Treatment of Autonomic-Mediated Orthostatic Intolerance in Children and Adolescents

Marcia L. Buck, Pharm.D., FCCP, FPPAG

Disclosures
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Abstract and Introduction

Introduction

Syncope or near-syncope spells are a relatively common occurrence in older children and adolescents. It has been estimated that 15–30% of adolescents will have at least one episode of syncope before reaching adulthood, with approximately half having multiple episodes.[1] Orthostatic intolerance, recurrent syncope or near-syncope when rising from a seated or lying position, may have an autonomic, cardiac, neurologic, psychiatric, or metabolic cause, or may be idiopathic. Approximately 70–75% of patients are diagnosed with autonomic-mediated orthostatic intolerance. This category includes common vasovagal syncope, as well as postural orthostatic tachycardia syndrome and orthostatic hypotension.[1–5]

Postural orthostatic tachycardia syndrome (POTS) is defined as syncope or near-syncope associated with dizziness, weakness, and tachycardia (an increase in heart rate of 30 bpm or more in the absence of hypotension) upon standing. In some patients, it has been associated with chronic fatigue after a triggering illness such as Epstein-Barr virus. The incidence of POTS in children and adolescents is much greater than that of orthostatic hypotension. In a recent analysis of 142 children diagnosed with orthostatic intolerance, autonomic testing identified POTS in 71% and orthostatic hypotension in only 5%.[2]

Most children and adolescents diagnosed with autonomic-mediated orthostatic intolerance need only education on maintaining adequate hydration, increasing dietary sodium intake, and removing known triggers.[1–5] Counter maneuvers (sitting or lying down when symptomatic) and conditioning exercises are also beneficial. Patients with recurrent syncope or orthostatic hypotension, however, may require additional treatment. Traditional therapies for syncope have included fludrocortisone and sodium chloride supplementation, alpha₁-adrenergic agonists, and beta-adrenergic blocking agents.
Irritable bowel syndrome and chronic fatigue six years after Giardia infection: a controlled prospective cohort study.

Abstract

BACKGROUND: Functional gastrointestinal disorders and fatigue may follow acute infections. This study aimed to estimate the persistence, prevalence and risk of irritable bowel syndrome and chronic fatigue six years after Giardia infection.

METHODS: Controlled prospective study of a cohort of 1252 individuals who had laboratory confirmed Giardia infection during a waterborne outbreak in 2004. In total, 748 cohort cases (exposed) and 878 matched controls responded to a postal questionnaire six years later (in 2010). Responses were compared to data from the same cohort three years before (in 2007).

RESULTS: The prevalences of irritable bowel syndrome (39.4%) by Rome III criteria and chronic fatigue (30.8%) in the exposed group six years after giardiasis were significantly elevated compared to controls with adjusted RR of 3.4 (95% CI: 2.9 to 3.9) and 2.9 (95% CI: 2.3 to 3.4) respectively.

In the exposed group the prevalence of irritable bowel syndrome decreased by 6.7% (RR: 0.85; 95% CI: 0.77 to 0.93), while the prevalence of chronic fatigue decreased by 15.3% from three to six years after Giardia infection (RR: 0.69, 95% CI: 0.62 to 0.77).

Giardia exposure was a significant risk factor for persistence of both conditions and increasing age was a risk factor for persisting chronic fatigue.

CONCLUSIONS: Giardia infection in a non-endemic setting is associated with an increased risk for irritable bowel syndrome and chronic fatigue six years later. The prevalences of both conditions decrease over time indicating that this intestinal protozoan parasite may elicit very long term, but slowly self-limiting, complications.

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An insight into the gastrointestinal component of fibromyalgia: clinical manifestations and potential underlying mechanisms.

Abstract

Fibromyalgia syndrome is characterized by chronic generalized pain accompanied by a broad symptomatologic spectrum. Besides chronic fatigue, sleep disturbances, headaches and cognitive dysfunction that are extensively described in the literature, a considerable proportion of patients with fibromyalgia experience gastrointestinal symptoms that are commonly overlooked in the studies that are not specifically dedicated to evaluate these manifestations.

Various attempts were undertaken to explore the gastrointestinal dimension of fibromyalgia. Several studies have demonstrated an elevated comorbidity of irritable bowel syndrome (IBS) among patients with fibromyalgia.

Other studies have investigated the frequency of presentation of gastrointestinal symptoms in fibromyalgia in a nonspecific approach describing several gastrointestinal complaints frequently reported by these patients such as abdominal pain, dyspepsia and bowel changes, among others.

Several underlying mechanisms that require further investigation could serve as potential explanatory hypotheses for the appearance of such manifestations.

These include sensitivity to dietary constituents such as gluten, lactose or FODMAPs or alterations in the brain-gut axis as a result of small intestinal bacterial overgrowth or subclinical enteric infections such as giardiasis.

The gastrointestinal component of fibromyalgia constitutes a relevant element of the multidisciplinary pathophysiologic mechanisms underlying fibromyalgia that need to be unveiled, as this would contribute to the adequate designation of relevant treatment alternatives corresponding to these manifestations.

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Rheumatol Int. 2014 Aug 15. [Epub ahead of print]

Celiac symptoms in patients with fibromyalgia: a cross-sectional study.

Abstract

Fibromyalgia is a chronic pain syndrome associated with numerous somatic symptoms including gastrointestinal manifestations of nonspecific nature. Celiac disease and nonglutten sensitivity frequently evolve in adults with gastrointestinal and extraintestinal symptoms similar to those found among patients with fibromyalgia.

The objective of the present study was to evaluate the presence of celiac-type symptoms among patients with fibromyalgia in comparison with healthy subjects and with those experienced by adult celiac patients and subjects with gluten sensitivity.

A list of typical celiac-type symptoms was developed, comparing the frequency of presentation of these symptoms between patients with fibromyalgia (N = 178) and healthy subjects (N = 131), in addition to those of celiac patients and gluten-sensitive patients reported in the literature.

The frequency of presentation of every celiac-type symptom, excepting anemia, was significantly higher among patients with fibromyalgia compared to controls (p < 0.0001).

Regarding the existing data in the literature, the prevalence of fatigue, depression, cognitive symptoms and cutaneous lesions predominated among patients with fibromyalgia, whereas the prevalence of gastrointestinal symptoms was higher among patients with fibromyalgia compared to gluten-sensitive patients and was similar among patients with fibromyalgia and celiac disease patient.

The symptomatological similarity of both pathologies, especially gastrointestinal symptoms, suggests that at least a subgroup of patients with fibromyalgia could experience subclinical celiac disease or nonceliac gluten intolerance.

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Immune derived opioidergic inhibition of viscerosensory afferents is decreased in Irritable Bowel Syndrome patients

Patrick A. Hughes, Melissa Moretta, Amanda Lim, Dallas J. Grasby, Daniel Bird, Stuart M. Brierley, Tobias Liebregts, Birgit Adam, L. Ashley Blackshaw, Gerald Holtmann, Peter Bampton, Peter Hoffmann, Jane M. Andrews, Heddy Zolab, Doreen Krumbiegel

Abstract

Alterations in the neuro-immune axis contribute towards viscerosensory nerve sensitivity and symptoms in Irritable Bowel Syndrome (IBS).

