RESEARCH ABSTRACTS April - August 2016 – Dr. Rosamund Vallings

Here is the latest set of 50 CFS/ME abstracts taken from prestigious medical journals and reports of current research. Year by year the research becomes more exciting as the many aspects of the underlying pathology of this illness are clarified. I realised recently that I first started seeing CFS/ME patients 50 years ago in 1966 – the aftermath of the Royal Free epidemic. We knew so little then. What a lot has happened since that time! So often we have been round and round in circles, and oscillated between psychological and physical health issues, but it seems at last the jigsaw puzzle is beginning to come together.

The 2 papers in this set that I find particularly inspiring are those by Sonya Marshall-Gradisnik and her team in Australia and the work of Maureen Hanson from New York. Both presented their work at the Invest in ME conference in London in May.

Sonya's paper outlines the likely probability that they have found a reliable biomarker – Their recently published paper reported examination of 678 Single nucleotide polymorphisms (SNPs). Eleven SNPs for TRP ion channel genes (*TRPC4*, *TRPC2*, *TRPM3*, and *TRPM8*) were identified in the ME/CFS group. Five of these SNPs were associated with *TRPM3*, while the remainder were associated with *TRPM8*, *TRPC2*, and *TRPC4* ($P<0.05$). There was a reduction of *TRPM3* receptors on B cells. This has the potential for a biomarker.

Griffith University's media release:

The research team from the National Centre for Neuroimmunology and Emerging Diseases (NCNED), Menzies Health Institute Queensland, has identified new markers that can be used to screen patients and is now looking to partner with diagnostic companies to bring a test to market. The screening test is expected to benefit all those with symptoms of the condition.

"Over the last four years, with support from the Queensland Government and philanthropic donors, we have identified unique markers in CFS patients," says Professor Marshall-Gradisnik.

"This screening test may be expected to become a laboratory standard to provide more certain, and cost-efficient, diagnosis for CFS. Currently patients may be undergoing a range of tests to diagnose for CFS which incurs a significant cost to the health care system."

"CFS, also known as myalgic encephalomyelitis (ME), affects up to 400,000 Australians, many of whom are housebound or bedbound. Patients are isolated and further stigmatised by disbelief of their condition.

"This illness has traditionally been difficult to diagnose, meaning that people can go for months without getting the care and attention they require. We are confident that the new screening test currently in development will provide efficient and increasingly accurate screening for people with CFS. This test may also be used to monitor and track the progression of their illness," says Professor Staines.

Maureen Hanson and her large team are also looking for biomarkers. Their paper: “Reduced diversity and altered composition of the gut microbiome in individuals with myalgic encephalomyelitis/chronic fatigue syndrome” concludes there is indication of dysbiosis of the gut microbiota in this disease and further suggest an increased incidence of microbial translocation, which may play a role in inflammatory symptoms in ME/CFS. This statement can help to explain so much.

Although the microbiome has been discussed by many researchers, Maureen and her team seem to be bringing it all together. They are also looking at other potential biomarkers such as NK cell activity and abnormal brain imaging.

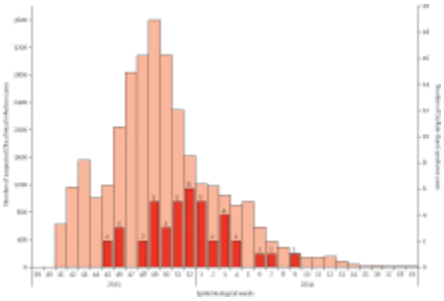
So in more than 50 years of research we have moved from trying to decipher a mysterious and unexpected illness on purely clinical grounds, to incredible immune, biochemical and physiological complexities made possible by brilliant researchers and 21st century equipment.

Guillain-Barré Syndrome outbreak associated with Zika virus infection in French Polynesia: a case-control study

Van-Mai Cao-Lormeau, PhD†, Alexandre Blake, MD†, Sandrine Mons, MSc, Stéphane Lastère, PharmD, Claudine Roche, MSc, Jessica Vanhomwegen, PhD, Timothée Dub, MPH, Laure Baudouin, MD, Anita Teissier, Philippe Larre, MD, Anne-Laure Vial, MSc, Christophe Decam, MD, Valérie Choumet, PhD, Susan K Halstead, PhD, Prof Hugh J Willison, PhD, Lucile Musset, PhD, Jean-Claude Manuguerra, PhD, Prof Philippe Despres, PhD, Prof Emmanuel Fournier, PhD, Henri-Pierre Mallet, MD, Didier Musso, MD, Prof Arnaud Fontanet, DrPH, Frédéric Ghawché, MD†

The Lancet Published Online: 29 February 2016
DOI: http://dx.doi.org/10.1016/S0140-6736(16)00562-6

Figures



Figure

Weekly cases of suspected Zika virus infections and Guillain-Barré syndrome in French Polynesia between October, 2013, and April, 2014

Summary

Background

Between October, 2013, and April, 2014, French Polynesia experienced the largest Zika virus outbreak ever described at that time. During the same period, an increase in Guillain-Barré syndrome was reported, suggesting a possible association between Zika virus and Guillain-Barré syndrome. We aimed to assess the role of Zika virus and dengue virus infection in developing Guillain-Barré syndrome.

Methods

In this case-control study, cases were patients with Guillain-Barré syndrome diagnosed at the Centre Hospitalier de Polynésie Française (Papeete, Tahiti, French Polynesia) during the outbreak period. Controls were age-matched, sex-matched, and residence-matched patients who presented at the hospital with a non-febrile illness (control group 1; n=98) and age-matched patients with acute Zika virus disease and no neurological symptoms (control group 2; n=70). Virological investigations included RT-PCR for Zika virus, and both microsphere immunofluorescent and seroneutralisation assays for Zika virus and dengue virus. Anti-glycolipid reactivity was studied in patients with Guillain-Barré syndrome using both ELISA and combinatorial microarrays.

Findings

42 patients were diagnosed with Guillain-Barré syndrome during the study period. 41 (98%) patients with Guillain-Barré syndrome had anti-Zika virus IgM or IgG, and all (100%) had neutralising antibodies against Zika virus compared with 54 (56%) of 98 in control group 1 (p<0·0001). 39 (93%) patients with Guillain-Barré syndrome had Zika virus IgM and 37 (88%) had experienced a transient illness in a median of 6 days (IQR 4–10) before the onset of neurological symptoms, suggesting recent Zika virus infection. Patients with Guillain-Barré syndrome had electrophysiological findings compatible with acute motor axonal neuropathy (AMAN) type, and had rapid evolution of disease (median duration of the installation and plateau phases was 6 [IQR 4–9] and 4 days [3–10], respectively). 12 (29%) patients required respiratory assistance. No patients died. Anti-glycolipid antibody activity was found in 13 (31%) patients, and notably against GA1 in eight (19%) patients, by ELISA and 19 (46%) of 41 by glycoarray at admission. The typical AMAN-associated anti-ganglioside antibodies were rarely present. Past dengue virus history did not differ significantly between patients with Guillain-Barré syndrome and those in the two control groups (95%, 89%, and 83%, respectively).

Interpretation

This is the first study providing evidence for Zika virus infection causing Guillain-Barré syndrome. Because Zika virus is spreading rapidly across the Americas, at risk countries need to prepare for adequate intensive care beds capacity to manage patients with Guillain-Barré syndrome.

Sleep Medicine Reviews December 2016 Volume 30, Pages 43–52

The effect of meditative movement on sleep quality: A systematic review

Fang Wang,,Othelia Eun-Kyoung Lee,Fan Feng,Michael V. Vitiello,Weidong Wang,Herbert Benson,Gregory L. Fricchione,John W. Denninger

DOI: http://dx.doi.org/10.1016/j.smrv.2015.12.001

Summary

The purpose of this systematic review was to identify and assess evidence related to the efficacy of meditative movement (MM) on sleep quality. We conducted a comprehensive review of relevant studies drawn from English and Chinese databases. Only randomized controlled trials (RCTs) reporting outcomes of the effects of MM (tai chi, qi gong, and yoga) on sleep quality were taken into consideration. Twenty-seven RCTs fulfilled our inclusion criteria and formed the basis for this review. Due to clinical heterogeneity, no meta-analysis was performed. Seventeen studies received a Jadad score of ⩾3 and were considered high-quality studies. Findings of the 17 studies showed that MM has beneficial effects for various populations on a range of sleep measures. Improvement in sleep quality was reported in the majority of studies and was often accompanied by improvements in quality of life, physical performance, and depression. However, studies to date generally have significant methodological limitations. Additional RCTs with rigorous research designs focusing on sleep quality or insomnia and testing specific hypotheses are needed to clearly establish the efficacy of MM in improving sleep quality and its potential use as an intervention for various populations.

Keywords:
Meditative movement, Sleep quality, Systematic review

Behavioral Sleep Medicine
Volume 14, Issue 2, 2016

The Use of Media as a Sleep Aid in Adults

DOI:10.1080/15402002.2014.963582

Liese Exelmans[a*] & Jan Van den Bulck[a]

pages 121-133

Abstract

A sample of 844 adults, aged 18–94 years old, was queried about media habits and sleep behavior in face-to-face interviews with standardized questionnaires. A substantial proportion of this sample reported using books (39.8%), television (31.2%), music (26.0%), Internet (23.2%), and videogames (10.3%) as a sleep aid. The use of media as sleep aids was associated with increased fatigue and higher scores on the Pittsburgh Sleep Quality Index (PSQI), indicating poorer sleep quality. There was no relationship with sleep duration. Finally, results suggest that media use coincides with later bedtimes, but also later rise times, a process called *time shifting*.

BMC Med. 2015 Feb 6;13:28. doi: 10.1186/s12916-014-0259-2

Central pathways causing fatigue in neuro-inflammatory and autoimmune illnesses.

Morris G, Berk M, Walder K, Maes M.

Abstract

BACKGROUND:

The genesis of severe fatigue and disability in people following acute pathogen invasion involves the activation of Toll-like receptors followed by the upregulation of proinflammatory cytokines and the activation of microglia and astrocytes. Many patients suffering from neuroinflammatory and autoimmune diseases, such as multiple sclerosis, Parkinson's disease and systemic lupus erythematosus, also commonly suffer from severe disabling fatigue. Such patients also present with chronic peripheral immune activation and systemic inflammation in the guise of elevated proinflammtory cytokines, oxidative stress and activated Toll-like receptors. This is also true of many patients presenting with severe, apparently idiopathic, fatigue accompanied by profound levels of physical and cognitive disability often afforded the non-specific diagnosis of chronic fatigue syndrome.

DISCUSSION:

Multiple lines of evidence demonstrate a positive association between the degree of peripheral immune activation, inflammation and oxidative stress, gray matter atrophy, glucose hypometabolism and cerebral hypoperfusion in illness, such as multiple sclerosis, Parkinson's disease and chronic fatigue syndrome. Most, if not all, of these abnormalities can be explained by a reduction in the numbers and function of astrocytes secondary to peripheral immune activation and inflammation. This is also true of the widespread mitochondrial dysfunction seen in otherwise normal tissue in neuroinflammatory, neurodegenerative and autoimmune diseases and in many patients with disabling, apparently idiopathic, fatigue. Given the strong association between peripheral immune activation and neuroinflammation with the genesis of fatigue the latter group of patients should be examined using FLAIR magnetic resonance imaging (MRI) and tested for the presence of peripheral immune activation.

SUMMARY:

It is concluded that peripheral inflammation and immune activation, together with the subsequent activation of glial cells and mitochondrial damage, likely account for the severe levels of intractable fatigue and disability seen in many patients with neuroimmune and autoimmune diseases.This would also appear to be the case for many patients afforded a diagnosis of Chronic Fatigue Syndrome.

PMID:

25856766

[PubMed - indexed for MEDLINE]

PMCID:

PMC4320458

Pain:

January 2016 - Volume 157 - Issue 1 - p 174–185

doi: 10.1097/j.pain.0000000000000348

Research Paper

Internet-delivered cognitive-behavioral treatment for adolescents with chronic pain and their parents: a randomized controlled multicenter trial

Palermo, Tonya M.[a,b,*]; Law, Emily F.[a,b]; Fales, Jessica[c]; Bromberg, Maggie H.[b]; Jessen-Fiddick, Tricia[b]; Tai, Gabrielle[b]

Abstract

Abstract: Internet-delivered interventions are emerging as a strategy to address barriers to care for individuals with chronic pain. This is the first large multicenter randomized controlled trial of Internet-delivered cognitive-behavioral therapy (CBT) for pediatric chronic pain. Participants included were 273 adolescents (205 females and 68 males), aged 11 to 17 years with mixed chronic pain conditions and their parents, who were randomly assigned in a parallel-group design to Internet-delivered CBT (n = 138) or Internet-delivered Education (n = 135). Assessments were completed before treatment, immediately after treatment, and at 6-month follow-up. All data collection and procedures took place online. The primary analysis used linear growth models. Results demonstrated significantly greater reduction on the primary outcome of activity limitations from baseline to 6-month follow-up for Internet CBT compared with Internet education (b = −1.13, *P* = 0.03). On secondary outcomes, significant beneficial effects of Internet CBT were found on sleep quality (b = 0.14, *P* = 0.04), on reducing parent miscarried helping (b = −2.66, *P* = 0.007) and protective behaviors (b = −0.19, *P* = 0.001), and on treatment satisfaction (*P* values < 0.05). On exploratory outcomes, benefits of Internet CBT were found for parent-perceived impact (ie, reductions in depression, anxiety, self-blame about their adolescent's pain, and improvement in parent behavioral responses to pain). In conclusion, our Internet-delivered CBT intervention produced a number of beneficial effects on adolescent and parent outcomes, and could ultimately lead to wide dissemination of evidence-based psychological pain treatment for youth and their families.

Cumulative Use of Strong Anticholinergics and Incident Dementia
A Prospective Cohort Study

Shelly L. Gray, PharmD, MS; Melissa L. Anderson, MS; Sascha Dublin, MD, PhD; Joseph T. Hanlon, PharmD, MS; Rebecca Hubbard, PhD; RodWalker, MS; Onchee Yu, MS; Paul K. Crane,MD, MPH; Eric B. Larson, MD, MPH

IMPORTANCE Many medications have anticholinergic effects. In general, anticholinergicinduced cognitive impairment is considered reversible on discontinuation of anticholinergic therapy. However, a few studies suggest that anticholinergicsmay be associated with an increased risk for dementia.

OBJECTIVE To examine whether cumulative anticholinergic use is associated with a higher risk for incident dementia.

DESIGN, SETTING, AND PARTICIPANTS Prospective population-based cohort study using data from the Adult Changes in Thought study in Group Health, an integrated health care delivery system in Seattle,Washington.We included 3434 participants 65 years or older with no dementia at study entry. Initial recruitment occurred from 1994 through 1996 and from 2000 through 2003. Beginning in 2004, continuous replacement for deaths occurred. All participants were followed up every 2 years. Data through September 30, 2012, were included in these analyses.

