournals.org/content/early/2013/03/09/brain.awt0...
Research article

**Association between alcohol consumption and symptom severity and quality of life in patients with fibromyalgia**

Chul H Kim, Ann Vincent, Daniel J Clauw, Connie A Luedtke, Jeffrey M Thompson, Terry D Schneekloth and Terry H Oh

* Corresponding author: Terry H Oh oh.terry@mayo.edu

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**Abstract (provisional)**

**Introduction**

Although alcohol consumption is a common lifestyle behavior with previous studies reporting positive effects of alcohol on chronic pain and rheumatoid arthritis, no studies to this date have examined alcohol consumption in patients with fibromyalgia. We examined the association between alcohol consumption and symptom severity and quality of life (QOL) in patients with fibromyalgia.

**Methods**

Data on self-reported alcohol consumption from 946 patients were analyzed. Subjects were grouped by level of alcohol consumption (number of drinks/week): none, low ([less than or equal to]3), moderate (>3 to 7), and heavy (>7). Univariate analyses were used to find potential confounders, and analysis of covariance was used to adjust for these confounders. Tukey HSD pairwise comparisons were used to determine differences between alcohol groups.

**Results**

Five hundred and forty-six subjects (58%) did not consume alcohol. Low, moderate, and heavy levels of alcohol consumption were reported for 338 (36%), 31 (3%), and 31 patients (3%), respectively. Employment status (P <0.001), education level (P = 0.009), body mass index (P = 0.002) and opioid use (P = 0.002) differed significantly among groups with drinkers having higher education, a lower BMI, and a lower frequency of unemployment and opioid use than nondrinkers. After adjusting for these differences, the measures including the number of tender points (P = 0.01), FIQ total score (P = 0.01), physical function (P <0.001), work missed (P = 0.005), job ability (P = 0.03), and pain (P = 0.001) differed across groups, as did the SF-36 subscales of physical functioning (P <0.001), pain index (P = 0.002), general health perception (P = 0.02), social functioning (P = 0.02), and the physical component summary (P <0.001).

Pairwise comparison among the 4 groups showed that the moderate and low alcohol drinkers had lower severity of fibromyalgia symptoms and better physical QOL than nondrinkers.

**Conclusions**

Our study demonstrates that low and moderate alcohol consumption was associated with lower fibromyalgia symptoms and better QOL compared to no alcohol consumption. The reasons for these results are unclear. Since recent studies have demonstrated that gamma-Aminobutyric Acid (GABA) levels are low in fibromyalgia, and alcohol is known to be a
GABA-agonist, future studies should examine whether alcohol could have a salutary effect on pain and other symptoms in fibromyalgia.

J Transl Med. 2013 Mar 20;11(1):68. [Epub ahead of print]

**Screening NK-, B- and T-cell phenotype and function in patients suffering from Chronic Fatigue Syndrome.**


**Abstract**

**BACKGROUND:**

Chronic Fatigue Syndrome (CFS) is a debilitating neuro-immune disorder of unknown etiology diagnosed by an array of clinical manifestations. Although several immunological abnormalities have been described in CFS, their heterogeneity has limited diagnostic applicability.

**METHODS:**

Immunological features of CFS were screened in 22 CFS diagnosed individuals fulfilling Fukuda criteria and 30 control healthy individuals. Peripheral blood T, B and NK cell function and phenotype were analyzed by flow cytometry in both groups.

**RESULTS:**

CFS diagnosed individuals showed similar absolute numbers of T, B and NK cells, with minor differences in the percentage of CD4+ and CD8+ T cells. B cells showed similar subset frequencies and proliferative responses between groups. Conversely, significant differences were observed in T cell subsets.

CFS individuals showed increased levels of T regulatory cells (CD25+/FOXP3+) CD4 T cells, and lower proliferative responses in vitro and in vivo. Moreover, CD8 T cells from the CFS group showed significantly lower activation and frequency of effector memory cells.

No clear signs of T-cell immunosenescence were observed. NK cells from CFS individuals displayed higher expression of NKp46 and CD69 but lower expression of CD25 in all NK subsets defined. Overall, T cell and NK cell features clearly clustered CFS individuals.

**CONCLUSIONS:**

Our findings suggest that alterations in T-cell phenotype and proliferative response along with the specific signature of NK cell phenotype may be useful to identify CFS individuals. The striking down modulation of T cell mediated immunity may help to understand intercurrent viral infections in CFS.

PMID:23514202[PubMed - as supplied by publisher]
Does Acetaminophen Activate Endogenous Pain Inhibition in Chronic Fatigue Syndrome/Fibromyalgia and Rheumatoid Arthritis? A Double-Blind Randomized Controlled Cross-over Trial.


Pain in Motion research group, Departments of Human Physiology and Rehabilitation Sciences, Faculty of Physical Education and Physiotherapy, Vrije Universiteit Brussels, Belgium.