Inhibitory factors secreted from immune cells inhibit colo-rectal afferents in health, and loss of this inhibition may lead to hypersensitivity and symptoms. We aimed to determine the immune cell type(s) responsible for opioid secretion in humans and whether this is altered in patients with IBS. The β-endorphin content of specific immune cell lineages in peripheral blood and colonic mucosal biopsies were compared between healthy subjects (HS) and IBS patients.

Peripheral blood mononuclear cell (PBMC) supernatants from HS and IBS patients were applied to colo-rectal sensory afferent endings in mice with post-inflammatory chronic visceral hypersensitivity (CVH). β-endorphin was identified predominantly in monocyte / macrophages relative to T or B cells in human PBMC and colonic lamina propria.

Monocyte derived β-endorphin levels and colonic macrophage numbers were lower in IBS patients than healthy subjects. PBMC supernatants from healthy subjects had greater inhibitory effects on colo-rectal afferent mechanosensitivity than those from IBS patients.

The inhibitory effects of PBMC supernatants were more prominent in CVH mice compared to healthy mice due to an increase in µ-opioid receptor expression in dorsal root ganglia neurons in CVH mice. Monocyte / macrophages are the predominant immune cell type responsible for β-endorphin secretion in humans.

IBS patients have lower monocyte derived β-endorphin levels than healthy subjects, causing less inhibition of colonic afferent endings. Consequently, altered immune function contributes toward visceral hypersensitivity in IBS.
Acta Clin Belg.

A multidisciplinary network for the care of abnormal fatigue and chronic fatigue syndrome in the provinces of East and West Flanders in Belgium.

Abstract

The organization of care for patients with the chronic fatigue syndrome (CFS) in tertiary care referral centres from 2002 onwards, was negatively evaluated by the Belgian Health Care Knowledge Centre on the endpoint of socio-professional reintegration.

Subsequently, the federal health authorities asked for the elaboration of a new and innovative model of stepped care, aiming at improved integration of diagnosis and treatment into primary care and between levels of health care for patients with CFS.

The reference centre of the University Hospital Ghent took the initiative of recruiting partners in the Belgian provinces of East and West Flanders to guarantee the care for patients with medically unexplained symptoms, in particular abnormal fatigue and CFS.

A new and innovative care model, in which general practitioners play a central role, emphasizes the importance of early recognition of the patient ‘at risk’, correct diagnosis and timely referral.

Early detection and intervention is essential in order to avoid or minimize illness progression towards chronicity, to safeguard opportunities for significant health improvement as well as to enhance successful socio-professional reintegration.

This approach covers both the large sample of patients developing somatic complaints without obvious disease in an early phase as well as the more limited group of patients with chronic illness, including CFS.

Cognitive behavioural therapy and graded exposure/exercise therapy are the evidence based main components of therapy in the latter. A biopsychosocial model underlies the proposed path of care.

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Methylation Profile of CD4+ T Cells in Chronic Fatigue Syndrome/Myalgic Encephalomyelitis

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Abstract

Objective: Methylation is known to regulate biological processes and alterations in methylation patterns have been associated with a variety of diseases. Chronic Fatigue Syndrome/Myalgic Encephalomyelitis (CFS/ME) is an unexplained disorder associated with immunological and molecular changes. CD4+T cells specifically, regulatory T cells (Tregs) have been implicated in CFS/ME patients where significant increases in Tregs have been observed in these patients. Therefore the objective of this study was to examine methylation in CD4+T cells from CFS/ME patients.

Methods: The study comprised twenty-five CFS/ME participants and eighteen controls aged between 25-60 years. A volume of 20 ml whole blood was collected from each participant and peripheral blood mononuclear cells were isolated via density gradient centrifugation. A negative isolation kit was used to isolate the CD4+T cells from the peripheral blood samples. Genome wide methylation studies were performed on isolated CD4+T cells using the Illumina Infinium 450 K Human methylation array system. Data analysis was performed using Genome studio and Partek Enrichment software.

Results: 120 CpGs were observed to be differentially methylated in the CFS/ME patients in comparison to the controls. Of these 70 were associated with known genes. The majority of the differential methylated regions in the CFS/ME patients were hypomethylated. Additionally, most of the genes with differentially methylated regions in the CFS/ME patients were responsible for apoptosis, cell development, cell function and metabolic activity.

Conclusion: The present study demonstrates that epigenetic changes in CD4+T cells may have a potential role in the immunological changes observed in CFS/ME patients.
Analyzing the Human Microbiome: A "How To" Guide for Physicians

Andrea D Tyler, PhD, Michelle I Smith, PhD, Mark S Silverberg, MD, PhD

Abstract and Introduction

Abstract

The application of high-throughput next-generation sequencing to the analysis of the human microbiome has led to a shift in our understanding of the etiology of complex diseases. In consequence, a great deal of literature can now be found exploring this complex system, and reviewing recent findings. Observations of alterations in the intestinal microbiome associating with inflammatory bowel disease and other chronic conditions are well supported and have been widely accepted by the research community. Yet, it can be difficult to objectively evaluate the importance of these results, given the wide variety of methodologies applied by different groups in the field. The aim of this review is to focus attention on the basic principles involved in microbiome analyses, and to describe factors that may have an impact on the accurate interpretation of results.

Introduction

Over the past several years, a great deal of study has been directed toward evaluating the microbes living in or on the human host—the human microbiome. The human microbiome is defined as the collection of organisms and their genomes, inhabiting different anatomical locations both in and on humans.\(^1\) The gut alone is home to hundreds of trillions of microorganisms and contains more genetic information than that which exists in the human genome.\(^2\) Changes in human-associated microbial communities have been implicated in the etiology and increased incidence of several chronic conditions including obesity, diabetes, and inflammatory bowel disease (IBD).\(^3\) Evidence for a role of these microbes in the etiology of IBD is quite well supported, and it has been reviewed elsewhere.\(^4\) The intestinal flora has also been implicated in the development of the immune system, being shown in several studies to have an important role in immune development.\(^11,12\) It has been argued that the increasingly "clean" environments typical of developed countries have contributed to reduced exposure of the immune system to microbes and infection and a subsequent increased prevalence of autoimmune conditions.\(^13\) This so-called "hygiene hypothesis" suggests that exposure to fewer bacteria, viruses, or eukaryotic parasites prevents the immune system from developing properly during childhood and adolescence, leading to dysregulation and disease. Thus, improvements in sanitation, increased use of antibiotics, and reduced exposure to pathogens, although exceedingly successful in improving public health, may have had unforeseen consequences on the function of the immune system. Evidence regarding the role of any single pathogenic organism in preventing or causing autoimmune disease is lacking, suggesting instead that "cleaner" environments may alter human microbial community composition as a whole, in turn preventing the development of host immune tolerance and homeostasis.