EXPOSURES Computerized pharmacy dispensing data were used to ascertain cumulative anticholinergic exposure, which was defined as the total standardized daily doses (TSDDs) dispensed in the past 10 years. The most recent 12 months of use was excluded to avoid use related to prodromal symptoms. Cumulative exposure was updated as participants were followed up over time.

MAIN OUTCOMES AND MEASURES Incident dementia and Alzheimer disease using standard diagnostic criteria. Statistical analysis used Cox proportional hazards regression models adjusted for demographic characteristics, health behaviors, and health status, including comorbidities.

RESULTS The most common anticholinergic classes used were tricyclic antidepressants, first-generation antihistamines, and bladder antimuscarinics. During a mean follow-up of 7.3 years, 797 participants (23.2%) developed dementia (637 of these [79.9%] developed Alzheimer disease). A 10-year cumulative dose-response relationship was observed for dementia and Alzheimer disease (test for trend, $P < .001$). For dementia, adjusted hazard ratios for cumulative anticholinergic use compared with nonuse were 0.92 (95%CI, 0.74-1.16) for TSDDs of 1 to 90; 1.19 (95%CI, 0.94-1.51) for TSDDs of 91 to 365; 1.23 (95%CI, 0.94-1.62) for TSDDs of 366 to 1095; and 1.54 (95%CI, 1.21-1.96) for TSDDs greater than 1095. A similar pattern of results was noted for Alzheimer disease. Results were robust in secondary, sensitivity, and post hoc analyses.

CONCLUSIONS AND RELEVANCE Higher cumulative anticholinergic use is associated with an increased risk for dementia. Efforts to increase awareness among health care professionals and older adults about this potential medication-related risk are important to minimize anticholinergic use over time.

JAMA Intern Med. doi:10.1001/jamainternmed.2014.7663
Published online January 26, 2015.
Invited Commentary
Supplemental content at
jamainternalmedicine.com

Author Affiliations: School of Pharmacy, University ofWashington, Seattle (Gray); Group Health Research Institute, Seattle,Washington (Anderson, Dublin, Hubbard,Walker, Yu, Larson); Department of Epidemiology, University ofWashington, Seattle (Dublin); Division of Geriatric Medicine, University of Pittsburgh, Pittsburgh, Pennsylvania (Hanlon); Department of Biostatistics, University ofWashington, Seattle (Hubbard); currently with the Department of Biostatistics and Epidemiology, Perelman School of Medicine, University of Pennsylvania,Philadelphia (Hubbard); Division of General Internal Medicine, University ofWashington, Seattle (Crane,Larson).

Corresponding Author: Shelly L. Gray, PharmD,MS, School of Pharmacy, University ofWashington, PO Box 357630, Seattle,WA 98195 (slgray@uw.edu).

ENDO 2016: The Endocrine Society Annual Meeting

Endocrine Society Advises Against Compounded Hormone Use

Miriam E Tucker | April 01, 2016

BOSTON — The Endocrine Society has issued a new scientific statement advising clinicians to avoid using custom-compounded hormones to treat menopausal symptoms, female sexual dysfunction, and thyroid disorders.

"Custom-compounded hormones should be reserved for situations in which a patient is allergic to or does not tolerate any of the FDA-approved therapies and treatment is necessary for his or her health," lead author Nanette Santoro, MD, professor and chair of obstetrics and gynecology at the University of Colorado School of Medicine in Aurora, said during a press briefing here at ENDO 2016, the annual meeting of the Endocrine Society. The statement was published online April 1, 2016 in the *Journal of Clinical Endocrinology and Metabolism*.

The statement is the latest in a series from medical societies, including the American College of Obstetricians and Gynecologists and the North American Menopause Society, cautioning against the use of custom-compounded, so-called "bioidentical" hormones. Nonetheless, many physicians are still prescribing them.

Indeed, Dr Santoro cited survey data that up to a quarter or a third of all menopause therapy prescriptions are for custom-compounded products, garnering about $1 billion in annual sales. "This to us seems somewhat absurd when we have a large variety of what are technically the same bioidentical hormones that are FDA approved….It's kind of unfortunate that we live in an era where this has become so widespread it's a very big business."

Custom-compounded products are potentially dangerous, she said, because added excipients can affect absorption, and those or other added ingredients could be contaminated or adulterated. Moreover, she noted, FDA-approved hormone products have well-characterized pharmacokinetics and efficacy and safety profiles. In contrast, "There's no such thing in the world of custom-compounded bioidentical hormones."

Endocrinologist Mark Sklar, MD, told *Medscape Medical News* that he agrees with the Endocrine Society's new statement and stance. "I think that there's no real reason to compound, especially gonadal hormones like estrogen or testosterone, because there are very good commercially available hormones now. They're well-made and well-tested, and there's consistency. With compounding there's not consistency in dosage."

Dr Sklar, who is an assistant professor of medicine and endocrinology at Georgetown University Medical Center and George Washington University Medical Center, Washington, DC, added, "People who advocate compounding tell patients that the compounded medications don't have the same side effects. The article states, as I previously believed, that there are probably side effects; they're just not tested with the compounded agents like they are with the commercially available hormones. So I do agree with the statement and would not promote compounding in my practice."

"Numerous FDA-Approved Formulations"

Aimed at primary-care clinicians as well as endocrinologists, the Endocrine Society's new document provides detailed reviews of the biology and pharmacology of sex steroids and thyroid-hormone action, including available clinical-trial data for the FDA-approved products

Key points

- There are numerous FDA-approved formulations, both oral and nonoral, that have been recommended for menopausal hormone therapy, and therefore there is no rationale for use of nonapproved products. Nonoral estradiol may be associated with a reduced risk for venous thromboembolism and stroke.
- Micronized progesterone (MP), which has a superior metabolic profile and possibly lower risk of breast cancer, is preferred by some experts as first-line progestin therapy for women taking menopausal hormone therapy. Although biochemically it is apparently beneficial, evidence demonstrating a benefit of MP on clinical outcomes is lacking.
- There is no rationale for using compounded progesterone preparations of unknown pharmacokinetics, because there are many on-label pharmaceutical-grade preparations available and a real risk of harm associated with inadequate progesterone dosing.
- There are no randomized, double-blind, placebo-controlled trials demonstrating efficacy of compounded bioidentical hormone therapy in alleviating menopausal symptoms or other clinical conditions.

- Moreover, there are no comparative-effectiveness studies of equivalent doses of compounded bioidentical hormones compared with FDA-approved hormone treatments.
- Transdermal patches, gels, and intramuscular preparations of bioidentical testosterone are available and FDA approved for use in men with hypogonadism.
- There are currently no FDA-approved testosterone preparations for women.
- Custom-compounded testosterone for women can result in overdosing and cause harm.
- There are currently no FDA-approved preparations of dehydroepiandrosterone (DHEA), and there are no indications for its use except perhaps for some women with a low libido associated with adrenal insufficiency.
- Non–FDA-approved preparations of DHEA have all the caveats related to dosing, pharmacokinetics, and safety associated with estradiol, progesterone, and testosterone.
- The use of custom-compounded bioidentical DHEA is unlikely to be beneficial and is potentially harmful to patients.
- Vaginal DHEA is currently undergoing testing as an alternative to vaginal estrogen for the treatment of menopausal vaginal atrophy, but there is no vaginal DHEA preparation that is FDA approved for clinical use at this time.
- Levothyroxine (LT4) is bioidentical and a highly effective and safe therapy and is the treatment of choice for hypothyroidism. The complex tissue-specific deiodinase system converts T4 to T3 and supplies the proper amount of T3 to each of the body's tissues according to its requirements.
- Clinicians should evaluate patients with persistent symptoms (despite adequate LT4 therapy) for other causes of their symptoms and encourage patients to engage in healthy lifestyle measures.
- Some of these patients may benefit from combination LT4/LT3 therapy, desiccated thyroid hormone, or compounded thyroid hormone, as long as symptoms and thyroid-stimulating hormone (TSH) (free T4) are monitored carefully.

Asked whether there was any type of patient for whom he might use a compounded hormone formulation, Dr Sklar replied, "Not with estrogen or testosterone. I don't see any reason for that." He had previously tried it with thyroid hormone, "but the levels were very variable and not reliable at all.

"The only indication I might try compounding is women who need testosterone, since there is no good commercially available testosterone. Sometimes you have to resort to compounding to get that….Some women complain of low libido. Low-dose testosterone sometimes works for that. But I don't use it that often."

In a written statement, Dagmar Anderson, vice president of communications for the International Academy of Compounding Pharmacists (IACP), told *Medscape Medical News*, "IACP believes the patient has the choice to opt for a compounded medication, and that decision should be made with his/her physician."

J Clin Endocrinol Metab. Published online April 1, 2016. Abstract

Med Sci Sports Exerc .2016 Apr 26. [Epub ahead of print]

Graded vs Intermittent Exercise Effects on Lymphocytes in Chronic Fatigue Syndrome.

Broadbent S[1], Coutts R.

[1]School of Health and Human Sciences, Southern Cross University, Lismore NSW, Australia.

Abstract

PURPOSE:

There is increasing evidence of immune system dysfunction in Chronic Fatigue Syndrome (CFS) but little is known of the regular exercise effects on immune cell parameters. This pilot study investigated the effects of graded and intermittent exercise on CD4 lymphocyte subset counts and activation compared to usual care.

METHODS:

24 CFS patients (50.2 ± 10 yr) were randomised to Graded exercise (GE), Intermittent exercise (IE) or usual care (UC) groups; 18 sedentary non-CFS participants (50.6 ± 10 yr) were controls (CTL) for blood and immunological comparisons. Outcome measures were pre- and post-intervention flow cytometric analyses of circulating lymphocyte subset cell counts, expression of CD3, CD4, CD25 and CD134, full blood counts and V[Combining Dot Above]O2peak RESULTS: Pre-intervention, CD3 cell counts and expression of CD4, CD25, CD134 and CD4CD25CD134 were significantly lower in GE, IE and UC compared to CTL ($f < 0.05$). Total lymphocyte concentration was significantly lower in GE and IE groups compared to CTL. There were significant post-intervention increases in (i) expression of CD4 and CD4CD25CD134 for GE and IE, but CD25 and CD134 for IE only; (ii) circulating counts of CD3 and CD4 for GE, and CD3, CD4, CD8, CD3CD4CD8, CD3CD16CD56, CD19 and CD45 for IE; (iii) neutrophil concentration for GE; (iv) V[Combining Dot Above]O2peak and elapsed test time for IE and GE, V[Combining Dot Above]Epeak for IE.

CONCLUSIONS:

Twelve weeks of GE and IE training significantly improved CD4 lymphocyte activation and aerobic capacity without exacerbating CFS symptoms. IE may be a more effective exercise modality with regard to enhanced CD4 activation in CFS patients.

PMID:

27116645

[PubMed - as supplied by publisher]

http://www.ncbi.nlm.nih.gov/pubmed/27020075

J Psychosom Res. 2016 Apr;83:40-5. doi:
10.1016/j.jpsychores.2016.02.004.

Treatment expectations influence the outcome of multidisciplinary rehabilitation treatment in patients with CFS.

Vos-Vromans DC, Huijnen IP, Rijnders LJ, Winkens B, Knottnerus JA, Smeets RJ.

Abstract

OBJECTIVE: To improve the effectiveness of treatment in patients with chronic fatigue syndrome it is worthwhile studying factors influencing outcomes. The aims of this study were (1) to assess the association of expectancy and credibility on treatment outcomes, and (2) to identify baseline variables associated with treatment expectancy and credibility.

METHODS: 122 patients were included in a randomized controlled trial of whom 60 received cognitive behavioural therapy (CBT) and 62 multidisciplinary rehabilitation treatment (MRT). Expectancy and credibility were measured with the credibility and expectancy questionnaire. Outcomes of treatment, fatigue, and quality of life (QoL), were measured at baseline and post-treatment. Multiple linear regressions were performed to analyse associations.

RESULTS: In explaining fatigue and the physical component of the QoL, the effect of expectancy was significant for MRT, whereas in CBT no such associations were found. The main effect of expectancy on the mental component of QoL was not significant. For credibility, the overall effect on fatigue and the physical component of QoL was not significant. In explaining the mental component of QoL, the interaction between treatment and credibility was significant.

However, the effects within each group were not significant. In the regression model with expectancy as dependent variable, only treatment centre appeared significantly associated. In explaining credibility, treatment centre, treatment allocation and depression contributed significantly.

CONCLUSIONS: For clinical practice it seems important to check the expectations of the patient, since expectations influence the outcome after MRT.

http://translational-medicine.biomedcentral.com/articles/10.1186/s1...

Altered neuroendocrine control and association to clinical symptoms in adolescent chronic fatigue syndrome: a cross-sectional study

Vegard Bruun Wyller, Valieria Vitelli, Dag Sulheim, Even Fagermoen, Anette Winger, Kristin Godang and Jens Bollerslev Journal of Translational Medicine201614:121

Abstract

Background: Chronic fatigue syndrome (CFS) is a common and disabling disorder, and a major threat against adolescent health. The pathophysiology is unknown, but alteration of neuroendocrine control systems might be a central element, resulting in attenuation of the hypothalamus–pituitary–adrenalin (HPA) axis and enhancement of the sympathetic/adrenal medulla (SAM) system.

This study explored differences in neuroendocrine control mechanisms between adolescent CFS patients and healthy controls, and whether characteristics of the control mechanisms are associated with important clinical variables within the CFS group.

Methods: CFS patients 12–18 years of age were recruited nation-wide to a single referral center as part of the NorCAPITAL project. A broad case definition of CFS was applied. A comparable group of healthy controls were recruited from local schools. A total of nine hormones were assayed and subjected to network analyses using the ARACNE algorithm. Symptoms were charted by a questionnaire, and daily physical activity was recorded by an accelerometer.

Results: A total of 120 CFS patients and 68 healthy controls were included. CFS patients had significantly higher levels of plasma norepinephrine, plasma epinephrine and plasma FT4, and significantly lower levels of urine cortisol/creatinine ratio. Subgrouping according to other case definitions as well as adjusting for confounding factors did not alter the results. Multivariate linear regression models as well as network analyses revealed different interrelations between hormones of the HPA axis, the SAM system, and the thyroid system in CFS patients and healthy controls. Also, single hormone degree centrality was associated with clinical markers within the CFS group.

Conclusion: This study reveals different interrelation between hormones of the HPA axis, the SAM system, and the thyroid system in CFS patients and healthy controls, and an association between hormone control characteristics and important clinical variables in the CFS group. These results add to the growing insight of CFS disease mechanisms.

Trial registration Clinical Trials NCT01040429

http://www.ncbi.nlm.nih.gov/pubmed/24433278

Suicidal ideation in patients with fibromyalgia: a cross-sectional study.

Calandre EP1, Navajas-Rojas MA, Ballesteros J, Garcia-Carrillo J, Garcia-Leiva JM, Rico-Villademoros F.

Abstract

Chronic pain, sleep disturbances, and depression, which are relevant symptoms of fibromyalgia syndrome, have been demonstrated to be associated with an increased likelihood of suicidal behaviors.

Mortality from suicide has been shown to be greater among patients with fibromyalgia. This study aimed to assess the prevalence of suicidal ideation among a sample of patients with fibromyalgia and to evaluate its relationship with the clinical symptomatology of fibromyalgia.