Abstract

BACKGROUND:

Although enhanced temporal summation (TS) and conditioned pain modulation (CPM), as characteristic for central sensitization, has been proved to be impaired in different chronic pain populations, the exact nature is still unknown.

OBJECTIVES:

We examined differences in TS and CPM in 2 chronic pain populations, patients with both chronic fatigue syndrome (CFS) and comorbid fibromyalgia (FM) and patients with rheumatoid arthritis (RA), and in sedentary, healthy controls, and evaluated whether activation of serotonergic descending pathways by acetaminophen improves central pain processing.

STUDY DESIGN:

Double-blind randomized controlled trial with cross-over design.

METHODS:

Fifty-three women (19 CFS/FM patients, 16 RA patients, and 18 healthy women) were randomly allocated to the experimental group (1 g acetaminophen) or the placebo group (1 g dextrose).

Participants underwent an assessment of endogenous pain inhibition, consisting of an evaluation of temporal summation with and without conditioned pain modulation (CPM). Seven days later groups were crossed-over. Patients and assessors were blinded for the allocation. RESULTS:

After intake of acetaminophen, pain thresholds increased slightly in CFS/FM patients, and decreased in the RA and the control group.

Temporal summation was reduced in the 3 groups and CPM at the shoulder was better overall, however only statistically significant for the RA group.

Healthy controls showed improved CPM for both finger and shoulder after acetaminophen, although not significant.

LIMITATIONS:

The influence of acetaminophen on pain processing is inconsistent, especially in the patient groups examined.

CONCLUSION:

This is the first study comparing the influence of acetaminophen on central pain processing in healthy controls and patients with CFS/FM and RA.

It seems that CFS/FM patients present more central pain processing abnormalities than RA patients, and that acetaminophen may have a limited positive effect on central pain inhibition, but other contributors have to be identified and evaluated.

Increased Brain White Matter Axial Diffusivity Associated with Fatigue, Pain and Hyperalgesia in Gulf War Illness.


Abstract

Background

Gulf War exposures in 1990 and 1991 have caused 25% to 30% of deployed personnel to develop a syndrome of chronic fatigue, pain, hyperalgesia, cognitive and affective dysfunction.

Methods

Gulf War veterans (n = 31) and sedentary veteran and civilian controls (n = 20) completed fMRI scans for diffusion tensor imaging. A combination of dolorimetry, subjective reports of pain and fatigue were correlated to white matter diffusivity properties to identify tracts associated with symptom constructs.

Results

Gulf War Illness subjects had significantly correlated fatigue, pain, hyperalgesia, and increased axial diffusivity in the right inferior fronto-occipital fasciculus. ROC generated thresholds and subsequent binary regression analysis predicted CMI classification based upon axial diffusivity in the right inferior fronto-occipital fasciculus.

These correlates were absent for controls in dichotomous regression analysis.

Conclusion

The right inferior fronto-occipital fasciculus may be a potential biomarker for Gulf War Illness. This tract links cortical regions involved in fatigue, pain, emotional and reward processing, and the right ventral attention network in cognition. The axonal neuropathological mechanism(s) explaining increased axial diffusivity may account for the most prominent symptoms of Gulf War Illness.
Heart rate variability during sleep and subsequent sleepiness in patients with chronic fatigue syndrome.

Togo F, Natelson BH., Educational Physiology Laboratory, Graduate School of Education, The University of Tokyo, Tokyo, Japan.

Abstract

We determined whether alterations in heart rate dynamics during sleep in patients with chronic fatigue syndrome (CFS) differed from controls and/or correlated with changes of sleepiness before and after a night in the sleep laboratory.

We compared beat-to-beat RR intervals (RRI) during nocturnal sleep, sleep structure, and subjective scores on visual analog scale for sleepiness in 18 CFS patients with 19 healthy controls aged 25-55 after excluding subjects with sleep disorders.

A short-term fractal scaling exponent (α1) of RRI dynamics, analyzed by the detrended fluctuation analysis (DFA) method, was assessed after stratifying patients into those who reported more or less sleepiness after the night's sleep (a.m. sleepier or a.m. less sleepy, respectively).

Patients in the a.m. sleepier group showed significantly (p<0.05) higher fractal scaling index α1 during non-rapid eye movement (non-REM) sleep (Stages 1, 2, and 3 sleep) than healthy controls, although standard polysomnographic measures did not differ between the groups.

The fractal scaling index α1 during non-REM sleep was significantly (p<0.05) higher than that during awake periods after sleep onset for healthy controls and patients in the a.m. less sleepy group, but did not differ between sleep stages for patients in the a.m. sleepier group.

For patients, changes in self-reported sleepiness before and after the night correlated positively with the fractal scaling index α1 during non-REM sleep (p<0.05).

These results suggest that RRI dynamics or autonomic nervous system activity during non-REM sleep might be associated with disrupted sleep in patients with CFS.

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