Perhaps surprisingly, bacteria exist only rarely in isolation, and are instead most commonly found in complex community assemblages in which numerous different organisms share a similar ecological niche.\(^14,15\) In many cases, these organisms are co-dependent on one another, requiring metabolic support from additional members of the community for survival.\(^16\) In addition, organisms residing in or upon higher-order taxa must maintain a delicate balance with the host, in order to ensure that both symbionts flourish.\(^17\) In most cases, the relationship between such organisms is mutually beneficial: gut microbes, for example, help with the digestion of nutrients, prevent colonization of the host by pathogenic organisms, and aid in the proper development of both the intestinal epithelium and immune system, while the host provides nutrients and a suitable habitat for bacterial growth.\(^18\) The importance of this relationship and its subsequent consequences for human health is only beginning to be understood, and it has resulted in a great deal of study being directed in this field.
Pain and Depression Treatment Possible in Fibromyalgia


LAS VEGAS, Nevada — Patients with fibromyalgia can safely be treated with the anticonvulsant drug pregabalin (Lyrica, Pfizer Inc) for their pain while at the same time being treated for depression, a new study shows.

Results of a double-blind study showed that pregabalin significantly improved mean pain scores compared with placebo in patients with fibromyalgia taking a selective serotonin reuptake inhibitor (SSRI) or a serotonin/norepinephrine reuptake inhibitor (SNRI).

Characterized by widespread musculoskeletal pain along with fatigue and sleep, memory, and mood problems, fibromyalgia is believed to affect the way the brain processes pain signals and is often accompanied by depression.

Pregabalin is an approved treatment for fibromyalgia, but previous clinical trials required patients to discontinue antidepressant treatment.

The new study results were presented here during PAINWeek by Richard Vissing, PharmD, senior director, field medical director, pain, North American Medical Affairs, Global Innovative Pharma Business, Pfizer Inc, Louisville, Kentucky. This study, supported by Pfizer Inc, was 1 of only 6 selected for a special poster presentation during the meeting.

Depression Diagnosis

The analysis included 193 patients with fibromyalgia age 18 years and older at 38 centers in the United States, Canada, Italy, and Spain. Most (93.3%) were female and white (93.8%), and their mean age was 50.1 years.

The participants had to have a documented diagnosis of depression and to have been taking a stable SSRI or SNRI to treat depression, not pain, for the previous 2 months. About half of the patients were receiving an SSRI and the other half an SNRI. At study onset, they had a mean pain score of 4 or more on a numeric rating scale where 0 indicates no pain and 10 the worst pain.

Patients were randomly assigned to placebo or pregabalin (150 to 450 mg/day) for 6 weeks and then crossed over to the other treatment for another 6 weeks, with a 2-week taper/washout in between. Patients continued to take their antidepressants for the duration of the trial.

Interestingly, Dr. Vissing noted that discontinuation rates were "very similar" for the 2 groups: 12.2% for those taking pregabalin and 12.4% for those receiving placebo.

Results showed that mean pain scores were significantly lower for pregabalin recipients than for placebo recipients (4.84 vs 5.45; difference, −0.61; 95% confidence interval, −0.91 to −0.31; P = .0001).

"The treatment differences were apparent as early as the first week of treatment and were maintained for the duration of the study," said Dr. Vissing. "And it didn't matter patients were taking an SSRI or an SNRI."

Pregabalin treatment was also significantly better than placebo on many secondary endpoints, including the number of patients with a 30% or greater and 50% or greater reduction in mean pain scores and scores for depression and anxiety (A and D) on the Hospital Anxiety and Depression Scale (HADS).

"We saw an improvement in HADS-D, but I think more importantly, you got these patients who were coming through who were on a stable antidepressant and we didn't worsen their depression," he said. "They didn't have to change their medication, so from a safety perspective, I think that's important to know."

Patients taking pregabalin also did better in terms of function as tested on the Fibromyalgia Impact Questionnaire (difference in score, −6.60; P < .0001) and on several sleep measures, including sleep quality.

Adverse events were reported in 77.3% of those taking pregabalin and 59.9% of those receiving placebo. The most common adverse events were dizziness and somnolence. This, said Dr. Vissing, is consistent with previous studies of pregabalin.

Co-chair of the poster session, Joseph Pergolizzi Jr, MD, assistant professor, medicine, Johns Hopkins University School of Medicine, Baltimore, Maryland, commented on the unique design of the study. As previous clinical trials required patients with fibromyalgia to discontinue antidepressant medication, the question of whether this population could be safely and effectively treated with pregabalin while taking antidepressants for comorbid depression was left open.

"So many fibromyalgia patients have comorbidity of depression and there is a general concern that pregabalin might worsen depression," said Dr. Vissing. "This study provided evidence that it did not. Many fibro patients are on multiple drugs, including antidepressants and pain meds, so it appears that concomitant use is safe and effective."

The study was funded by Pfizer Inc. Dr. Vissing is employed with Pfizer. Dr. Pergolizzi is a consultant with Iroko Pharmaceuticals; receives grant or research support from Inspiion Pharmaceuticals, INSYS Therapeutics Inc, Johnson & Johnson Services Inc, Mundipharma International, and Purdue Pharma LP; and is on the speakers bureau for AstraZeneca, Grunenthal USA Inc, Iroko Pharmaceuticals, LLC, Janssen Pharmaceuticals Inc, and Purdue Pharma LP.
Use of single-nucleotide polymorphisms (SNPs) to distinguish gene expression subtypes of chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME)

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Abstract

Aims We have reported gene expression changes in patients with chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME) and the fact that such gene expression data can be used to identify subtypes of CFS/ME with distinct clinical phenotypes. Due to the difficulties in using a comparative gene expression method as an aid to CFS/ME disease and subtype-specific diagnosis, we have attempted to develop such a method based on single-nucleotide polymorphism (SNP) analysis.

Methods To identify SNP allele associations with CFS/ME and CFS/ME subtypes, we tested genomic DNA of patients with CFS/ME (n=108), patients with endogenous depression (n=17) and normal blood donors (n=68) for 504 human SNP alleles located within 88 CFS-associated human genes using the SNP Genotyping GoldenGate Assay (Illumina, San Diego, California, USA). 360 ancestry informative markers (AIM) were also examined.

Results 21 SNPs were significantly associated with CFS/ME compared with depression and normal groups. 148 SNP alleles had a significant association with one or more CFS/ME subtypes. For each subtype, associated SNPs tended to be grouped together within particular genes. AIM SNPs indicated that 4 subjects were of Asian origin while the remainder were Caucasian. Hierarchical clustering of AIM data revealed the relatedness between 2 couples of patients with CFS only and confirmed the overall heterogeneity of all subjects.

Conclusions This study provides evidence that human SNPs located within CFS/ME associated genes are associated with particular genomic subtypes of CFS/ME. Further work is required to develop this into a clinically useful subtype-specific diagnostic test.
Stress management skills, cortisol awakening response, and post-exertional malaise in Chronic Fatigue Syndrome.