Baseline data from fibromyalgia patients willing to participate in different clinical studies were collected. Outcome measures included the Fibromyalgia Impact Questionnaire, the Beck Depression Inventory, the Pittsburgh Sleep Quality Index, the Brief Pain Inventory, and the SF-12 Health Survey.

The scores for these scales were compared between patients with and without suicidal ideation. The presence of suicidal ideation was assessed using the answer provided to item 9 of the Beck Depression Inventory.

The results were adjusted by age, sex, total comorbidity, and time since diagnosis with multiple linear regression. The sample comprised 373 patients of whom one hundred and seventy-nine (48%) reported suicidal ideation: 148 (39.7%) reported passive suicidal ideation and 31 (8.3%) active suicidal ideation.

Suicidal ideation was markedly associated with depression, anxiety, sleep quality, and global mental health, whereas only weak relationships were observed between suicidal ideation and both pain and general physical health.

http://www.ncbi.nlm.nih.gov/pubmed/27125909

Ubiquinol-10 supplementation improves autonomic nervous function and cognitive function in chronic fatigue syndrome.

Fukuda S, Nojima J, Kajimoto O, Yamaguti K, Nakatomi Y, Kuratsune H, Watanabe Y.

Abstract

The aim of this study was to evaluate the benefit of oral ubiquinol-10 supplementation in CFS patients using an open-label study and a randomized, double-blinded, placebo-controlled (RCT) study.

Twenty patients with CFS were randomly enrolled in an 8-week open-label oral ubiquinol-10 (150 mg ubiquinol-10/day) study. The patients and the attending physicians were not blinded to the supplementation.

Forty-three patients with CFS were randomly assigned to receive either ubiquinol-10 (150 mg/day) or placebo every day for 12 weeks. The patients and the attending physicians were blinded to the supplementation, and a total of 31 patients (N = 17 in the ubiquinol group and 14 in the placebo group) completed the study.

The beneficial effects of ubiquinol-10 were observed in the open-label study we conducted prior to the RCT. The RCT results suggest that supplementation with ubiquinol-10 for 12 weeks is effective for improving several CFS symptoms.

http://www.ncbi.nlm.nih.gov/pubmed/27118360

Q fever: a contemporary case series from a Belgian hospital.

Vanderbeke L, Peetermans WE, Saegeman V, De Munter P.

Abstract

OBJECTIVES: Q fever is a global zoonosis that can cause both acute and chronic infections in humans through aerogenic transmission. Although Q fever was discovered already 80 years ago, this infectious disease remains largely unknown. We studied a case series in a Belgian tertiary care hospital.

METHODS: A laboratory and file query at our department was performed to detect patients who were newly diagnosed with Q fever from 01 January 2005 to 01 October 2014.

RESULTS: In total, 10 acute Q fever and 5 chronic Q fever infections were identified. An aspecific flu-like illness was the prevailing manifestation of acute Q fever, while this was infective endocarditis in chronic Q fever cases. Noteworthy are the high percentage of myocarditis cases in the acute setting and one case of amyloidosis as a manifestation of chronic Q fever. No evolution from acute to chronic Q fever was noted; overall outcome for both acute and chronic Q fever was favourable with a 94% survival rate.

DISCUSSION: Q fever is an infectious disease characterised by a variable clinical presentation. Detection requires correct assessment of the clinical picture in combination with a laboratory confirmation.
Treatment and follow-up are intended to avoid a negative outcome.

http://www.ncbi.nlm.nih.gov/pubmed/27123773

Progressive brain changes in patients with chronic fatigue syndrome: A longitudinal MRI study.

Shan ZY, Kwiatek R, Burnet R, Del Fante P, Staines DR, Marshall-Gradisnik SM, Barnden LR.

Abstract

PURPOSE: To examine progressive brain changes associated with chronic fatigue syndrome (CFS).

MATERIALS AND METHODS: We investigated progressive brain changes with longitudinal MRI in 15 CFS and 10 normal controls (NCs) scanned twice
6 years apart on the same 1.5 Tesla (T) scanner. MR images yielded gray matter (GM) volumes, white matter (WM) volumes, and T1- and T2-weighted signal intensities (T1w and T2w). Each participant was characterized with Bell disability scores, and somatic and neurological symptom scores. We tested for differences in longitudinal changes between CFS and NC groups, inter group differences between pooled CFS and pooled NC populations, and correlations between MRI and symptom scores using voxel based morphometry. The analysis methodologies were first optimized using simulated atrophy.

RESULTS: We found a significant decrease in WM volumes in the left inferior fronto-occipital fasciculus (IFOF) in CFS while in NCs it was unchanged (family wise error adjusted cluster level P value, $P_{FWE} < 0.05$). This longitudinal finding was consolidated by the group comparisons which detected significantly decreased regional WM volumes in adjacent regions ($P_{FWE} < 0.05$) and decreased GM and blood volumes in contralateral regions ($P_{FWE} < 0.05$). Moreover, the regional GM and WM volumes and T2w in those areas showed significant correlations with CFS symptom scores ($P_{FWE} < 0.05$).

CONCLUSION: The results suggested that CFS is associated with IFOF WM deficits which continue to deteriorate at an abnormal rate. J. Magn.
Reson. Imaging 2016.

http://fibromyalgianewstoday.com/2016/04/04/leptin-tied-to-bodily-p...9

Leptin Tied to Bodily Pain, Predicts Fibromyalgia Pain Levels, Researchers Say

Magdalena Kegel

Leptin – a factor well-known for its role in controlling appetite – might be a driver of bodily pain, according to a new report.
Investigating levels of the molecule in both women with fibromyalgia and healthy women has provided scientists with clues of the underlying processes of pain signaling and might lead to better future pain treatments.

Last week, Fibromyalgia News Today reported on the scientific progress of a research team from the University of Alabama at Birmingham, investigating brain-immune interactions in fibromyalgia patients. The study described the team's efforts to understand leptin's role in pain signaling.

Earlier research has shown that the appetite-controlling molecule is also regulated by sleep and infection, and has been linked to inflammatory diseases such as rheumatoid arthritis, lupus, and multiple sclerosis.

The report, titled "Association of Leptin with Body Pain in Women," is actually composed of two studies. The first small pilot study followed three women over 25 days who were affected by fibromyalgia, analyzing both leptin and pain on a daily basis.

The findings, published in the Journal of Women's Health, show that leptin levels fluctuated along with reported pain, with higher levels on days when women experienced more pain.

The second study explored previously collected data from the Women's Health Initiative (WHI) Observational Study. The study, performed between 1993 and 1998, offered the research team blood samples and data on bodily pain, as well as participants' BMI levels. The group consisted of 5,676 postmenopausal women, representative of the general population.

Analyzing this large group of women, the researchers found that both leptin and BMI were associated with bodily pain, independent of each other.

The evidence of a link between leptin and pain in the second study was rather weak. This could have been a consequence of blood samples and pain ratings not taken on the same occasion, since the first study indicated that leptin levels could fluctuate several times over consecutive days, making the prospect of finding a link small. Most women in the large sample also were not likely to suffer from a pain condition.

However, the researchers believe a potential link between leptin and pain might be more evident in pain conditions, as was the case in the three fibromyalgia women. They also caution that, given the daily fluctuations, levels need to be measured on consecutive occasions to provide a more clear picture of the factor's role in pain signaling.

While none of the studies presents evidence that leptin causes pain, the results point researchers in a direction worth exploring for pain conditions such as fibromyalgia.

http://bmcpediatr.biomedcentral.com/articles/10.1186/s12887-016-059...

Tracking post-infectious fatigue in clinic using routine Lab tests

Jeanna M. Harvey, Gordon Broderick Alanna Bowie, Zachary M. Barnes, Ben Z. Katz, Maurice R. G. O'Gorman, ***Suzanne D. Vernon***, Mary Ann Fletcher, ***Nancy G. Klimas*** and, Renee Taylor

Abstract

Background: While biomarkers for chronic fatigue syndrome (CFS) are beginning to emerge they typically require a highly specialized clinical laboratory. We hypothesized that subsets of commonly measured laboratory markers used in combination could support the diagnosis of post-infectious CFS (PI-CFS) in adolescents following infectious mononucleosis (IM) and help determine who might develop persistence of symptoms.

Methods: Routine clinical laboratory markers were collected prospectively in 301 mono-spot positive adolescents, 4 % of whom developed CFS (n = 13). At 6, 12, and 24 months post-diagnosis with IM, 59 standard tests were performed including metabolic profiling, liver enzyme panel, hormone profiles, complete blood count (CBC), differential white blood count (WBC), salivary cortisol, and urinalysis. Classification models separating PI-CFS from controls were constructed at each time point using stepwise subset selection.

Results: Lower ACTH levels at 6 months post-IM diagnosis were highly predictive of CFS (AUC p = 0.02). ACTH levels in CFS overlapped with healthy controls at 12 months, but again showed a trend towards a deficiency at 24 months.

Conversely, estradiol levels depart significantly from normal at 12 months only to recover at 24 months (AUC p = 0.02). Finally, relative neutrophil count showed a significant departure from normal at 24 months in CFS (AUC p = 0.01). Expression of these markers evolved differently over time between groups.

Conclusions: Preliminary results suggest that serial assessment of stress and sex hormones as well as the relative proportion of innate immune cells measured using standard clinical laboratory tests may support the diagnosis of PI-CFS in adolescents with IM.

http://www.ncbi.nlm.nih.gov/pubmed/27110826

Diagnostics (Basel). 2016 Apr 22;6(2). pii: E16.

The Relationship between Age and Illness Duration in Chronic Fatigue Syndrome.

Kidd E, Brown A, McManimen S, Jason LA, Newton JL, Strand EB.

Abstract

Chronic fatigue syndrome (CFS) is a debilitating illness, but it is unclear if patient age and illness duration might affect symptoms and functioning of patients. In the current study, participants were categorized into four groups based upon age (under or over age 55) and illness duration (more or less than 10 years). The groups were compared on functioning and symptoms.

Findings indicated that those who were older with a longer illness duration had significantly higher levels of mental health functioning than those who were younger with a shorter or longer illness duration and the older group with a shorter illness duration.

The results suggest that older patients with an illness duration of over 10 years have significantly higher levels of mental health functioning than the three other groups.

For symptoms, the younger/longer illness duration group had significantly worse immune and autonomic domains than the older/longer illness group.

In addition, the younger patients with a longer illness duration displayed greater autonomic and immune symptoms in comparison to the older group with a longer illness duration.

These findings suggest that both age and illness duration need to be considered when trying to understand the influence of these factors on patients.

http://www.ncbi.nlm.nih.gov/pubmed/27105483

Fibromyalgia syndrome pathology and environmental influences on afflictions with medically unexplained symptoms.

Albrecht PJ, Rice FL.

Abstract

Fibromyalgia syndrome (FMS) is a clinical disorder predominant in females with unknown etiology and medically unexplained symptoms (MUS), similar to other afflictions, including irritable bowel syndrome (IBS), chronic fatigue syndrome (CFS), post-traumatic stress disorder (PTSD), Gulf War illness (GFI), and others.

External environmental stimuli drive behavior and impact physiologic homeostasis (internal environment) via autonomic functioning. These environments directly impact the individual affective state (mind), which feeds back to regulate physiology (body).

FMS has emerged as a complex disorder with pathologies identified among neurotransmitter and enzyme levels, immune/cytokine functionality, cortical volumes, cutaneous innervation, as well as an increased frequency among people with a history of traumatic and/or emotionally negative events, and specific personality trait profiles. Yet, quantitative physical evidence of pathology or disease etiology among FMS has been limited (as with other afflictions with MUS).

Previously, our group published findings of increased peptidergic sensory innervation associated with the arterio-venous shunts (AVS) in the glabrous hand skin of FMS patients, which provides a plausible mechanism for the wide-spread FMS symptomology.

This review focuses on FMS as a model affliction with MUS to discuss the implications of the recently discovered peripheral innervation alterations, explore the role of peripheral innervation to central sensitization syndromes (CSS), and examine possible estrogen-related mechanisms through which external and internal environmental factors may contribute to FMS etiology and possibly other afflictions with MUS.

PMID:27105483 [PubMed - as supplied by publisher]

http://www.ncbi.nlm.nih.gov/pubmed/27098385

J Health Psychol. 2016. pii: 1359105316643376. [Epub ahead of print]

The psychological impact of dependency in adults with chronic fatigue syndrome/myalgic encephalomyelitis: A qualitative exploration.

Williams AM, Christopher G, Jenkinson E.

Abstract

Chronic fatigue syndrome/myalgic encephalomyelitis can limit functional capacity, producing various degrees of disability and psychological distress.

Semi-structured interviews explored the experiences of adults with chronic fatigue syndrome/myalgic encephalomyelitis being physically dependent on other people for help in daily life, and whether physical dependency affects their psychological well-being.

Thematic analysis generated six themes: loss of independence and self-identity, an invisible illness, anxieties of today and the future, catch-22, internalised anger, and acceptance of the condition.

The findings provide insight into the psychological impact of dependency. Implications for intervention include better education relating to chronic fatigue syndrome/myalgic encephalomyelitis for family members, carers, and friends; ways to communicate their needs to others who may not understand chronic fatigue syndrome/myalgic encephalomyelitis; and awareness that acceptance of the condition could improve psychological well-being.

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4508058/

PLoS One. 2015 Jul 20;10(7):e0132774. doi:
10.1371/journal.pone.0132774. eCollection 2015.

Achieving Remission in Gulf War Illness: A Simulation-Based Approach to Treatment Design.

Craddock TJ, Del Rosario RR, Rice M, Zysman JP, Fletcher MA, Klimas NG, Broderick G.

Abstract

Gulf War Illness (GWI) is a chronic multi-symptom disorder affecting up to one-third of the 700,000 returning veterans of the 1991 Persian Gulf War and for which there is no known cure. GWI symptoms span several of the body's principal regulatory systems and include debilitating fatigue, severe musculoskeletal pain, cognitive and neurological problems.

Using computational models, our group reported previously that GWI might be perpetuated at least in part by natural homeostatic regulation of the neuroendocrine-immune network. In this work, we attempt to harness these regulatory dynamics to identify treatment courses that might produce lasting remission.

Towards this we apply a combinatorial optimization scheme to the Monte Carlo simulation of a discrete ternary logic model that represents combined hypothalamic-pituitary-adrenal (HPA), gonadal (HPG), and immune system regulation in males.

In this work we found that no single intervention target allowed a robust return to normal homeostatic control. All combined interventions leading to a predicted remission involved an initial inhibition of Th1 inflammatory cytokines (Th1Cyt) followed by a subsequent inhibition of glucocorticoid receptor function (GR).

These first two intervention events alone ended in stable and lasting return to the normal regulatory control in 40% of the simulated cases.

Applying a second cycle of this combined treatment improved this predicted remission rate to 2 out of 3 simulated subjects (63%).

These results suggest that in a complex illness such as GWI, a multi-tiered intervention strategy that formally accounts for regulatory dynamics may be required to reset neuroendocrine-immune homeostasis and support extended remission.

http://translational-medicine.biomedcentral.com/articles/10.1186/s1...