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Abstract

Chronic Fatigue Syndrome (CFS) is characterized in part by debilitating fatigue typically exacerbated by cognitive and/or physical exertion, referred to as post-exertional malaise (PEM). In a variety of populations, the cortisol awakening response (CAR) has stood out as a marker of endocrine dysregulation relevant to the experience of fatigue, and may therefore be particularly relevant in CFS. This is the first study to examine PEM and the CAR in a sample of individuals with CFS. The CAR has also been established as a stress-sensitive measure of HPA axis functioning. It follows that better management of stress could modulate the CAR, and in turn PEM. In this cross-sectional study, we hypothesized that greater Perceived Stress Management Skills (PSMS) would relate to lower reports of PEM, via the impact of PSMS on the CAR. A total of 117 adults (72% female) with a CFS diagnosis completed self-report measures of PSMS and PEM symptomatology and a two-day protocol of saliva collection. Cortisol values from awakening and 30 min post-awakening were used to compute the CAR. Regression analyses revealed that greater PSMS related to greater CAR and greater CAR related to less PEM severity. Bootstrapped analyses revealed an indirect effect of PSMS on PEM via the CAR, such that greater PSMS related to less PEM, via a greater CAR. Future research should examine these trends longitudinally and whether interventions directed at improving stress management skills are accompanied by improved cortisol regulation and less PEM in individuals with CFS.

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KEYWORDS:

Chronic Fatigue Syndrome; Cortisol; HPA axis; Stress management

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PMCID:
The role of hypocortisolism in chronic fatigue syndrome.

Nijhof SL, Rutten JM, Uiterwaal CS, Bleijenberg G, Kimpen JL, Putte EM.

Abstract

BACKGROUND:

There is accumulating evidence of hypothalamic-pituitary-adrenal (HPA) axis hypofunction in chronic fatigue syndrome (CFS). However, knowledge of this hypofunction has so far come exclusively from research in adulthood, and its clinical significance remains unclear. The objective of the current study was to assess the role of the HPA-axis in adolescent CFS and recovery from adolescent CFS.

METHOD:

Before treatment, we compared the salivary cortisol awakening response of 108 diagnosed adolescent CFS patients with that of a reference group of 38 healthy peers. Salivary cortisol awakening response was measured again after 6 months of treatment in CFS patients.

RESULTS:

Pre-treatment salivary cortisol levels were significantly lower in CFS-patients than in healthy controls. After treatment recovered patients had a significant rise in salivary cortisol output attaining normalization, whereas non-recovered patients improved slightly, but not significantly. The hypocortisolism found in CFS-patients was significantly correlated to the amount of sleep. Logistic regression analysis showed that an increase of one standard deviation in the difference between pre- and post-treatment salivary cortisol awakening response was associated with a 93% higher odds of recovery (adjusted OR 1.93 (1.18 to 3.17), p=0.009). Pre-treatment salivary cortisol did not predict recovery.

CONCLUSIONS:

Hypocortisolism is associated with adolescent CFS. It is not pre-treatment cortisol but its change to normalization that is associated with treatment success. We suggest that this finding may have clinical implications regarding the adaptation of future treatment strategies.

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Cytokine


**The role of cytokines in the cerebrospinal fluids of patients with Chronic Fatigue Syndrome/Myalgic Encephalomyelitis (CFS/ME)**

- Sonya Marshall-Gradiski, Gunnar Gottschalk, Sandra Ramos, Ekua Benu, Don Staines, Dan Peterson
- DOI: 10.1016/j.cyto.2014.07.022
- Objectives

Previous research has provided evidence for a dysregulation in cytokine levels in the periphery of patients with Chronic Fatigue Syndrome/Myalgic Encephalomyelitis (CFS/ME). To date few studies have examined cytokines in the cerebrospinal fluid. The purpose of this research is to examine the role of cytokines in the symptom presentation of CFS/ME patients.

**Methods**

Cerebrospinal fluid (CSF) was collected from 18 CFS/ME patients and 5 healthy controls. The CSF samples were examined for the expression of 27 cytokines [interleukin (IL)-1β, IL-1ra, IL-2, IL-4, IL-6, IL-7, IL-8, IL-9, IL-10, IL-12p70, IL-13, IL-15, IL-17, basic FGF, eotaxin, G-CSF, GM-CSF, IFN-γ, IP-10, MCP-1 (MCAF), MIP-1α, MIP-1β, PDGF-BB, RANTES, TNF-α and VEGF] using the bio-plex human cytokine 27-plex assay.

**Results**

Of the cytokines examined, only four were significantly reduced in the CFS/ME patients in comparison to the controls.

**Conclusions**

The results show a decrease in pro-inflammatory cytokines in the CSF of CFS/ME patients and this may contribute to the clinical disease progression.

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High-Throughput Sequencing of Plasma MicroRNA in Chronic Fatigue Syndrome/Myalgic Encephalomyelitis

By E. W. Brenu et al.

www.ProHealth.com
• September 30, 2014

By E. W. Brenu et al.

Abstract

Background: MicroRNAs (miRNAs) are known to regulate many biological processes and their dysregulation has been associated with a variety of diseases including Chronic Fatigue Syndrome/Myalgic Encephalomyelitis (CFS/ME). The recent discovery of stable and reproducible miRNA in plasma has raised the possibility that circulating miRNAs may serve as novel diagnostic markers. The objective of this study was to determine the role of plasma miRNA in CFS/ME.

Results: Using Illumina high-throughput sequencing we identified 19 miRNAs that were differentially expressed in the plasma of CFS/ME patients in comparison to non-fatigued controls. Following RT-qPCR analysis, we were able to confirm the significant up-regulation of three miRNAs (hsa-miR-127-3p, hsa-miR-142-5p and hsa-miR-143-3p) in the CFS/ME patients.

Conclusion: Our study is the first to identify circulating miRNAs from CFS/ME patients and also to confirm three differentially expressed circulating miRNAs in CFS/ME patients, providing a basis for further study to find useful CFS/ME biomarkers.

Two age peaks in the incidence of chronic fatigue syndrome/myalgic encephalomyelitis: A population-based registry study from Norway
Inger J Bakken, Kari Tveito, Nina Gunnes, Sara Ghaderi, Camilla Stoltenberg, Lil Trogstad, Siri E Håberg and Per Magnus


Abstract (provisional)

Background: The aim of the current study was to estimate sex- and age-specific incidence rates of chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME) using population-based registry data. CFS/ME is a debilitating condition with large impact on patients and their families. The etiology is unknown, and the distribution of the disease in the general population has not been well described.

Methods: Cases of CFS/ME were identified in the Norwegian Patient Register (NPR) for the years 2008 to 2012. The NPR is nationwide and contains diagnoses assigned by specialist health care services (hospitals and outpatient clinics). We estimated sex- and age-specific incidence rates by dividing the number of new cases of CFS/ME in each category by the number of person years at risk. Incidence rate ratios were estimated by Poisson regression with sex, age categories, and year of diagnosis as covariates.

Results: A total of 5,809 patients were registered with CFS/ME during 2008 to 2012. The overall incidence rate was 25.8 per 100,000 person years (95% confidence interval (CI): 25.2 to 26.5). The female to male incidence rate ratio of CFS/ME was 3.2 (95% CI: 3.0 to 3.4). The incidence rate varied strongly with age for both sexes, with a first peak in the age group 10 to 19 years and a second peak in the age group 30 to 39 years.

Conclusions: Early etiological clues can sometimes be gained from examination of disease patterns. The strong female preponderance and the two age peaks suggest that sex- and age-specific factors may modulate the risk of CFS/ME.
Health Psychol. 2014 Sep;33(9):1092-1101.

The impact of significant other expressed emotion on patient outcomes in chronic fatigue syndrome.
Band R, Barrowclough C, Wearden A., School of Psychological Sciences, University of Manchester.

Abstract

Objective: Previous literature has identified the importance of interpersonal processes for patient outcomes in chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME), particularly in the context of significant other relationships. The current study investigated expressed emotion (EE), examining the independent effects of critical comments and emotional overinvolvement (EOI) in association with patient outcomes.

Method: Fifty-five patients with CFS/ME and their significant others were recruited from specialist CFS/ME services. Significant other EE status was coded from a modified Camberwell Family Interview. Patient outcomes (fatigue severity, disability, and depression) were derived from questionnaire measures.

Forty-four patients (80%) completed follow-up questionnaires 6-months after recruitment.

Results: Significant other high-EE categorized by both high levels of critical comments and high EOI was predictive of worse fatigue severity at follow-up.

High-critical EE was associated with higher levels of patient depressive symptoms longitudinally; depressive symptoms were observed to mediate the relationship between high critical comments and fatigue severity reported at follow-up.

There were higher rates of high-EE in parents than in partners, and this was because of higher rates of EOI in parents.

Conclusions: Patients with high-EE significant others demonstrated poorer outcomes at follow-up compared with patients in low-EE dyads. One mechanism for this appears to be as a result of increased patient depression.

Future research should seek to further clarify whether the role of interpersonal processes in CFS/ME differs across different patient-significant other relationships.

The development of significant other-focused treatment interventions may be particularly beneficial for both patients and significant others.

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Elevated plasma biomarkers of chronic inflammation in Gulf War illness

Gerhard Johnson, Billie Slater, Linda Leis and Ronald Bach, Hematology/Oncology Department of Veterans Affairs Health Care System Minneapolis MN

Abstract

As many as 200,000 veterans of the 1990-1991 Gulf War suffer from unexplained chronic multisymptom illnesses collectively known as Gulf War Illness (GWI). Symptoms of GWI may include muscle and joint pain, unexplained fatigue, and cognitive impairment. The etiology of GWI is undetermined, and no effective treatment has been defined.

Objective: To determine if blood abnormalities exist in veterans with GWI that could lead to the identification of potential therapeutic targets.

Methods: Eighty-five gulf war veterans were enrolled. Subjects with GWI were identified by standard (CDC-10) criteria. Data derived from subjects with GWI (58) were compared to those without GWI (27).

Multi-Analyte Profiling of plasma proteins was performed and analyzed by the Mann-Whitney rank sum test. Results: Five of 89 proteins were significantly elevated (p<0.05) in the GWI subjects: C-reactive protein (CRP) (1.75-fold), leptin (1.67-fold), interleukin-1 beta (1.66-fold), brain-derived neurotropic factor (1.59-fold), and matrix metalloproteinase-9 (1.14-fold).

The 14 individuals in this study with the highest CRP levels, as much as 10-fold above the median, were all in the GWI group.

Conclusion: The biomarker evidence is consistent with activation of the innate immune system. It supports the hypothesis that chronic inflammation is a component of GWI pathophysiology.
High flow variant postural orthostatic tachycardia syndrome amplifies the cardiac output response to exercise in adolescents.
Pianosi PT, Goodloe AH, Soma D, Parker KO, Brands CK, Fischer PR, Department of Pediatric and Adolescent Medicine, Mayo Clinic.

Abstract

Postural orthostatic tachycardia syndrome (POTS) is characterized by chronic fatigue and dizziness and affected individuals by definition have orthostatic intolerance and tachycardia. There is considerable overlap of symptoms in patients with POTS and chronic fatigue syndrome (CFS), prompting speculation that POTS is akin to a deconditioned state.

We previously showed that adolescents with postural orthostatic tachycardia syndrome (POTS) have excessive heart rate (HR) during, and slower HR recovery after, exercise - hallmarks of deconditioning.

We also noted exaggerated cardiac output during exercise which led us to hypothesize that tachycardia could be a manifestation of a high output state rather than a consequence of deconditioning.

We audited records of adolescents presenting with long-standing history of any mix of fatigue, dizziness, nausea, who underwent both head-up tilt table test and maximal exercise testing with measurement of cardiac output at rest plus 2-3 levels of exercise, and determined the cardiac output (\(\dot{Q}\)) versus oxygen uptake (\(\dot{V}_O_2\)) relationship.

Subjects with chronic fatigue were diagnosed with POTS if their HR rose \(\geq 40\) beat\(\cdot\)min\(^{-1}\) with head-up tilt. Among 107 POTS patients the distribution of slopes for the \(\dot{Q}\) versus \(\dot{V}_O_2\) relationship was skewed toward higher slopes but showed two peaks with a split at \(\sim 7.0\) L\(\cdot\)min\(^{-1}\) per L\(\cdot\)min\(^{-1}\), designated as normal (5.08 ± 1.17, \(N = 66\)) and hyperkinetic (8.99 ± 1.31, \(N = 41\)) subgroups. In contrast, cardiac output rose appropriately with in 141 patients with chronic fatigue but without POTS, exhibiting a normal distribution and an average slope of 6.10 ± 2.09 L\(\cdot\)min\(^{-1}\) per L\(\cdot\)min\(^{-1}\).

Mean arterial blood pressure and pulse pressure from rest to exercise rose similarly in both groups.

We conclude that 40% of POTS adolescents demonstrate a hyperkinetic circulation during exercise. We attribute this to failure of normal regional vasoconstriction during exercise, such that patients must increase flow through an appropriately vasodilated systemic circulation to maintain perfusion pressure.

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Efficacy of memantine in the treatment of fibromyalgia: A double-blind, randomised, controlled trial with 6-month follow-up

Bárbara Olivan-Blázquez, Paola Herrera-Mercadal, Marta Puebla-Guedea, Mari-Cruz Pérez-Yus, Eva Andrés, Nicolas Fayed, Yolanda López del Hoyo, Rosa Magallon, Miquel Roca, Javier Garcia-Campayo

Summary

Memantine has shown efficacy in the treatment of pain and other clinical variables (depression, anxiety, quality of life, function, clinical impression) in patients with fibromyalgia.

Abstract

Fibromyalgia (FM) is a prevalent and disabling chronic disease. Recent studies have found elevated levels of glutamate in several brain regions, leading to hypotheses about the usefulness of glutamate-blocking drugs such as memantine in the treatment of FM. The aim of this study was to evaluate the efficacy of memantine in the treatment of pain and other clinical variables (global function, clinical impression, depression, anxiety, quality of life) in FM patients. A double-blind, parallel randomised controlled trial was developed. A total of 63 patients diagnosed with FM were recruited from primary health care centres in Zaragoza, Spain. Memantine was administered at doses of 20 mg/d after 1 month of titration. Assessments were carried out at baseline, posttreatment, and 3- and 6-month follow-up. Compared with a placebo group, memantine significantly decreased ratings on a pain visual analogue scale (Cohen's $d = 1.43$ at 6 months) and pain measured with a sphygmomanometer ($d = 1.05$). All other secondary outcomes except anxiety also improved, with moderate-to-large effect sizes at 6 months. Compared with placebo, the absolute risk reduction obtained with memantine was 16.13% (95% confidence interval = 2.0% to 32.6%), and the number needed to treat was 6.2 (95% confidence interval = 3 to 47). Tolerance was good, with dizziness (8 patients) and headache (4 patients) being the most frequent side effects of memantine. Although additional studies with larger sample sizes and longer follow-up times are needed, this study provides preliminary evidence of the utility of memantine for the treatment of FM.