ERK1/2, MEK1/2 and p38 downstream signalling molecules impaired in CD56dimCD16+ and CD56brightCD16dim/− natural killer cells in Chronic Fatigue Syndrome/Myalgic Encephalomyelitis patients

Teilah Kathryn Huth, Donald Staines, and Sonya Marshall-Gradisnik

Abstract

Background: Natural Killer (NK) cell effector functions are dependent on phosphorylation of the mitogen-activated protein kinases (MAPK) pathway to produce an effective immune response for the clearance of target cells infected with viruses, bacteria or malignantly transformed cells. Intracellular signals activating NK cell cytokine production and cytotoxic activity are propagated through protein phosphorylation of MAPKs including MEK1/2, ERK1/2, p38 and JNK.

Reduced NK cell cytotoxic activity is consistently reported in Chronic Fatigue Syndrome/Myalgic Encephalomyelitis (CFS/ME) patients and intracellular signalling by MAPK in NK cells remains to be investigated. Therefore, the purpose of this paper was to investigate MAPK downstream signalling molecules in NK cell phenotypes from CFS/ME patients.

Methods: Flow cytometric protocols were used to measure phosphorylation of the MAPK pathway in CD56brightCD16dim/− and CD56dimCD16+ NK cells following stimulation with K562 tumour cells or phorbol-12-myristate-13-acetate plus ionomycin. NK cell cytotoxic activity, degranulation, lytic proteins and cytokine production were also measured as markers for CD56brightCD16dim/− and CD56dimCD16+ NK cell function using flow cytometric protocols.

Results: CFS/ME patients (n = 14) had a significant decrease in ERK1/2 in CD56dimCD16+ NK cells compared to the non-fatigued controls (n = 11) after incubation with K562 cells. CD56brightCD16dim/− NK cells from CFS/ME patients had a significant increase in MEK1/2 and p38 following incubation with K562 cells.

Conclusions: This is the first study to report significant differences in MAPK intracellular signalling molecules in CD56dimCD16+ and CD56brightCD16dim/− NK cells from CFS/ME patients. The current results highlight the importance of intracellular signalling through the MAPK pathway for synergistic effector function of CD56dimCD16+ and CD56brightCD16dim/− NK cells to ensure efficient clearance of target cells. In CFS/ME patients, dysfunctional MAPK signalling may contribute to reduced NK cell cytotoxic activity.

http://www.tandfonline.com/doi/abs/10.1080/21641846.2016.1167470?jo...

A comparative polysomnography analysis of sleep in healthy controls and patients with chronic fatigue syndrome

Zoe M. Gotts, Vincent Deary, Julia L. Newton & Jason G. Ellis

ABSTRACT

Background: Sleep disturbance affects almost 95% of people with chronic fatigue syndrome (CFS). However, existing studies of sleep in CFS have shown mixed results and methodological issues prevent between-study comparisons.

Purpose: To redress this, the present study aimed to investigate whether there are differences in the sleep of patients with CFS and healthy controls, using a comparative analysis of polysomnography over three consecutive nights.

Methods: Twenty-two patients with CFS (1994 Centers for Disease Control and Prevention criteria) and 22 healthy controls underwent three nights of polysomnographic sleep assessment. Groups were compared on their objective sleep variables derived from the third night of assessment, to allow for participant adaptation to the sleep study.

Results: 9.1% of patients met criteria for an objectively verifiable sleep disorder. Differences in sleep were observed between CFS patients and healthy controls on four objectively derived sleep variables (wake after sleep onset, sleep efficiency, percentage wake and REM Latency). In addition, people with CFS reported more severe symptoms of insomnia than healthy controls.

Conclusions: The study reports on key differences in sleep between people with CFS and healthy individuals. The potential presence of a sleep disorder in this patient population is high, it is therefore important that during early evaluation, a detailed history of sleep is taken to rule out a sleep disorder in CFS. In addition, patients with CFS show poorer sleep as defined by objectively derived measures and also self-report poorer quality sleep. Improving sleep is a potential treatment target in CFS.

http://www.ncbi.nlm.nih.gov/pubmed/25801843

CNS Neurol Disord Drug Targets. 2015;14(7):838-54.

The Toll-Like Receptor Radical Cycle Pathway: A New Drug Target in Immune-Related Chronic Fatigue.

Lucas K, Morris G, Anderson G, Maes M.

Abstract

In this review we discuss that peripheral and central activation of the Toll-like receptor 2/4 (TLR2/4) Radical Cycle may underpin the pathophysiology of immune-related chronic fatigue secondary to other medical diseases and conditions.

The TLR Radical Cycle plays a role in illnesses and conditions that are disproportionately commonly comorbid with secondary chronic fatigue, including a) neuroinflammatory disorders, e.g. Parkinson's disease, stroke, depression, psychological stressors, and b) systemic disorders, e.g. (auto)immune disorders, chronic obstructive pulmonary disease, ankylosing spondylitis, chronic kidney disease, inflammatory bowel disease, cardiovascular disease, incl. myocardial infarction, cancer and its treatments.

Increased TLR signaling is driven by activated immuneinflammatory and oxidative and nitrosative stress pathways, pathogen derived molecular patterns, including lipopolysaccharides, and damage associated molecular patterns (DAMPs).

Newly formed redox-derived DAMPs, secondary to oxidative processes, may further activate the TLR complex leading to an auto-amplifying TLR Radical feedback loop. Increased gut permeability with translocation of gram negative bacteria and LPS, which activates the TLR Radical Cycle, is another pathway that may play a role in most of the abovementioned diseases and the secondary fatigue accompanying them.

It is concluded that secondary fatigue may be associated with activation of the TLR Radical Cycle pathway due to activated immune-inflammatory pathways, classical and redox-derived DAMPs and PAMPs plays a role in its pathophysiology.

Such an activation of the TLR Radical Cycle pathway may also explain why the abovementioned conditions are primed for an increased expression of secondary chronic fatigue.

Targeting the TLR Radical Cycle pathway may be an effective method to treat TLR-Radical Cycle-related diseases such as secondary chronic fatigue.

PMID:25801843 [PubMed - indexed for MEDLINE]

http://www.ncbi.nlm.nih.gov/pubmed/27045557

Expert Rev Clin Pharmacol. 2016 Apr 5. [Epub ahead of print]

Efficacy of rintatolimod (Ampligen) in the treatment of chronic fatigue syndrome/ myalgic encephalomyelitis (cfs/me).

Mitchell WM.

Abstract

Chronic fatigue syndrome/ Myalgic encephalomyelitis (CFS/ME) is a poorly understood seriously debilitating disorder in which disabling fatigue is an universal symptom in combination with a variety of variable symptoms. The only drug in advanced clinical development is rintatolimod, a mismatched double stranded polymer of RNA (dsRNA).

Rintatolimod is a restricted Toll-Like Receptor 3 (TLR3) agonist lacking activation of other primary cellular inducers of innate immunity (e.g.- cytosolic helicases). Rintatolimod also activates interferon induced proteins that require dsRNA for activity (e.g.- 2'-5' adenylate synthetase, protein kinase R).

Rintatolimod has achieved statistically significant improvements in primary endpoints in Phase II and Phase III double-blind, randomized, placebo-controlled clinical trials with a generally well tolerated safety profile and supported by open-label trials in the United States and Europe.

The chemistry, mechanism of action, clinical trial data, and current regulatory status of rintatolimod for CFS/ME including current evidence for etiology of the syndrome are reviewed.

fulltext- http://bmjopen.bmj.com/content/6/4/e010277.full

BMJ Open 2016;6:e010277 doi:10.1136/bmjopen-2015-010277

How do women with chronic fatigue syndrome/myalgic encephalomyelitis rate quality and coordination of healthcare services? A cross-sectional study

Anne Helen Hansen, Olaug S Lian

Abstract

Objective: To test the association between self-rated health and self-rated degree of chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME), and CFS/ME patients' assessment of quality of primary care, specialist care and coordination of care.

Design: Cross-sectional study.

Setting: Self-reported questionnaire data from women members of The Norwegian ME Association obtained in 2013.

Participants: 431 women with CFS/ME aged 16–73 years.

Main outcome measure: The participants' assessment of quality in primary care, specialist care and in coordination of care (good/very good or poor/very poor). Main explanatory variables: self-rated health and self-rated degree of CFS/ME.

Results: Quality of care was rated poor by 60.6% in primary care, by 47.7% in specialist care, and by 71.2% regarding coordination of care.
Poorer self-rated health increased the probability of rating quality in primary care poor, particularly among women 40 years and over (OR 2.38, 95% CI 1.63 to 3.49), women with university education (OR 2.57, CI 1.68 to 3.94), and owing to less frequent general practitioner (GP) visits (OR 2.46, CI 1.60 to 3.78). Poorer self-rated health increased the probability of rating quality poor in specialist care (OR 1.38, CI
1.05 to 1.82), but not in coordination of care. A more severe CFS/ME was associated with a higher probability of rating quality in primary care poor (OR 0.61, CI 0.38 to 0.93). Frequent visitors and those with a long GP relationship were less likely to report primary care quality as poor.

Conclusions: A large proportion of women with CFS/ME rated quality of care poor/very poor in primary care, specialist care and in coordination of care. The dissatisfaction was higher for primary care than for specialist care. Overall, poorer self-rated health and a more severe CFS/ME were associated with lower quality scores in primary and specialist care, but not in coordination of care. Healthcare services, as assessed by women with CFS/ME, do have a large potential for improvement.

fulltext- http://www.sciencedirect.com/science/article/pii/S2213158216300584

Autonomic correlations with MRI are abnormal in the brainstem vasomotor centre in Chronic Fatigue Syndrome

Leighton R. Barnden, Richard Kwiatek, Benjamin Crouch, Richard Burnet, Peter Del Fante

Highlights

• For the first time in CFS, we performed MRI regressions with steady state BP and HR.
• Vasomotor centre, midbrain and hypothalamus correlations were abnormal in CFS.
• MRI group comparisons between CFS and controls detected no differences.
• Regulatory nuclei and peripheral effectors/sensors appear to function correctly.
• Signalling between brainstem/midbrain regulatory nuclei appears to be impaired.

Abstract

Autonomic changes are often associated with the chronic fatigue syndrome (CFS), but their pathogenetic role is unclear and brain imaging investigations are lacking. The vasomotor centre and, through it, nuclei in the midbrain and hypothalamus play a key role in autonomic nervous system regulation of steady state blood pressure (BP) and heart rate (HR).

In this exploratory cross-sectional study, BP and HR, as indicators of autonomic function, were correlated with volumetric and T1- and T2-weighted spin-echo (T1w and T2w) brain MRI in 25 CFS subjects and 25 normal controls (NC).

Steady state BP (systolic, diastolic and pulse pressure) and HR in two postures were extracted from 24 h blood pressure monitoring.

We performed (1) MRI versus autonomic score interaction-with-group regressions to detect locations where regression slopes differed in the CFS and NC groups (collectively indicating abnormality in CFS), and (2) MRI regressions in the CFS and NC groups alone to detect additional locations with abnormal correlations in CFS.

Significant CFS regressions were repeated controlling for anxiety and depression (A&D). Abnormal regressions were detected in nuclei of the brainstem vasomotor centre, midbrain reticular formation and hypothalamus, but also in limbic nuclei involved in stress responses and in prefrontal white matter.

Group comparisons of CFS and NC did not find MRI differences in these locations. We propose therefore that these regulatory nuclei are functioning correctly, but that two-way communication between them is impaired in CFS and this affects signalling to/from peripheral effectors/sensors, culminating in inverted or magnified correlations.

This single explanation for the diverse abnormal correlations detected here consolidates the conclusion for a brainstem/midbrain nerve conduction deficit inferred earlier (Barnden et al., 2015). Strong correlations were also detected in isolated NC regressions.

http://www.ncbi.nlm.nih.gov/pubmed/26088214

Curr Rheumatol Rev. 2015;11(2):109-15.

Cytokine and immune system abnormalities in fibromyalgia and other central sensitivity syndromes.

Staud R.

Abstract

The nervous system as well as the immune system use common signaling molecules for intra- and inter-system communications. Specifically, both entities produce a similar array of peptide and non-peptide transmitters that act on a common set of receptors present in the two systems. One important set of such signaling molecules are cytokines.

The wide distribution of cytokine receptors throughout the body, including the immune and the nervous system allows direct communication between these two entities. In addition to cytokines the nervous system and immune system also communicate with each other using shared ligands such as neurotransmitters and neuroendocrine hormones, and their respective receptors.

Some of the most important clinical interactions between these two systems are associated with the "sickness response" as well as pain and analgesia. This "sickness response" which has been frequently attributed to inflammatory cytokines, strongly resembles the core symptoms of fibromyalgia and other Central Sensitivity Syndromes (CSS).

Therefore a large number of research studies have focused on the relationship between peripheral cytokines and CSS. However, a lack of consistent associations was observed between CSS symptoms and peripheral cytokines which seem to suggest that maybe cytokines abnormalities of the central nervous system contribute to the pathogenesis of these illnesses.

Better knowledge of cytokine -nervous system interactions may ultimately benefit the development of interventions that improve CSS manifestations including the "sickness response" and chronic pain.

PMID:26088214 [PubMed - indexed for MEDLINE]

http://www.nejm.org/doi/full/10.1056/NEJMoa1505425#t=article

Randomized Trial of Longer-Term Therapy for Symptoms Attributed to Lyme Disease

Anneleen Berende, M.D., Hadewych J.M. ter Hofstede, M.D., Ph.D., Fidel J. Vos, M.D., Ph.D., Henriët van Middendorp, Ph.D., Michiel L. Vogelaar, M.Sc., Mirjam Tromp, Ph.D., Frank H. van den Hoogen, M.D., Ph.D., A. Rogier T. Donders, Ph.D., Andrea W.M. Evers, Ph.D., and Bart Jan Kullberg, M.D., Ph.D.

Background: The treatment of persistent symptoms attributed to Lyme disease remains controversial. We assessed whether longer-term antibiotic treatment of persistent symptoms attributed to Lyme disease leads to better outcomes than does shorter-term treatment.

Methods: In a randomized, double-blind, placebo-controlled trial conducted in Europe, we assigned patients with persistent symptoms attributed to Lyme disease — either related temporally to proven Lyme disease or accompanied by a positive IgG or IgM immunoblot assay for Borrelia burgdorferi — to receive a 12-week oral course of doxycycline, clarithromycin plus hydroxychloroquine, or placebo. All study groups received open-label intravenous ceftriaxone for 2 weeks before initiating the randomized regimen.

The primary outcome measure was health-related quality of life, as assessed by the physical-component summary score of the RAND-36 Health Status Inventory (RAND SF-36) (range, 15 to 61, with higher scores indicating better quality of life), at the end of the treatment period at week 14, after the 2-week course of ceftriaxone and the 12-week course of the randomized study drug or placebo had been completed.

Results: Of the 281 patients who underwent randomization, 280 were included in the modified intention-to-treat analysis (86 patients in the doxycycline group, 96 in the clarithromycin–hydroxychloroquine group, and 98 in the placebo group).