Keywords: Chronic pain, Fibromyalgia, Memantine, Randomised controlled trial
Cytokine profiles of chronic fatigue syndrome and multiple sclerosis patients


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Available online 16 September 2014

Aims

Chronic Fatigue Syndrome (CFS) and Multiple Sclerosis (MS) are both disorders with severe neuroimmune symptoms, including cognitive impairment, immune dysfunction and abnormal cytokine expression. The purpose of this study was to assess the T helper (Th) 1, Th2 and Th17 cytokine profiles of CFS and MS patients.

Methods

This study measured the cytokine profiles of CFS patients (n = 16; mean age 49.88, SD 9.542), MS patients (n = 16; mean age 52.75, SD 12.809) and healthy controls (n = 16; mean age 50.06, SD 11.846). The diagnostic selection method used to identify CFS patients was the International Consensus Criteria. Cytokines were measured from serum using a Bio-Plex Pro™ kit for Th1 (IFN-γ, TNF-α), Th2 (IL-4, IL-6, IL-10, IL-13) and Th17 (IL-17) cell cytokines.

Results

When the three groups were compared, it was found that TNF-α (p = 0.011, p = 0.012), IL-4 (p = 0.000, p = 0.000), IL-6 (p = 0.039, p = 0.031), IL-13 (p = 0.000, p = 0.000) and IL-17 (p = 0.004, p = 0.038) were all significantly higher in MS patients compared with CFS patients and controls respectively. However, in the MS patients and CFS patients, serum levels of IL-13 and IFN-γ were significantly higher (p < 0.001) compared with the controls. IFN-γ was significantly different between MS and CFS (p = 0.001), with MS exhibiting higher IFN-γ serum levels.

Conclusion

Cytokines patterns supported both Th1 and Th2 cytokine profiles in CFS and MS. Similarities in the cytokine profiles of MS and CFS, combined with the already acknowledged similarities in immune cell function and symptoms, suggests a neuroimmune pathology for CFS with parallels to that of MS. Additional studies into the cytokine profiles of both CFS and MS should be conducted, with larger sample sizes, to further expand the understanding of the pathologies of both disorders.

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Metabolism in chronic fatigue syndrome.

Armstrong CW, McGregor NR, Butt HL, Gooley PR.

Abstract

Chronic fatigue syndrome (CFS) is a poorly understood condition that presents as long-term physical and mental fatigue with associated symptoms of pain and sensitivity across a broad range of systems in the body. The poor understanding of the disorder comes from the varying clinical diagnostic definitions as well as the broad array of body systems from which its symptoms present. Studies on metabolism and CFS suggest irregularities in energy metabolism, amino acid metabolism, nucleotide metabolism, nitrogen metabolism, hormone metabolism, and oxidative stress metabolism. The overwhelming body of evidence suggests an oxidative environment with the minimal utilization of mitochondria for efficient energy production. This is coupled with a reduced excretion of amino acids and nitrogen in general. Metabolomics is a developing field that studies metabolism within a living system under varying conditions of stimuli. Through its development, there has been the optimisation of techniques to do large-scale hypothesis-generating untargeted studies as well as hypothesis-testing targeted studies. These techniques are introduced and show an important future direction for research into complex illnesses such as CFS.

PMID:

25344988
Science/Tech

Chronic Fatigue Patients Suffer 3 Major Brain Abnormalities; Findings May Lead To Clearer Diagnosis

Oct 29, 2014 11:03 AM By Shweta Iyer

The incessant fatigue characterized by chronic fatigue syndrome (CFS) that affects between one and four million Americans is often quite difficult to diagnose. But a new study, which found three distinct differences between the brains of patients with CFS and those of healthy people, promises to revolutionize diagnosis and provide insight into the underlying mechanisms of the condition.

"CFS (Chronic Fatigue Syndrome) is one of the greatest scientific and medical challenges of our time," said Dr. Jose Montoya, from the Stanford University School of Medicine, in a press release. His words, in effect, summarize the difficulty doctors face in diagnosing CFS, which is often mistaken for other conditions. Up until now, researchers have also been unable to find any underlying medical conditions that explain its onset. Characterized by extreme fatigue that lasts for six months or longer, CFS worsens with physical and mental activity but doesn’t improve with rest.

Chronic headaches, food intolerance, sore throat, enlargement of the lymph nodes, gastrointestinal problems, abnormal blood-pressure and heart-rate events, and hypersensitivity to light, noise or other sensations are the other hallmarks of this condition, say the researchers. An accurate estimation is difficult to determine for the one-to-four million range of Americans affected by the condition because the initial symptoms are often mistaken for conditions such as hypochondria.

But the new study, published in Radiology, will help in more accurate diagnosis. "Using a trio of sophisticated imaging methodologies, we found that CFS patients' brains diverge from those of healthy subjects in at least three distinct ways," said coauthor Michael Zeineh.

Montoya, who has been tracking around 200 suspected patients for several years, says that CFS can affect a patient long-term, even as long as 30 years. This new diagnosis will not only provide a CFS-specific diagnostic biomarker, but may also help in “identifying the area or areas of the brain where the disease has hijacked the central nervous system,” Montoya said.

The investigators compared brain images of 15 CFS patients with 14 healthy age-and sex-matched controls. The study found the following key differences.

- CFS patients had an overall reduction in brain white matter than healthy controls.
- CFS patients showed a consistent abnormality in the right arcuate fasciculus, a particular part of a nerve tract that connects the frontal lobe and temporal lobe.
- CFS patients had thickened gray matter at the two areas of the brain connected by the right arcuate fasciculus, compared to the controls.

While reduction in the white matter was expected, what surprised the researchers was the abnormality in the right arcuate fasciculus. A relatively unexplored region of the brain, the team found that there was a strong correlation between the degree of abnormality in a CFS patient's right arcuate fasciculus and the severity of the patient's condition, as assessed by performance on a standard psychometric test used to evaluate fatigue.

The findings are a huge step forward, but the researchers are quick to point that more extensive studies need to be conducted to corroborate these findings.

Reduction of Intraepidermal Nerve Fiber Density (IENFD) in the skin biopsies of patients with fibromyalgia: A controlled study


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Highlights

• Our study confirms and expands prior observations of reduced IENFD in FM patients.
• FM patients with or without autoimmune disorders have significantly reduced IENFD.
• There is no autoimmune dysfunction in FM patients based on skin immunopathology.
• Skin biopsy is useful to explore pain mechanisms or underlying SFN in FM patients.

Abstract

Objectives: Fibromyalgia (FM) is one of the most common chronic pain syndromes. Various pathogenetic mechanisms have been implicated but none is proven. Our scope was to determine if Intraepidermal Nerve Fiber Density (IENFD) is reduced in the skin of FM patients, as observed in patients with painful small fiber sensory neuropathy (SFSN).

Design, setting and participants: We prospectively studied 46 FM patients (5 men and 41 women), aged 29 to 76 (mean: 52.5) years, diagnosed according to the ACR 2010 criteria, and 34 controls (18 women and 16 men) aged 19 to 84 (mean: 31.7) years. IENFD was measured using published guidelines and immune markers were sought immunocytochemically. In 30 FM patients, pain intensity was assessed with the Neuropathic Pain Symptom Inventory (NPSI), a scale validated for neuropathic pain.

Results: 15 of 46 (32.6%) FM patients had reduced IENFD [range: 0.6–12.5 fibers/mm (mean: 4.83 SD: 2.5)], compared to healthy controls [2.8–11.5 fibers/mm (mean: 7.35, SD: 1.85)] (p < 0.0001). No significant correlation was noticed between NPSI scores and IENFD. No difference in the Langerhans cells, the major Antigen Presenting Cells (APCs) in the epidermis, or in IL-6 staining, was noted between FM and controls. IENFD was equally reduced in a subset of FM patients who also had another autoimmune disease.

Conclusion: This is one of the largest series of FM patients demonstrating a significant reduction of IENFD in their skin biopsies. The findings indicate that in a subset of FM patients, the pain syndrome is, at least partially, of neuropathic origin. Skin biopsy may prove a useful tool and a potential biomarker in future studies of FM patients.
Abnormal accumulation of intestinal fluid following ingestion of an unabsorbable carbohydrate in patients with irritable bowel syndrome: an MRI study

R. Undseth, A. Berstad, N.-E. Kløw, K. Arnljot, K. S. Moi and J. Valeur

Abstract

Background: Postprandial discomfort following intake of poorly absorbable, but fermentable carbohydrates is a common complaint in patients with irritable bowel syndrome (IBS). We used lactulose as a model substance for this group of symptom triggering carbohydrates, aiming to visualize the intestinal response in IBS patients compared to healthy controls.

Methods: Patients with IBS according to Rome III criteria (n = 52) and healthy controls (n = 16) underwent a lactulose challenge test. By using magnetic resonance imaging, we measured small bowel water content (SBWC), and distension (diameter) of the distal ileum and the colon, both in fasting state and 1 h after ingestion of 10 g lactulose. We recorded symptoms after lactulose ingestion.

Key Results: Lactulose provoked significantly more symptoms in IBS patients than in healthy controls (p < 0.0001). SBWC increased more in the patient group compared to the control group (p = 0.0005). The postprandial diameter of the terminal ileum was larger in patients with IBS and the postprandial diameter of the ascending colon was smaller in patients with diarrhea-predominant phenotype (IBS-D). Symptoms were not correlated with change in SBWC (r = 0.05; p = 0.11), nor to the diameters of the terminal ileum or the colon.

Conclusions & Inferences: Compared to healthy controls, IBS patients developed more symptoms and had an abnormal accumulation of fluid in the small bowel in response to ingestion of the unabsorbable carbohydrate lactulose. This may be due to impaired motor activity of the small intestine or impaired function of the ileocecal segment.


**Metabolism in chronic fatigue syndrome.**
Armstrong CW, McGregor NR, Butt HL, Gooley PR.

**Abstract**

Chronic fatigue syndrome (CFS) is a poorly understood condition that presents as long-term physical and mental fatigue with associated symptoms of pain and sensitivity across a broad range of systems in the body. The poor understanding of the disorder comes from the varying clinical diagnostic definitions as well as the broad array of body systems from which its symptoms present.

Studies on metabolism and CFS suggest irregularities in energy metabolism, amino acid metabolism, nucleotide metabolism, nitrogen metabolism, hormone metabolism, and oxidative stress metabolism. The overwhelming body of evidence suggests an oxidative environment with the minimal utilization of mitochondria for efficient energy production.

This is coupled with a reduced excretion of amino acids and nitrogen in general. Metabolomics is a developing field that studies metabolism within a living system under varying conditions of stimuli. Through its development, there has been the optimisation of techniques to do large-scale hypothesis-generating untargeted studies as well as hypothesis-testing targeted studies. These techniques are introduced and show an important future direction for research into complex illnesses such as CFS.

PMID: 25344988 [PubMed - in process]
What is in a name? Comparing diagnostic criteria for chronic fatigue syndrome with or without fibromyalgia.

Department of Rehabilitation Sciences and Physiotherapy, Faculty of Medicine and Health Sciences, Ghent University, Ghent, Belgium.

Abstract

The current study had two objectives.

(1) to compare objective and self-report measures in patients with chronic fatigue syndrome (CFS) according to the 1994 Center for Disease Control (CDC) criteria, patients with multiple sclerosis (MS), and healthy controls, and

(2) to contrast CFS patients who only fulfill CDC criteria to those who also fulfill the criteria for myalgic encephalomyelitis (ME), the 2003 Canadian criteria for ME/CFS, or the comorbid diagnosis of fibromyalgia (FM).

One hundred six participants (48 CFS patients diagnosed following the 1994 CDC criteria, 19 MS patients, and 39 healthy controls) completed questionnaires assessing symptom severity, quality of life, daily functioning, and psychological factors.

Objective measures consisted of activity monitoring, evaluation of maximal voluntary contraction and muscle recovery, and cognitive performance. CFS patients were screened whether they also fulfilled ME criteria, the Canadian criteria, and the diagnosis of FM. CFS patients scored higher on symptom severity, lower on quality of life, and higher on depression and kinesiophobia and worse on MVC, muscle recovery, and cognitive performance compared to the MS patients and the healthy subjects. Daily activity levels were also lower compared to healthy subjects.

Only one difference was found between those fulfilling the ME criteria and those who did not regarding the degree of kinesiophobia (lower in ME), while comorbidity for FM significantly increased the symptom burden. CFS patients report more severe symptoms and are more disabled compared to MS patients and healthy controls.

Based on the present study, fulfillment of the ME or Canadian criteria did not seem to give a clinically different picture, whereas a diagnosis of comorbid FM selected symptomatically worse and more disabled patients.

PMID: 25308475 [PubMed - as supplied by publisher]
Criteria for the Diagnosis of Fibromyalgia: Validation of the Modified 2010 Preliminary American College of Rheumatology Criteria and the Development of Alternative Criteria

DOI: 10.1002/acr.22301

Arthritis Care & Research

Volume 66, Issue 9, pages 1364–1373, September 2014


Objective

To validate the 2011 modification of the 2010 American College of Rheumatology (ACR) preliminary criteria for the diagnosis of fibromyalgia (2011ModCr) and develop alternative criteria in a sample of patients with diverse pain disorders that are commonly seen in everyday practice by pain specialists, rheumatologists, and psychologists.

Methods

Eight clinicians from geographically varied locations in the US evaluated patients with chronic pain and psychiatric disorders using a standard set of questions that included the 2011ModCr questions, the Symptom Impact Questionnaire (SIQR), a 28-area pain location inventory (PLI), and the Short Form 36. Alternative diagnostic criteria were developed from the same data set using logistic regression and receiver operating curve analysis.