The SF-36 physical-component summary score did not differ significantly among the three study groups at the end of the treatment period, with mean scores of 35.0 (95% confidence interval [CI], 33.5 to 36.5) in the doxycycline group, 35.6 (95% CI, 34.2 to 37.1) in the clarithromycin–hydroxychloroquine group, and 34.8 (95% CI, 33.4 to 36.2) in the placebo group (P=0.69; a difference of 0.2 [95% CI, –2.4 to 2.8] in the doxycycline group vs. the placebo group and a difference of 0.9 [95% CI, –1.6 to 3.3] in the clarithromycin–hydroxychloroquine group vs. the placebo group); the score also did not differ significantly among the groups at subsequent study visits (P=0.35).

In all study groups, the SF-36 physical-component summary score increased significantly from baseline to the end of the treatment period (P<0.001). The rates of adverse events were similar among the study groups. Four serious adverse events thought to be related to drug use occurred during the 2-week open-label ceftriaxone phase, and no serious drug-related adverse event occurred during the 12-week randomized phase.

Conclusions: In patients with persistent symptoms attributed to Lyme disease, longer-term antibiotic treatment did not have additional beneficial effects on health-related quality of life beyond those with shorter-term treatment. (Funded by the Netherlands Organization for Health Research and Development ZonMw; PLEASE ClinicalTrials.gov number, NCT01207739.)

https://www.dovepress.com/getfile.php?fileID=29668

Natural killer cells and single nucleotide polymorphisms of specific ion channels and receptor genes in myalgic encephalomyelitis/chronic fatigue syndrome

Authors Marshall-Gradisnik S, Huth T, Chacko A, Johnston S, Smith P, Staines D

Aim: The aim of this paper was to determine natural killer (NK) cytotoxic activity and if single nucleotide polymorphisms (SNPs) and genotypes in transient receptor potential (TRP) ion channels and acetylcholine receptors (AChRs) were present in isolated NK cells from previously identified myalgic encephalomyelitis (ME)/chronic fatigue syndrome (CFS) patients.

Subjects and methods: A total of 39 ME/CFS patients (51.69±2 years
old) and 30 unfatigued controls (47.60±2.39 years old) were included in this study. Patients were defined according to the 1994 Centers for Disease Control and Prevention criteria. Flow cytometry protocols were used to examine NK cytotoxic activity.

A total of 678 SNPs from isolated NK cells were examined for 21 mammalian TRP ion channel genes and for nine mammalian AChR genes via the Agena Bioscience iPlex Gold assay. SNP association and genotype was determined using analysis of variance and Plink software.

Results: ME/CFS patients had a significant reduction in NK percentage lysis of target cells (17%±4.68%) compared with the unfatigued control group (31%±6.78%). Of the 678 SNPs examined, eleven SNPs for TRP ion channel genes (TRPC4, TRPC2, TRPM3, and TRPM8) were identified in the ME/CFS group. Five of these SNPs were associated with TRPM3, while the remainder were associated with TRPM8, TRPC2, and TRPC4 ($P<0.05$).

Fourteen SNPs were associated with nicotinic and muscarinic AChR genes: six with CHRNA3, while the remainder were associated with CHRNA2, CHRNB4, CHRNA5, and CHRNE ($P<0.05$). There were sixteen genotypes identified from SNPs in TRP ion channels and AChRs for TRPM3 (n=5), TRPM8 (n=2), TRPC4 (n=3), TRPC2 (n=1), CHRNE (n=1), CHRNA2 (n=2), CHRNA3 (n=1), and CHRNB4 (n=1) ($P<0.05$).

Conclusion: We identified a number of SNPs and genotypes for TRP ion channels and AChRs from isolated NK cells in patients with ME/CFS, suggesting these SNPs and genotypes may be involved in changes in NK cell function and the development of ME/CFS pathology.

These anomalies suggest a role for dysregulation of Ca2+ in AChR and TRP ion channel signaling in the pathomechanism of ME/CFS.

J Clin Pathol doi:10.1136/jclinpath-2015-203502

Laboratory assessment of vitamin B_{12} status

1. **Dominic J Harrington**[1,2]

+ Author Affiliations

1. [1]*The Nutristasis Unit, St Thomas' Hospital NHS Foundation Trust, London, UK*
2. [2]*Division of Women's Health, School of Medicine, King's College London, London, UK*

1. **Correspondence to** Dr Dominic J Harrington, The Nutristasis Unit, 4th Floor North Wing (Viapath), St Thomas' Hospital NHS Foundation Trust, Westminster Bridge Road, London SE1 7EH; UK; Dominic.Harrington@viapath.co.uk

- **Received** 8 January 2016
- **Revised** 19 April 2016
- **Accepted** 20 April 2016
- **Published Online First** 11 May 2016

Abstract

The detection and correction of vitamin B_{12} (B_{12}) deficiency prevents megaloblastic anaemia and potentially irreversible neuropathy and neuropsychiatric changes. B_{12} status is commonly estimated using the abundance of the vitamin in serum, with ~148 pmol/L (200 ng/L) typically set as the threshold for diagnosing deficiency. Serum B_{12} assays measure the sum of haptocorrin-bound and transcobalamin-bound (known as holotranscobalamin) B_{12}. It is only holotranscobalamin that is taken up by cells to meet metabolic demand. Although receiver operator characteristic curves show holotranscobalamin measurement to be a moderately more reliable marker of B_{12} status than serum B_{12}, both assays have an indeterminate range. Biochemical evidence of metabolic abnormalities consistent with B_{12} insufficiency is frequently detected despite an apparently sufficient abundance of the vitamin. Laboratory B_{12} status markers that reflect cellular utilisation rather than abundance are available. Two forms of B_{12} act as coenzymes for two different reactions. Methionine synthase requires methylcobalamin for the remethylation of methionine from homocysteine. A homocysteine concentration >20 µmol/L may suggest B_{12} deficiency in folate-replete patients. In the second B_{12}-dependent reaction, methylmalonyl-CoA mutase uses adenosylcobalamin to convert methylmalonyl-CoA to succinyl-CoA. In B_{12} deficiency excess methylmalonyl-CoA is hydrolysed to methylmalonic acid. A serum concentration >280 nmol/L may suggest suboptimal status in young patients with normal renal function. No single laboratory marker is suitable for the assessment of B_{12} status in all patients. Sequential assay selection algorithms or the combination of multiple markers into a single diagnostic indicator are both approaches that can be used to mitigate inherent limitations of each marker when used independently.

Vitamin B12 May Slow Brain Aging

Liam Davenport

| May 11, 2016

Individuals with increased levels of circulating homocysteine have faster rates of brain changes associated with aging than other people, whereas higher levels of vitamin B12 are associated with slower rates of brain aging, new research suggests.

Babak Hooshmand, MD, PhD, Center for Alzheimer Research–Aging Research Center, Karolinska Institutet, Stockholm, Sweden, and colleagues found that total brain volume losses were lower in individuals with higher baseline vitamin B12 levels, whereas the opposite was true of those with increased homocysteine levels.

"Vitamin B12 and tHcy [total homocysteine] might be independent predictors of markers of brain aging in elderly individuals without dementia," the investigators write.

They add, "[I]f the association is causal, supplementation with B vitamins may be effective for prevention of brain damage due to increased levels of total homocysteine. Adequately timed and powered randomized clinical trials are needed to determine efficient treatment guidelines."

The research was published online April 27 in *JAMA Psychiatry*.

Homocysteine and Brain Tissue Loss

The researchers examined data on 501 participants aged 60 years and older from the Swedish National Study on Aging and Care, in Kungsholmen. All participants were free of dementia at baseline. Of these, 299 underwent repeated structural brain MRI between 2001 and 2009.

At baseline and at each follow-up, participants underwent a thorough clinical examination, an interview, and assessment. Data on sociodemographic characteristics, medical history, drug use, and cognitive function were collected.

Venous blood samples were collected at baseline, from which circulating levels of vitamin B12, red blood cell folate, and sulfur amino acids were determined. These were correlated with changes in brain tissue volumes and total white matter hyperintensity (WMH) over 6 years.

Between baseline and the 6-year follow-up, the mean total brain tissue (TBT) volume decreased from 74.3% to 71.6% of the total cranial volume ($P < .001$), whereas the mean WMH volume increased from 0.0004% to 0.0007% ($P < .001$).

Multiadjusted linear mixed model analysis revealed that increased baseline levels of vitamin B12 and holotranscobalamin (the biologically active fraction of B12) were associated with a decreased rate of TBT volume loss, at respective beta values of 0.048 ($P < .001$) and 0.040 ($P = .002$) for each standard deviation increase.

Furthermore, the researchers found that each standard deviation increase in total homocysteine levels was linked to more rapid rates of TBT volume loss, at a beta value of -0.035 ($P = .02$).

Increases in total homocysteine levels were also associated with increases in the progression of WMH in individuals with a systolic blood pressure >140 mmHg, at 0.000019 per standard deviation increase ($P = .047$).

The results suggested that there was no association between markers of brain aging and levels of red blood folate and other sulfur amino acid.

Modest Effect

Commenting on the findings for *Medscape Medical News*, E. Sherwood Brown, MD, PhD, professor of psychiatry and director of the Psychoneuroendocrine Research Program at the University of Texas Southwestern Medical Center, Dallas, described the study as "interesting," with the "main plus" being the large sample size.

Dr Brown noted that although similar studies have been published, "the longitudinal aspect of looking at the vitamin levels as a predictor of later changes is somewhat novel...and might offer some insights into ways to maybe prevent cognitive decline or decline in brain volume or even dementia."

Dr Brown emphasized that although the researchers took into account a range of variables related to vitamin B12 and homocysteine, "it's very hard to know whether it's the levels of them per se or whether they're somehow a marker for some other lifestyle health factors that are really the culprit here, and that's certainly a legitimate limitation."

In future studies, Dr Brown would like to see cognitive data along with the brain structural data to identify clinical correlates for the findings, as well as multiple measures of the vitamin and homocysteine levels.

"I think the other cautionary note to throw in there is, even though the relationships were highly significant...the effect you're seeing is always pretty modest. I think you'd have to put all this in the context of one of probably many factors that might influence the degree of brain aging over time," he concluded.

B12 Trial Warranted

Dr Hooshmand agreed with Dr Brown that it would have been valuable to have multiple vitamin B12 and homocysteine assessments for the current analysis.

"It is ideal if we have brain measures three times over 6 years, but the better situation is also to have vitamin B12 three times over 6 years," he said, adding that the team plans on taking multiple vitamin measurements in future studies.

Nevertheless, he believes that the finding of an association between vitamin B12 levels and brain volume loss suggests that a randomized controlled trial of vitamin B12 supplementation is warranted to determine whether it could prevent brain aging.

"But not everyone will benefit from supplementation," Dr Hooshmand told *Medscape Medical News*. "Those who have low levels of these vitamins, those who have clinical signs of vitamin B12 deficiency...those are the people who will benefit from receiving the supplements."

He also pointed to the single-center, randomized VITACOG study, in which 271 individuals older than 70 years who had mild cognitive impairment received supplementation with high-dose folic acid and vitamins B6 and B12.

"They lost less brain compared to people who had normal homocysteine and normal vitamin levels, meaning that those with high levels of homocysteine or with clinical or biochemical vitamin deficiency can benefit from supplementation," said Dr Hooshmand.

Funding was provided by the Swedish Ministry of Health and Social Affairs, the Stockholm County Council, and the Stockholm municipality. The study was supported by grants from the Academy of Finland, Lipididiet, the Swedish Research Council, the Swedish Council for Working Life and Social Research, the Karolinska Institutet, the Axa Research Fund, the Alzheimer's Research and Prevention Foundation, the Salama bint Hamdan Al Nahyan Foundation, the Alzheimer Foundation, Hjärnfonden, the Norwegian Research Council, the Charles Wolfson Charitable Trust, private foundations, and the Erityisvaltionosuus. Several authors have numerous ties with industry, which are listed in the original article. Dr Brown has disclosed no relevant financial relationships.

JAMA Psychiatry. Published online April 27, 2016. Abstract

Excessive Folate, B12 in Pregnancy Dramatically Ups Autism Risk

Pam Harrison

| May 12, 2016

BALTIMORE — Excessive levels of plasma folate and vitamin B12 during pregnancy have been linked to a dramatic increase in autism risk in offspring, new research shows.

Investigators at Johns Hopkins University, Baltimore, found that when maternal plasma folate levels and vitamin B12 levels are >59 nmol/L and >600 pmol/L, respectively, autism risk is increased more than 17-fold.

The findings were presented at the International Meeting for Autism Research (IMFAR) 2016.

"When we looked at the vitamin supplementation evidence, we saw what our colleagues see — that indeed, women who took vitamin supplementation during pregnancy had a lower risk of autism in their children and that is very consistent with the literature," principal investigator Daniele Fallin, PhD, director, Wendy Klag Center for Autism and Developmental Disabilities, John Hopkins Bloomberg School of Public Health, said during a press briefing. "But when we looked at women who had excessively high levels of folate, we saw that very high levels of folate in the mother were responsible for about a twofold increased risk for autism in their child [P = .007], and when we looked at B12, women who had excessively high levels of B12 had a threefold increased risk for their child to have autism [P = .001], while women who had extreme levels of both folate and vitamin B12 had a 17.6 times greater risk of having their child diagnosed with an ASD [autism spectrum disorder] later on [P < .001]," she added.

"So for now, the public health message is, supplementation is good, but there may be a subset of women whose levels are extremely high, and these extreme levels may be harmful."

Led by Ramkripa Raghavan, MPH, investigators analyzed data from 1391 mother-child pairs enrolled in the Boston Birth Cohort, an ongoing, longitudinal study that includes a predominantly low- income, minority population.

The study included children born between 1998 and 2013 who were followed from birth through childhood. At the time of delivery, maternal serum folate and vitamin B12 levels were analyzed. Mothers were asked whether they took a multivitamin supplement during pregnancy and, if so, how often.

A total of 107 infants were diagnosed with autism, Asperger syndrome, and/or pervasive developmental disorder not otherwise specified and were categorized as having ASD.

Investigators noted that levels of both nutrients varied from deficiency levels of plasma folate (<13.5 nmol/L) and vitamin B12 (<200 pmol/L) to excessive levels of plasma folate (>59 nmol/L) and vitamin B12 (>600 pmol/L).

Dr Fallin said that the team was not able to determine whether excessive plasma folate and vitamin B12 levels corresponded to a certain level of intake of both supplements during pregnancy.

"In our study, we were not able to connect precise vitamin use and later folate and B12 levels in these mothers. But, generally speaking, it's important to appreciate that levels of folate in blood are not just a function of supplement intake. They are also a function of diet and a genetic makeup that can change dramatically how easily a person retains or clears folate," she said.

She acknowledged that it is important to establish what constitutes a safe and effective intake of supplements for women during pregnancy.

A Balanced Approach

Geraldine Dawson, MD, president of the International Society for Autism Research and professor of psychiatry and behavioral science at Duke University School of Medicine, Durham, North Carolina, told *Medscape Medical News* that it has long been known that diet and vitamin supplementation are very important for fetal brain development.

"Now we're also seeing that it's also important for lowering the risk that your child will have autism," she added.

Future research will help to identify exactly what levels of vitamins pregnant women need to take, she said.

"But I think the new finding here is that we've been focusing on the need for supplementation of vitamin B and also folate, but now we're also seeing that we don't want to take too much — that if you have very high levels of these nutrients, that this is not optimal," Dr Dawson said.

"So the next step is to define what the right level is, but I think the message so far is to take moderate levels of supplements and not to overdo it, but certainly don't 'under-do' it, either."

Dr Fallin has disclosed no relevant financial relationships.

International Meeting for Autism Research (IMFAR) 2016: Abstract 149.004, to be presented May 13, 2016.

Rheumatology International

pp 1-11 First online: 07 April 2016

The effects of long- and short-term interdisciplinary treatment approaches in women with fibromyalgia: a randomized controlled trial

- Ilknur Saral**Affiliated with**Department of Physical Medicine and Rehabilitation, Istanbul Faculty of Medicine, Istanbul UniversityDepartment of Physical Medicine and Rehabilitation, Faculty of Medicine, Istanbul Medipol University
- , Dilsad Sindel**Affiliated with**Department of Physical Medicine and Rehabilitation, Istanbul Faculty of Medicine, Istanbul University
- , Sina Esmaeilzadeh**Affiliated with**Department of Physical Medicine and Rehabilitation, Istanbul Faculty of Medicine, Istanbul University Email author
- , Hanife Ozlem Sertel-Berk**Affiliated with**Department of Clinical Psychology, Faculty of Letters, Istanbul University
- , Aydan Oral**Affiliated with**Department of Physical Medicine and Rehabilitation, Istanbul Faculty of Medicine, Istanbul UniversityAbstract

We investigated the effects of long- and short-term interdisciplinary treatment approaches for reducing symptoms and improving health-related quality of life (HRQoL) and physical functions of patients with fibromyalgia and compared the effects of two different interdisciplinary treatment approaches. We conducted a prospective, randomized, controlled trial involving 66 women with fibromyalgia eligible for the study at a university hospital setting. The patients were randomized into three groups (allocation ratio 1:1:1) using a computer-generated random numbers: a long-term interdisciplinary treatment group (LG, $n = 22$) that participated in 10 sessions (3-h once-weekly session for 10 weeks) of cognitive behavioral therapy (CBT) together with exercise training and other fibromyalgia related educational programs (two full days); a short-term interdisciplinary treatment group (SG, $n = 22$) that received two full days of educational, exercise, and CBT programs; and a control group (CG, $n = 22$). The patients were evaluated at baseline and 6 months after treatment using the visual analog scale (pain, fatigue, and sleep), Fibromyalgia Impact Questionnaire, Beck Depression Inventory, Short Form-36, tender point numbers, and pressure algometry as primary outcomes. The statistical analysis was confined to the 'per-protocol' set. No blinding was performed. The number of patients analyzed was 21 in the LG, 19 in the SG, and 19 in the CG. The intensity of pain ($p < 0.001$), severity of fatigue ($p = 0.048$), number of tender points ($p = 0.002$), and pressure pain threshold ($p = 0.012$) decreased significantly in both the LG and SG groups compared with controls. Moreover, physical functions ($p = 0.017$) and physical components of the HRQoL ($p = 0.036$) improved significantly in the intervention groups compared with the controls. However, there was no significant difference between intervention groups and the control group at the end of study in terms of quality of sleep ($p = 0.055$), severity of depressive symptoms ($p = 0.696$), and mental components of the HRQoL ($p = 0.229$). Finally, with the exception of the severity of fatigue and physical components of the HRQoL, there was no obvious significant difference between the efficacies of the two treatment approaches when compared with controls; the long-term treatment was found more effective in reducing pain than the short-term. Both, long- and short-term interdisciplinary treatments were effective in reducing the severity of some symptoms and disease activity in patients with fibromyalgia. The short-term program well meets the needs of women with fibromyalgia particularly in relation to pain and health status as measured using FIQ; however, a long-term program may be beneficial in reducing fatigue and improving physical function to a higher extent.

Keywords
Fibromyalgia Treatment Multidisciplinary Interdisciplinary Multicomponent Cognitive behavioral therapy

A Role for the Intestinal Microbiota and Virome in Myalgic Encephalomyelitis / Chronic Fatigue Syndrome (ME/CFS)?

Navena Navaneetharaja, Verity Griffiths, Tom Wileman and Simon R. Carding
http://www.mdpi.com/2077-0383/5/6/55

Published: 6 June 2016

This article provides a comprehensive review of the current evidence supporting an infectious aetiology for ME/CFS leading us to propose the novel concept that the intestinal microbiota and in particular members of the virome are a source of the “infectious” trigger of the disease.

Such an approach has the potential to identify disease biomarkers and influence therapeutics, providing much-needed approaches in preventing and managing a disease desperately in need of confronting.

Center of Excellence for ME (http://ldifme.org/a-uk-centre/) Invest in ME Research wish to establish a Centre of Excellence for ME – a centre which would exist to bring discovery, knowledge, and effective treatments to patients with ME and possibly, in future, other illnesses that are caused by acquired dysregulation of both the immune system and the nervous system.

The proposed centre would become a Centre of Excellence in the treatment of ME in Europe and would attract researchers, physicians and healthcare staff from around the UK and Europe and USA. It will be based at Europe’s largest grouping of scientific institutes – Norwich Research Park.

International collaboration is facilitated by the annual Invest in ME International Conference and Biomedical Resarchers into ME Colloquium (http://bit.ly/1Wpsxg8), and now also by the European ME Research Group (http://bit.ly/28RuFIY) formed by the European ME Alliance (http://bit.ly/28X1QOU), which is a member of the European Federation of Neurological Associations (http://bit.ly/1WKm2mE). Source : http://bit.ly/28V7XTj

- vol. 112 no. 49
- > Steven W. Cole, 15142–15147, doi: 10.1073/pnas.1514249112

Myeloid differentiation architecture of leukocyte transcriptome dynamics in perceived social isolation

Steven W. Cole[a,b], John P. Capitanio[c,d], Katie Chun[c,d], Jesusa M. G. Arevalo[a,b], Jeffrey Ma[a,b], and John T. Cacioppo[e,f,g,1]

Edited by Burton H. Singer, University of Florida, Gainesville, FL, and approved October 21, 2015 (received for

Significance

Perceived social isolation (PSI) (loneliness) is linked to increased risk of chronic disease and mortality, and previous research has implicated up-regulated inflammation and down-regulated antiviral gene expression (the conserved transcriptional response to adversity; CTRA) as a potential mechanism for such effects. The present studies used integrative analyses of transcriptome regulation in high-PSI humans and rhesus macaques to define the basis for such effects in neuroendocrine-related alterations in myeloid immune cell population dynamics. CTRA up-regulation also preceded increases in PSI, suggesting a reciprocal mechanism by which CTRA gene expression may both propagate PSI and contribute to its related disease risks.

Abstract

To define the cellular mechanisms of up-regulated inflammatory gene expression and down-regulated antiviral response in people experiencing perceived social isolation (loneliness), we conducted integrative analyses of leukocyte gene regulation in humans and rhesus macaques. Five longitudinal leukocyte transcriptome surveys in 141 older adults showed up-regulation of the sympathetic nervous system (SNS), monocyte population expansion, and up-regulation of the leukocyte conserved transcriptional response to adversity (CTRA). Mechanistic analyses in a macaque model of perceived social isolation confirmed CTRA activation and identified selective up-regulation of the $CD14^{++}/CD16^{-}$ classical monocyte transcriptome, functional glucocorticoid desensitization, down-regulation of Type I and II interferons, and impaired response to infection by simian immunodeficiency virus (SIV). These analyses identify neuroendocrine-related alterations in myeloid cell population dynamics as a key mediator of CTRA transcriptome skewing, which may both propagate perceived social isolation and contribute to its associated health risks.

Footnotes

- ↵[1]To whom correspondence should be addressed. Email: Cacioppo@uchicago.edu.

- Author contributions: S.W.C., J.P.C., and J.T.C. designed research; S.W.C., J.P.C., K.C., J.M.G.A., J.M., and J.T.C. performed research; S.W.C. contributed new reagents/analytic tools; S.W.C., J.P.C., and J.T.C. analyzed data; and S.W.C., J.P.C., and J.T.C. wrote the paper.

- The authors declare no conflict of interest.

- This article is a PNAS Direct Submission.

- www.pnas.org/lookup/suppl/doi:10.1073/pnas.1514249112/-/DCSupplemental.

Progressive Brain Changes In Patients With Chronic Fatigue Syndrome: A Longitudinal MRI Study

Zack Y. Shan, PhD, Richard Kwiatek, MBBS, Richard Burnett, MBBS, Peter Del Fante, MBBS, Donald R.Staines, MBBS, Sonya M.Marshall-Gradisnik, PhD, and Leighton R.Barnden, PhD

Abstract

Purpose To examine progressive brain changes associated with chronic fatigue syndrome (CFS).

Materials and Methods We investigated progressive brain changes with longitudinal MRI in 15 CFS and 10 normal controls (NCs) scanned twice 6 years apart on the same 1.5 Tesla (T) scanner. MR images yielded gray matter (GM) volumes, white matter (WM) volumes, and T1- and T2-weighted signal intensities (T1w and T2w). Each participant was characterized with Bell disability scores, and somatic and neurological symptom scores. We tested for differences in longitudinal changes between CFS and NC groups, inter group differences between pooled CFS and pooled NC populations, and correlations between MRI and symptom scores using voxel based morphometry. The analysis methodologies were first optimized using simulated atrophy.

Results We found a significant decrease in WM volumes in the left inferior fronto-occipital fasciculus (IFOF) in CFS while in NCs it was unchanged (family wise error adjusted cluster level P value, $P_{FWE} < 0.05$). This longitudinal finding was consolidated by the group comparisons which detected significantly decreased regional WM volumes in adjacent regions ($P_{FWE} < 0.05$) and decreased GM and blood volumes in contralateral regions ($P_{FWE} < 0.05$). Moreover, the regional GM and WM volumes and T2w in those areas showed significant correlations with CFS symptom scores ($P_{FWE} < 0.05$).

Conclusion The results suggested that CFS is associated with IFOF WM deficits which continue to deteriorate at an abnormal rate.

Source & complete research: http://onlinelibrary.wiley.com/doi/10.1002/jmri.25283/epdf

The Biological Challenge Of Myalgic Encephalomyelitis / Chronic Fatigue Syndrome: A Solvable Problem.

Professor Jonathan Edwards, along with several ME/CFS patients and a carer with scientific backgrounds have coauthored a peer-reviewed editorial (http://bit.ly/1OwHnQX) on the disease that appears in the latest issue of the journal Fatigue: Biomedicine, Health & Behavior (http://bit.ly/1OwH5JM).

The article is titled, The biological challenge of myalgic encephalomyelitis/chronic fatigue syndrome: a solvable problem (http://bit.ly/1OwHnQX). The paper has gained over 1600 views in the three days since publication, making it already Fatigue's second most-read paper since the journal began in 2013.

The paper is an overview of the most promising developments in biomedical research into ME/CFS. The authors "call on the wider biomedical research community to actively target this condition" and make a "concerted effort."

Simon McGrath, an ME/CFS patient well-known for his blogs (http://bit.ly/1WVGHqP) on the science of the illness, was one of the editorial's authors. He said, "We felt it was time to make the case for biomedical research, aiming to summarise the most promising research, while acknowledging its limitations".

He added, "The aim of the paper is to provide a 'way in' to biological ME/CFS research for researchers who might be interested but were overwhelmed by the vast literature of mainly unconfirmed findings, or those who doubted there was anything of merit in biological research."

The paper includes what he described as "the most interesting studies, including the two-day exercise challenge, changes in gene expression after moderate exercise, and brain scans indicating microglia activation". The editorial also highlights the promising rituximab treatment pilot studies and ongoing trial (http://bit.ly/1V75emz).

http://www.ncbi.nlm.nih.gov/pubmed/27362406

Novel characterisation of mast cell phenotypes from peripheral blood mononuclear cells in chronic fatigue syndrome/myalgic encephalomyelitis patients.

Nguyen T, Johnston S, Chacko A, Gibson D, Cepon J, Smith P, Staines D, Marshall-Gradisnik S.

Abstract

BACKGROUND: Mast cells (MCs) mediate inflammation through neuropeptides and cytokines, along with histamine and reactive oxygen species (ROS). Chronic Fatigue Syndrome/Myalgic Encephalomyelitis (CFS/ME) is an illness characterized by an unexplained disabling fatigue with multiple physiological impairments as well as dysregulated cytokine profiles.

OBJECTIVE: To determine mast cell phenotypes in isolated human PBMCs, in healthy controls and in CFS/ME patients. Second, determine receptor expression of RAGE and its ligand high mobility group box 1 protein (HMGB1).

METHOD: Moderately severe CFS/ME patients (n=12, mean age 39.25±SD3.52 years), severe CFS/ME patients (n=6, mean age 43.00±SD4.02 years) and healthy controls (n=13, mean age 42.69±SD3.87 years) were included in this study. CFS/ME patients were classified according to the 2011 International Consensus Criteria. LSRFortessa X-20 Flow cytometry was used for the identification of phenotypic peripheral mast cell population in PBMCs using an exclusion marker Lin2 cocktail (anti-CD3, anti-CD14, anti-CD19, anti-CD20 and anti-CD56) and inclusion markers (CD117, CD34, FCεRI, chymase, HLA-DR and CD154) following comparative investigation. HMGB1 and soluble RAGE expression in plasma was measured by sandwich ELISA assay.

RESULTS: There was a significant increase in CD117+CD34+FCεRI-chymase- mast cell populations in moderate and severe CFS/ME patients compared with healthy controls. There was a significant increase in CD40 ligand and MHC-II receptors on differentiated mast cell populations in the severe CFS/ME compared with healthy controls and moderate CFS/ME.

There were no significant differences between groups for HMGB1 and sRAGE.

CONCLUSIONS: This preliminary study investigates mast cell phenotypes from PBMCs in healthy controls. We report significant increase of naïve MCs in moderate and severe CFS/ME patients compared with healthy controls. Moreover, a significant increase in CD40 ligand and MHC-II receptors on differentiated mast cells in severe CFS/ME patients.

Peripheral MCs may be present in CFS/ME pathology however, further investigation to determine their role is required.

PMID:27362406DOI:10.12932/AP0711

fulltext- http://openheart.bmj.com/content/3/1/e000381.long

Reduced cardiac volumes in chronic fatigue syndrome associate with plasma volume but not length of disease: a cohort study

Julia L Newton, Andreas Finkelmeyer, George Petrides, James Frith, Tim Hodgson, Laura Maclachlan, Guy MacGowan, and Andrew M Blamire

Abstract

Objectives To explore potential mechanisms that underpin the cardiac abnormalities seen in chronic fatigue syndrome (CFS) using non-invasive cardiac impedance, red cell mass and plasma volume measurements.