Results

Complete data on 321 patients were evaluated; there were 135 patients with fibromyalgia (according to the 1990 ACR criteria) and 186 patients with 16 other common chronic pain problems. Comparing the 2011ModCr with the 1990 ACR criteria provided a sensitivity of 83%, a specificity of 67%, and a correct classification of 74%. Alternative criteria were derived from the 10-item symptom score from the SIQR symptoms and the 28-area PLI. Maximal diagnostic accuracy was obtained with ≥17 pain sites (range 0–28) and an SIQR symptom score of ≥21 (range 0–50). These alternative criteria had a diagnostic sensitivity of 81%, a specificity of 80%, and a correct classification of 80%.

Conclusion

The 2011ModCr had robust operating characteristics. Alternative criteria based on symptom items from the SIQR and pain locations from the PLI had comparable operating characteristics, with somewhat better specificity and ease of use.
Does oral Coenzyme Q10 plus NADH supplementation improve fatigue and biochemical parameters in Chronic Fatigue Syndrome?

Dr. JESUS CASTRO-MARRERO, Ph.D., Prof. Mario D. Cordero, Dr. Maria Jose Segundo, Naia Saez-Francas, Dr. Natalia Calvo, Dr. Lourdes Román-Malo, Luisa Aliste, Prof. Tomas Fernandez de Sevilla, Dr. Jose Alegre-Martin

ABSTRACT

Chronic Fatigue Syndrome (CFS) is a chronic and extremely debilitating illness characterized by prolonged fatigue and multiple symptoms with unknown cause, diagnostic test, or universally effective treatment. Inflammation, oxidative stress, mitochondrial dysfunction, and CoQ10 deficiency have been well documented in CFS.

We conducted an 8-weeks randomized, double-blind, placebo-controlled trial to evaluate the benefits of oral CoQ10 (200 mg/day) plus NADH (20 mg/day) supplementation on fatigue and biochemical parameters in 73 Spanish CFS patients.

This study was registered in ClinicalTrials.gov (NCT02063126). A significant improvement of fatigue showing a reduction in FIS total score (p< 0.05) was reported in treated group vs. placebo. In addition, a recovery of the biochemical parameters was also reported. NAD+/NADH (p< 0.001), CoQ10 (p< 0.05), ATP (p< 0.05) and citrate synthase (p< 0.05) were significantly higher and lipoperoxides (p< 0.05) were significantly lower in blood mononuclear cells (BMCs) of the treated group.

These observations lead to the hypothesis that the oral CoQ10 plus NADH supplementation could confer potential therapeutic benefits on fatigue and biochemical parameters in CFS. Larger sample trials are warranted to confirm these findings.


J Med Food. 2014 Nov 17. [Epub ahead of print]

The Gut Microbiome and the Brain.
Galland L.

Abstract

Abstract The human gut microbiome impacts human brain health in numerous ways:

(1) Structural bacterial components such as lipopolysaccharides provide low-grade tonic stimulation of the innate immune system. Excessive stimulation due to bacterial dysbiosis, small intestinal bacterial overgrowth, or increased intestinal permeability may produce systemic and/or central nervous system inflammation.

(2) Bacterial proteins may cross-react with human antigens to stimulate dysfunctional responses of the adaptive immune system.

(3) Bacterial enzymes may produce neurotoxic metabolites such as D-lactic acid and ammonia. Even beneficial metabolites such as short-chain fatty acids may exert neurotoxicity.

(4) Gut microbes can produce hormones and neurotransmitters that are identical to those produced by humans. Bacterial receptors for these hormones influence microbial growth and virulence. (5) Gut bacteria directly stimulate afferent neurons of the enteric nervous system to send signals to the brain via the vagus nerve.

Through these varied mechanisms, gut microbes shape the architecture of sleep and stress reactivity of the hypothalamic-pituitary-adrenal axis.

They influence memory, mood, and cognition and are clinically and therapeutically relevant to a range of disorders, including alcoholism, chronic fatigue syndrome, fibromyalgia, and restless legs syndrome.

Their role in multiple sclerosis and the neurologic manifestations of celiac disease is being studied. Nutritional tools for altering the gut microbiome therapeutically include changes in diet, probiotics, and prebiotics.
Meditation for Migraines: A Pilot Randomized Controlled Trial

Rebecca Erwin Wells MD, MPH, Rebecca Burch MD, Randall H. Paulsen MD, Peter M. Wayne PhD, Timothy T. Houle PhD, Elizabeth Loder MD, MPH


Abstract and Introduction

Abstract

Objective Our objective was to assess the safety, feasibility, and effects of the standardized 8-week mindfulness-based stress reduction (MBSR) course in adults with migraines.

Background Stress is a well-known trigger for headaches. Research supports the general benefits of mind/body interventions for migraines, but there are few rigorous studies supporting the use of specific standardized interventions. MBSR is a standardized 8-week mind/body intervention that teaches mindfulness meditation/yoga. Preliminary research has shown MBSR to be effective for chronic pain syndromes, but it has not been evaluated for migraines.

Methods We conducted a randomized controlled trial with 19 episodic migraineurs randomized to either MBSR (n = 10) or usual care (n = 9). Our primary outcome was change in migraine frequency from baseline to initial follow-up. Secondary outcomes included change in headache severity, duration, self-efficacy, perceived stress, migraine-related disability/impact, anxiety, depression, mindfulness, and quality of life from baseline to initial follow-up.

Results MBSR was safe (no adverse events), with 0% dropout and excellent adherence (daily meditation average: 34 ± 11 minutes, range 16-50 minutes/day). Median class attendance from 9 classes (including retreat day) was 8 (range [3, 9]); average class attendance was 6.7 ± 2.5. MBSR participants had 1.4 fewer migraines/month (MBSR: 3.5 to 1.0 vs control: 1.2 to 0 migraines/month, 95% confidence interval CI [−4.6, 1.8], \( P = .38 \)), an effect that did not reach statistical significance in this pilot sample. Headaches were less severe, although not significantly so (−1.3 points/ headache on 0–10 scale, [−2.3, 0.09], \( P = .053 \)) and shorter (−2.9 hours/headache, [−4.6, −0.02], \( P = .043 \)) vs control. Migraine Disability Assessment and Headache Impact Test-6 dropped in MBSR vs control (−12.6, [−22.0, −1.0], \( P = .017 \) and −4.8, [−11.0, −1.0], \( P = .043 \), respectively). Self-efficacy and mindfulness improved in MBSR vs control (13.2 [1.0, 30.0], \( P = .035 \) and 13.1 [3.0, 26.0], \( P = .035 \) respectively).

Conclusions MBSR is safe and feasible for adults with migraines. Although the small sample size of this pilot trial did not provide power to detect statistically significant changes in migraine frequency or severity, secondary outcomes demonstrated this intervention had a beneficial effect on headache duration, disability, self-efficacy, and mindfulness. Future studies with larger sample sizes are warranted to further evaluate this intervention for adults with migraines. This study was prospectively registered (ClinicalTrials.gov identifier NCT01545466).