Methods Cardiac MR (MR) examinations were performed using 3 T Philips Intera Achieva scanner (Best, NL) in participants with CFS (Fukuda;
n=47) and matched case-by-case controls. Total volume (TV), red cell volume (RCV) and plasma volume (PV) measurements were performed (41 CFS and 10 controls) using the indicator dilution technique using simultaneous 51-chromium labelling of red blood cells and 125-iodine labelling of serum albumin.

Results The CFS group length of history (mean±SD) was 14±10 years. Patients with CFS had significantly reduced end-systolic and end-diastolic volumes together with reduced end-diastolic wall masses (all p<0.0001). Mean±SD RCV was 1565±443 mL with 26/41 (63%) having values below 95% of expected. PV was 2659±529 mL with 13/41 (32%) <95% expected.

There were strong positive correlations between TV, RCV and PV and cardiac end-diastolic wall mass (all p<0.0001; r2=0.5).

Increasing fatigue severity correlated negatively with lower PV (p=0.04; r2=0.2). There were no relationships between any MR or volume measurements and length of history, suggesting that deconditioning was unlikely to **be the cause of these abnormalities.**

Conclusions This study confirms an association between reduced cardiac volumes and blood volume in CFS. Lack of relationship between length of disease, cardiac and plasma volumes suggests findings are not secondary to deconditioning. The relationship between plasma volume and severity of fatigue symptoms suggests a potential therapeutic target in CFS.

fulltext- https://microbiomejournal.biomedcentral.com/articles/10.1186/s40168...

Reduced diversity and altered composition of the gut microbiome in individuals with myalgic encephalomyelitis/chronic fatigue syndrome

Ludovic Giloteaux, Julia K. Goodrich, William A. Walters, Susan M. Levine, Ruth E. Ley and Maureen R. Hanson

Abstract

Background Gastrointestinal disturbances are among symptoms commonly reported by individuals diagnosed with myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS). However, whether ME/CFS is associated with an altered microbiome has remained uncertain. Here, we profiled gut microbial diversity by sequencing 16S ribosomal ribonucleic acid (rRNA) genes from stool as well as inflammatory markers from serum for cases (n = 48) and controls (n = 39). We also examined a set of inflammatory markers in blood: C-reactive protein (CRP), intestinal fatty acid-binding protein (I-FABP), lipopolysaccharide (LPS), LPS-binding protein (LBP), and soluble CD14 (sCD14).

Results We observed elevated levels of some blood markers for microbial translocation in ME/CFS patients; levels of LPS, LBP, and sCD14 were elevated in ME/CFS subjects. Levels of LBP correlated with LPS and sCD14 and LPS levels correlated with sCD14. Through deep sequencing of bacterial rRNA markers, we identified differences between the gut microbiomes of healthy individuals and patients with ME/CFS.

We observed that bacterial diversity was decreased in the ME/CFS specimens compared to controls, in particular, a reduction in the relative abundance and diversity of members belonging to the Firmicutes phylum. In the patient cohort, we find less diversity as well as increases in specific species often reported to be pro-inflammatory species and reduction in species frequently described as anti-inflammatory.

Using a machine learning approach trained on the data obtained from 16S rRNA and inflammatory markers, individuals were classified correctly as ME/CFS with a cross-validation accuracy of 82.93 %.

Conclusions Our results indicate dysbiosis of the gut microbiota in this disease and further suggest an increased incidence of microbial translocation, which may play a role in inflammatory symptoms in ME/CFS.

http://www.ncbi.nlm.nih.gov/pubmed/27329758

Attentional and interpretive bias towards illness-related information in chronic fatigue syndrome: A systematic review.

Hughes A, Hirsch C, Chalder T, Moss-Morris R.

Abstract

PURPOSE: Chronic fatigue syndrome (CFS) is characterized by severe and debilitating fatigue. Studies based on self-report measures suggest negative illness representations, related symptom interpretations, and heightened symptom focusing are maintaining factors of fatigue. This study reviews studies which have investigated these cognitive biases using experimental methods, to (1) review the evidence for information processing biases in CFS; (2) determine the nature of these biases, that is the stages cognitive biases occur and for what type of stimuli; and (3) provide directions for future methodologies in this area.

METHODS: Studies were included that measured attention and interpretation bias towards negative and illness-related information in people with CFS and in a comparison group of healthy controls. PubMed, Ovid, CINAHL, PsycINFO, Web of Science, and EThOS were searched until December 2014.

RESULTS: The evidence for cognitive biases was dependent on the methodology employed as well as the type and duration of the stimuli presented.

Modified Stroop studies found weak evidence of an attentional bias in CFS populations, whereas visual-probe studies consistently found an attentional bias in CFS groups for health-threatening information presented for 500 ms or longer. Interpretative bias studies which required elaborative processing, as opposed to a spontaneous response, found an illness-related interpretive bias in the CFS group compared to controls.

CONCLUSIONS: Some people with CFS have biases in the way they attend to and interpret somatic information. Such cognitive processing biases may maintain illness beliefs and symptoms in people with CFS. This review highlights methodological issues in experimental design and makes recommendations to aid future research to forge a consistent approach in cognitive processing research. Statement of contribution What is already known on this subject?

Studies based on self-report measures suggest negative illness representations, related symptom interpretations, and heightened symptom focusing contribute to the maintenance of chronic fatigue. Experimental studies in other clinical populations, such as patients with anxiety, depression, and chronic pain, have identified illness-specific biases in how information is implicitly attended to and interpreted, which has a causal role in these conditions. What does this study add? This is the first review of implicit cognitive processes in chronic fatigue syndrome (CFS).

Sustained attention and negative interpretations of somatic information may reinforce negative illness beliefs. Cognitive processes have a role to play in the cognitive behavioural model of CFS.

http://www.ncbi.nlm.nih.gov/pubmed/27255790

Distress in significant others of patients with chronic fatigue syndrome: A systematic review of the literature.

Harris K, Band RJ, Cooper H, Macintyre VG, Mejia A, Wearden AJ.

Abstract

Statement of contribution What is already known on this subject?

Chronic fatigue syndrome (CFS/ME) entails considerable economic, social, and personal costs. Uncertainties exist around diagnosis and management. This may lead to particular difficulties for significant others trying to support patients. What does this study add? Few studies have examined distress and its correlates in significant others of people with CFS/ME. Significant others report elevated levels of distress on quantitative measures.

PURPOSE:The objective of this study was to systematically review existing empirical research assessing levels and correlates of distress in significant others of patients with chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME).

METHODS:Systematic searches in CINAHL, Web of Science and PsycINFO were conducted in August 2014. The search was repeated in January 2015 to check for newly published articles. Studies published in English with quantitative, qualitative, or mixed designs exploring distress, poor subjective health, poor mental health, reduced quality of life and well-being, and symptoms of depression and anxiety in significant others (>18 years) of children and adults with CFS/ME were included.
Quality appraisal of included studies was carried out. Quantitative and qualitative studies were summarized separately.

RESULTS: Six articles met eligibility criteria. Two quantitative studies with significant others of adult patients, and one quantitative and two mixed-methods studies with significant others of child patients showed moderate to high levels of distress. One qualitative study (adult patients) found minimal evidence of distress and that acceptance of CFS/ME was related to better adjustment. In the quantitative and mixed-methods studies, significant others who attributed some level of responsibility for symptoms to the patient, or who were female, or whose partners had poorer mental health, had higher levels of distress.

CONCLUSIONS: The small number of studies to date, the contrary evidence from a qualitative study, and the limited data available on levels of distress in significant others of patients with CFS/ME mean that our conclusion that distress levels are elevated is provisional. We recommend that future qualitative studies focus on this particular topic. Further longitudinal studies exploring correlates of distress within the context of a predictive theoretical model would be helpful.

fultext- https://www.dovepress.com/getfile.php?fileID=30423

Epidemiological characteristics of chronic fatigue- syndrome/myalgic encephalomyelitis in Australian patients

Samantha C Johnston, Donald R Staines, Sonya M Marshall-Gradisnik

National Centre for Neuroimmunology and Emerging Diseases, Menzies Health Institute Queensland, 2School of Medical Sciences, Griffith University, Parklands, QLD, Australia

Abstract

Background: No epidemiological investigations have previously been conducted in Australia according to the current clinical definitions of chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME). The aim of this study was to describe sociodemographic and illness characteristics of Australian patients with CFS/ME.

Methods: A cross-sectional survey on the medical history of patients enrolled in an Australian CFS/ME research database between April 2013 and April 2015. Participants were classified according to Fukuda criteria and International Consensus Criteria.

Results: A total of 535 patients diagnosed with CFS/ME by a primary care physician were identified. The mean age of all patients was 46.4 years (standard deviation 12.0); the majority were female (78.61%), Caucasian, and highly educated. Of these, 30.28% met Fukuda criteria.

A further 31.96% met both Fukuda criteria and International Consensus Criteria. There were 14.58% reporting chronic fatigue but did not meet criteria for CFS/ME and 23.18% were considered noncases due to exclusionary conditions. Within those meeting CFS/ME criteria, the most common events prior to illness included cold or flu, gastrointestinal illness, and periods of undue stress.

Of the 60 symptoms surveyed, fatigue, cognitive, and short-term memory symptoms, headaches, muscle and joint pain, unrefreshed sleep, sensory disturbances, muscle weakness, and intolerance to extremes of temperature were the most commonly occurring symptoms (reported by more than two-thirds of patients). Significant differences in symptom occurrence between Fukuda- and International Consensus Criteria-defined cases were also identified.

Conclusion: This is the first study to summarize sociodemographic and illness characteristics of a cohort of Australian CFS/ME patients.
This is vital for identifying potential risk factors and predictors associated with CFS/ME and for guiding decisions regarding health care provision, diagnosis, and management.

http://www.ncbi.nlm.nih.gov/pubmed/27143625

Factors determining fatigue in the chronic fatigue syndrome: a path analysis.

Tobback E, Hanoulle I, Mariman A, Delesie L, Pevernagie D, Vogelaers D

Abstract

OBJECTIVES: To explore the interrelationship of different dimensions (fatigue, neuroticism, sleep quality, global mental and physical
health) in patients with chronic fatigue syndrome (CFS).

METHODS: Patients meeting the Fukuda criteria of CFS filled out two independent fatigue scales (Fatigue Questionnaire, FQ and Checklist Individual Strength, CIS), NEO-Five Factor Inventory (NEO-FFI), Pittsburgh Sleep Quality Index (PSQI) and Medical Outcomes Study 36-item Short Form Health Survey (SF36). Exploratory and confirmatory path analyses were performed.

RESULTS: Out of 226 eligible patients, 167 subjects were included (mean age 39.13 years, SD 10.14, 92% female). In a first exploratory path analysis, using FQ for assessment of fatigue, night-time PSQI sleep quality had a direct effect on SF36 physical quality of life
(PQoL) and no effect on FQ fatigue. This was confirmed by a subsequent path analysis with CIS fatigue and by confirmatory path analyses in 81 patients. These unexpected results raised the question whether FQ or CIS fatigue sufficiently operationalizes fatigue in CFS patients.

CONCLUSIONS: Poor sleep quality seems to directly impact on mental quality of life (MQoL) and PQoL without mediation of fatigue assessed with FQ and CIS. A more cohesive framework needs to be developed with more comprehensive clinical tools for the different dimensions in the construct of CFS.

Ann Rheum Dis doi:10.1136/annrheumdis-2016-209724

EULAR revised recommendations for the management of fibromyalgia

Professor G J Macfarlane et al

Correspondence to Professor G J Macfarlane, Epidemiology Group, University of Aberdeen, School of Medicine, Medical Sciences and Nutrition, Polwarth Building, Foresterhill, Aberdeen, Scotland AB25 2ZD, UK; g.j.macfarlane@abdn.ac.uk

Received 15 April 2016 Revised 10 June 2016 Accepted 14 June 2016 Published Online First 4 July 2016

Abstract

Objective The original European League Against Rheumatism recommendations for managing fibromyalgia assessed evidence up to 2005. The paucity of studies meant that most recommendations were ‘expert opinion’.

Methods A multidisciplinary group from 12 countries assessed evidence with a focus on systematic reviews and meta-analyses concerned with pharmacological/non-pharmacological management for fibromyalgia. A review, in May 2015, identified eligible publications and key outcomes assessed were pain, fatigue, sleep and daily functioning. The Grading of Recommendations Assessment, Development and Evaluation system was used for making recommendations.

Results 2979 titles were identified: from these 275 full papers were selected for review and 107 reviews (and/or meta-analyses) evaluated as eligible. Based on meta-analyses, the only ‘strong for’ therapy-based recommendation in the guidelines was exercise. Based on expert opinion, a graduated approach, the following four main stages are suggested underpinned by shared decision-making with patients. Initial management should involve patient education and focus on non-pharmacological therapies. In case of non-response, further therapies (all of which were evaluated as ‘weak for’ based on meta-analyses) should be tailored to the specific needs of the individual and may involve psychological therapies (for mood disorders and unhelpful coping strategies), pharmacotherapy (for severe pain or sleep disturbance) and/or a multimodal rehabilitation programme (for severe disability).

Conclusions These recommendations are underpinned by high-quality reviews and meta-analyses. The size of effect for most treatments is relatively modest. We propose research priorities clarifying who will benefit from specific interventions, their effect in combination and organisation of healthcare systems to optimise outcome.

British Journal of General Practice

Chronic fatigue syndrome: is the biopsychosocial model responsible for patient dissatisfaction and harm?

Keith J Geraghty, Aneez Esmail

DOI: 10.3399/bjgp16X686473 Published 1 August 2016

In 1977 George Engel wrote about the need for an ‘integrated approach’ in medicine that moved the focus beyond biological mechanisms of disease to include all pertinent aspects of illness presentation, setting out a ‘biopsychosocial model’.[1] Around the same time, McEvedy and Beard asserted that the disease ‘*benign myalgic encephalomyelitis*’, described by Ramsay at the Royal Free Hospital, London, was nothing more than a case of ‘mass hysteria’.[2] In the 1980s, doctors combined theories of neurasthenia, hysteria, and somatoform illness, to reconstitute ME as ‘*chronic fatigue syndrome*’. Psychiatrists argued that CFS was best understood using a biopsychosocial (BPS) framework, being perhaps triggered by viral illness (biology), but maintained by certain personality traits (psychology) and social conditions (sociology).[3] Although the BPS model holds much utility in understanding ‘illness’ in a wider context, many sufferers of CFS reject the notion that their illness is psychologically or socially derived. Significant numbers of patients report difficult interactions with doctors that leave them feeling dissatisfied, disbelieved, and distressed. In this article, we question whether or not the BPS model generates ‘harms’ for CFS patients, and we ask if other, alternative approaches might be more preferable to both patients and GPs.

PloS One:2016 Jul 18;11(7):e0159386. doi: 10.1371/journal.pone.0159386. eCollection 2016.

Neuromuscular Strain Increases Symptom Intensity in Chronic Fatigue Syndrome.

Rowe PC[1], Fontaine KR[2], Lauver M[1], Jasion SE[1], Marden CL[1], Moni M[1], Thompson CB[3], Violand RL[4].

Author information

- [1]Department of Pediatrics, Johns Hopkins University School of Medicine, Baltimore, Maryland, United States of America.
- [2]Department of Health Behavior, University of Alabama at Birmingham School of Public Health, Birmingham, Alabama, United States of America.
- [3]Department of Biostatistics, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland, United States of America.
- [4]Rick Violand, PT LLC, Ellicott City, Maryland, United States of America.

Abstract

Chronic fatigue syndrome (CFS) is a complex, multisystem disorder that can be disabling. CFS symptoms can be provoked by increased physical or cognitive activity, and by orthostatic stress. In preliminary work, we noted that CFS symptoms also could be provoked by application of longitudinal neural and soft tissue strain to the limbs and spine of affected individuals. In this study we measured the responses to a straight leg raise neuromuscular strain maneuver in individuals with CFS and healthy controls. We randomly assigned 60 individuals with CFS and 20 healthy controls to either a 15 minute period of passive supine straight leg raise (true neuromuscular strain) or a sham straight leg raise. The primary outcome measure was the symptom intensity difference between the scores during and 24 hours after the study maneuver compared to baseline. Fatigue, body pain, lightheadedness, concentration difficulties, and headache scores were measured individually on a 0-10 scale, and summed to create a composite symptom score. Compared to individuals with CFS in the sham strain group, those with CFS in the true strain group reported significantly increased body pain (P = 0.04) and concentration difficulties (P = 0.02) as well as increased composite symptom scores (all P = 0.03) during the maneuver. After 24 hours, the symptom intensity differences were significantly greater for the CFS true strain group for the individual symptom of lightheadedness (P = 0.001) and for the composite symptom score (P = 0.005). During and 24 hours after the exposure to the true strain maneuver, those with CFS had significantly higher individual and composite symptom intensity changes compared to the healthy controls. We conclude that a longitudinal strain applied to the nerves and soft tissues of the lower limb is capable of increasing symptom intensity in individuals with CFS for up to 24 hours. These findings support our preliminary observations that increased mechanical sensitivity may be a contributor to the provocation of symptoms in this disorder.

PMID:

27428358

PMCID:

PMC4948885

DOI:

10.1371/journal.pone.0159386

Reduced diversity and altered composition of the gut microbiome in individuals with myalgic encephalomyelitis/chronic fatigue syndrome

- Ludovic Giloteaux[1], Julia K. Goodrich[1, 2], William A. Walters[1, 2], Susan M. Levine[3], Ruth E. Ley[1, 2] and
- Maureen R. Hanson[1]Email author

Microbiome20164:30

DOI: 10.1186/s40168-016-0171-4

Received: 29 February 2016

Accepted: 11 May 2016

Published: 23 June 2016

Abstract

Background

Gastrointestinal disturbances are among symptoms commonly reported by individuals diagnosed with myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS). However, whether ME/CFS is associated with an altered microbiome has remained uncertain. Here, we profiled gut microbial diversity by sequencing 16S ribosomal ribonucleic acid (rRNA) genes from stool as well as inflammatory markers from serum for cases ($n = 48$) and controls ($n = 39$). We also examined a set of inflammatory markers in blood: C-reactive protein (CRP), intestinal fatty acid-binding protein (I-FABP), lipopolysaccharide (LPS), LPS-binding protein (LBP), and soluble CD14 (sCD14).

Results

We observed elevated levels of some blood markers for microbial translocation in ME/CFS patients; levels of LPS, LBP, and sCD14 were elevated in ME/CFS subjects. Levels of LBP correlated with LPS and sCD14 and LPS levels correlated with sCD14. Through deep sequencing of bacterial rRNA markers, we identified differences between the gut microbiomes of healthy individuals and patients with ME/CFS. We observed that bacterial diversity was decreased in the ME/CFS specimens compared to controls, in particular, a reduction in the relative abundance and diversity of members belonging to the Firmicutes phylum. In the patient cohort, we find less diversity as well as increases in specific species often reported to be pro-inflammatory species and reduction in species frequently described as anti-inflammatory. Using a machine learning approach trained on the data obtained from 16S rRNA and inflammatory markers, individuals were classified correctly as ME/CFS with a cross-validation accuracy of 82.93 %.

Conclusions

Our results indicate dysbiosis of the gut microbiota in this disease and further suggest an increased incidence of microbial translocation, which may play a role in inflammatory symptoms in ME/CFS.

Keywords

Myalgic encephalomyelitis Chronic fatigue syndrome Inflammation Lipopolysaccharides Microbiome Microbial translocation Beta-diversity

2016 May 31;49(1):27. doi: 10.1186/s40659-016-0087-2.

Novel identification and characterisation of Transient receptor potential melastatin 3 ion channels on Natural Killer cells and B lymphocytes: effects on cell signalling in Chronic fatigue syndrome/Myalgic encephalomyelitis patients.

Nguyen T[1,2], Staines D[3,4], Nilius B[5], Smith P[3], Marshall-Gradisnik S[3,4].

Author information

- [1]The National Centre for Neuroimmunology and Emerging Diseases, Menzies Health Institute, Griffith University, Parklands Drive, Southport, Mailbox 68, Gold Coast, 4222, Australia. thao.nguyen2@griffithuni.edu.au.
- [2]School of Medical Science, Griffith University, Gold Coast, Australia. thao.nguyen2@griffithuni.edu.au.
- [3]The National Centre for Neuroimmunology and Emerging Diseases, Menzies Health Institute, Griffith University, Parklands Drive, Southport, Mailbox 68, Gold Coast, 4222, Australia.
- [4]School of Medical Science, Griffith University, Gold Coast, Australia.
- [5]Department of Molecular Cell Biology, Laboratory of Ion Channel Research, KU Leuven University, 49 Herestraat, Leuven, B-3000, Belgium.

Abstract

BACKGROUND:

Transient receptor potential melastatin 3 (TRPM3) cation channels are ubiquitously expressed by multiple cells and have an important regulatory role in calcium-dependent cell signalling to help maintain cellular homeostasis. TRPM3 protein expression has yet to be determined on Natural Killer (NK) cells and B lymphocytes. Multiple single nucleotide polymorphisms have been reported in TRPM3 genes from isolated peripheral blood mononuclear cells, NK and B cells in Chronic fatigue syndrome/Myalgic encephalomyelitis (CFS/ME) patients and have been proposed to correlate with illness presentation. The object of the study was to assess TRPM3 surface expression on NK and B lymphocytes from healthy controls, followed by a comparative investigation examining TRPM3 surface expression, and cytoplasmic and mitochondrial calcium influx in CD19(+) B cells, CD56(bright) and CD56(dim) cell populations from CFS/ME patients.

RESULTS:

TRPM3 cell surface expression was identified for NK and B lymphocytes in healthy controls (CD56(bright) TRPM3 35.72 % ± 7.37; CD56(dim) 5.74 % ± 2.00; B lymphocytes 2.05 % ± 0.19, respectively). There was a significant reduction of TRPM3 surface expression on CD19(+) B cells (1.56 ± 0.191) and CD56(bright) NK cells (17.37 % ± 5.34) in CFS/ME compared with healthy controls. Anti-CD21 and anti-IgM conjugated biotin was cross-linked with streptavidin,and subsequently treatment with thapsigargin. This showed a significant reduction in cytoplasmic calcium ion concentration in CD19(+) B lymphocytes. CD56(bright) NK cells also had a significant decrease in cytoplasmic calcium in the presence of 2-APB and thapsigargin in CFS/ME patients.

CONCLUSIONS:

The results from this preliminary investigation identify, for the first time, TRPM3 surface expression on both NK and B lymphocytes in healthy controls. We also report for the first time, significant reduction in TRPM3 cell surface expression in NK and B lymphocytes, as well as decreased intracellular calcium within specific conditions in CFS/ME patients. This warrants further examination of these pathways to elucidate whether TRPM3 and impaired calcium mobilisation has a role in CFS/ME.

PMID:27245705

PMCID:PMC4888729

DOI:10.1186/s40659-016-0087-2

Proc Natl Acad Sci U S A. 2016 Aug 29. pii: 201607571. [Epub ahead of print]

Metabolic features of chronic fatigue syndrome.

Naviaux RK[1], Naviaux JC[2], Li K[3], Bright AT[3], Alaynick WA[3], Wang L[3], Baxter A[4], Nathan N[4], Anderson W[4], Gordon E[4].

Author information

Abstract

More than 2 million people in the United States have myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS). We performed targeted, broad-spectrum metabolomics to gain insights into the biology of CFS. We studied a total of 84 subjects using these methods. Forty-five subjects (n = 22 men and 23 women) met diagnostic criteria for ME/CFS by Institute of Medicine, Canadian, and Fukuda criteria. Thirty-nine subjects (n = 18 men and 21 women) were age- and sex-matched normal controls. Males with CFS were 53 (±2.8) y old (mean ± SEM; range, 21-67 y). Females were 52 (±2.5) y old (range, 20-67 y). The Karnofsky performance scores were 62 (±3.2) for males and 54 (±3.3) for females. We targeted 612 metabolites in plasma from 63 biochemical pathways by hydrophilic interaction liquid chromatography, electrospray ionization, and tandem mass spectrometry in a single-injection method. Patients with CFS showed abnormalities in 20 metabolic pathways. Eighty percent of the diagnostic metabolites were decreased, consistent with a hypometabolic syndrome. Pathway abnormalities included sphingolipid, phospholipid, purine, cholesterol, microbiome, pyrroline-5-carboxylate, riboflavin, branch chain amino acid, peroxisomal, and mitochondrial metabolism. Area under the receiver operator characteristic curve analysis showed diagnostic accuracies of 94% [95% confidence interval (CI), 84-100%] in males using eight metabolites and 96% (95% CI, 86-100%) in females using 13 metabolites. Our data show that despite the heterogeneity of factors leading to CFS, the cellular metabolic response in patients was homogeneous, statistically robust, and chemically similar to the evolutionarily conserved persistence response to environmental stress known as dauer.

KEYWORDS:

cell danger response; chronic fatigue syndrome; dauer; metabolomics; mitochondria

PMID:

27573827

DOI: 10.1073/pnas.1607571113

Höck et al. J Clin Nephrol Ren Care 2016, 2:008
Volume 2 | Issue 1

Journal of
Clinical Nephrology and Renal Care

Review Article: Open Access

A Review on the Potential Role of Vitamin D and Mineral Metabolism on Chronic Fatigue Illnesses

*Anna Dorothea Höck**

Internal Medicine, 50935 Cologne, Germany

***Corresponding author:** *Anna Dorothea Hoeck, MD, Internal Medicine, Mariawaldstraße 7, 50935 Köln, Germany, E-Mail: ad.hoeck@t-online.de*

Abstract

The aim of this report is to review the effects of vitamin D-deficiency on chronic mineral deregulation and its clinical consequences. Recent research data are presented including the effects of vitamin D3-induced calcium sensing receptor (CaSR), fibroblast growth factor 23 (FGF23), the cofactor of FGF1-receptor α-klotho (αKl) and the interplay with each other and with vitamin D3-repressed parathormone (PTH). The importance of persistent calcium- and phosphate deregulation following long-standing vitamin D3-deficiency for cellular functions and resistance to vitamin D3 treatment is discussed. It is proposed that chronic fatiguing illnesses might be result from mineral deregulations that are barely detected by routine laboratory workups because of compensatory changes in bone mineral stores.

Keywords

Vitamin D3-deficiency, Mineral regulation, Calcium-sensing receptor, Fibroblast-growth-factor-23, Alpha-klotho, Parathormone, Chronic fatigue

by any kind of cell stress as long as sufficient 25-hydroxyvitamin D3 (25OHD3) is available [8-11].

1,25(OH)2D3 induces in addition the gene expression of following important mineral regulators such as calcium-sensing-receptor (CaSR), Fibroblast Growth Factor-23 (FGF23) and its co-receptor α-Klotho (αKL, also FGF23/αKL in this paper), yet represses the gene expression of parathormone (PTH) [2,6,12-16]. These mineral regulators, like 1,25(OH)2D3 itself, act not only via gene expression, but also modulate cell functions directly by rapid non-genomic actions. This contributes substantially to the high complexity and adaptability of mineral regulation [2,6,12,17-21].

Low vitamin D3, low dietary calcium and high phosphate intake occur frequently

Vitamin D3-insufficiency/deficiency is a common condition arising from prevalent indoor activities and use of sunscreens with high protection factor. Lacking sunlight is frequent in patients

1,25-Dihydroxyvitamin D and Klotho: A Tale of Two Renal Hormones Coming of Age

Mark R. Haussler[*,1], G. Kerr Whitfield[*], Carol A. Haussler[*], Marya S. Sabir[†], Zainab Khan[†], Ruby Sandoval[†], Peter W. Jurutka[*,†]

[*]Department of Basic Medical Sciences, University of Arizona College of Medicine, Phoenix, Arizona, USA
[†]School of Mathematical and Natural Sciences, Arizona State University, Glendale, Arizona, USA
[1]Corresponding author: e-mail address: haussler@email.arizona.edu

Abstract

1,25-Dihydroxyvitamin D_3 (1,25D) is the renal metabolite of vitamin D that signals through binding to the nuclear vitamin D receptor (VDR). The ligand–receptor complex transcriptionally regulates genes encoding factors stimulating calcium and phosphate absorption plus bone remodeling, maintaining a skeleton with reduced risk of age-related osteoporotic fractures. 1,25D/VDR signaling exerts feedback control of Ca/PO_4 via regulation of FGF23, klotho, and CYP24A1 to prevent age-related, ectopic calcification, fibrosis, and associated pathologies. Vitamin D also elicits xenobiotic detoxification, oxidative stress reduction, neuroprotective functions, antimicrobial defense, immunoregulation, anti-inflammatory/anticancer actions, and cardiovascular benefits. Many of the healthspan advantages conferred by 1,25D are promulgated by its induction of klotho, a renal hormone that is an anti-aging enzyme/coreceptor that protects against skin atrophy, osteopenia, hyperphosphatemia, endothelial dysfunction, cognitive defects, neurodegenerative disorders, and impaired hearing. In addition to the high-affinity 1,25D hormone, low-affinity nutritional VDR ligands including curcumin, polyunsaturated fatty acids, and anthocyanidins initiate VDR signaling, whereas the longevity principles resveratrol and SIRT1 potentiate VDR signaling. 1,25D exerts actions against neural excitotoxicity and induces serotonin mood elevation to support cognitive function and prosocial behavior. Together, 1,25D and klotho maintain the molecular signaling systems that promote growth (p21), development (Wnt), antioxidation (Nrf2/FOXO), and homeostasis (FGF23) in tissues crucial for normal physiology, while simultaneously guarding against malignancy and degeneration. Therefore, liganded-VDR modulates the expression of a "fountain of youth" array of genes, with the klotho target emerging as a major player in the facilitation of health span by delaying the chronic diseases of aging.

Vitamins and Hormones, Volume 100
ISSN 0083-6729
http://dx.doi.org/10.1016/bs.vh.2015.11.005