GULF WAR ILLNESS

No Updates this Week for Gulf War Illness or Chronic Multisymptom Illness.

CHRONIC FATIGUE SYNDROME

Relationship satisfaction, communication self-efficacy, and chronic fatigue syndrome-related fatigue.

Milrad SF[1], Hall DL[2], Jutagir DR[3], Lattie EG[4], Czaja SJ[5], Perdomo DM[5], Ironson G[1], Doss BD[1], Mendez A[1], Fletcher MA[6], Klimas N[6], Antoni MH[7].

Soc Sci Med. **2019 Jul 16**;237:112392. doi: 10.1016/j.socscimed.2019.112392. PMID: 31377502. [Epub ahead of print]

RATIONALE: Relationship dissatisfaction has been linked with worse health outcomes in many patient populations, though the mechanism(s) underlying this effect are unclear. Among patients with chronic fatigue syndrome (CFS) and their partners, there is evidence for a bi-directional association between poorer relationship satisfaction and the severity of CFS-related fatigue.

OBJECTIVE: Here, we hypothesized that relationship dissatisfaction negatively impacts fatigue severity through greater depression and less patient satisfaction about communication about symptoms to partners.

METHOD: Baseline data were drawn from diagnosed CFS patients (N = 150) participating in a trial testing the efficacy of a stress management intervention. Data derived from fatigue severity (Fatigue Symptom Index, FSI), depression (Center for Epidemiologic Survey-Depression, CES-D), relationship quality (Dyadic Adjustment Scale, DAS) and communication satisfaction (Patient Symptom Disclosure Satisfaction, PSDS) questionnaires were used for bootstrapped indirect effect analyses using parallel mediation structural equation modeling in Mplus (v8). Age and BMI were entered as covariates.

RESULTS: Greater relationship satisfaction predicted greater communication satisfaction ($p < 0.01$) and lower CES-D scores ($p < 0.01$), which in turn were each significantly related to greater fatigue severity ($p < 0.05$). Tests of the indirect paths indicated that relationship satisfaction had a significant effect on fatigue severity through both constructs, but primarily via depression. There was no direct association between relationship satisfaction and fatigue severity after the intermediate variables (depression, communication satisfaction) were included in the model.

CONCLUSION: Results highlight the importance of considering depression and communication-related factors when examining the effects of relationship satisfaction on CFS symptoms such as fatigue. Further mechanism-based, longitudinal research might identify relationship-related mediating variables that can be targeted therapeutically.

The IDO Metabolic Trap Hypothesis for the Etiology of ME/CFS.

Kashi AA[1], Davis RW[1,2], Phair RD[3].

Diagnostics (Basel). **2019 Jul 26**;9(3). pii: E82. doi: 10.3390/diagnostics9030082. PMID: 31357483.

Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) is a debilitating noncommunicable disease brandishing an enormous worldwide disease burden with some evidence of inherited genetic risk. Absence of measurable changes in patients' standard blood work has necessitated ad hoc symptom-driven therapies and a dearth of mechanistic hypotheses regarding its etiology and possible cure. A new hypothesis, the indolamine-2,3-dioxygenase (IDO) metabolic trap, was developed and formulated as a mathematical model. The historical occurrence of ME/CFS outbreaks is a singular feature of the disease and implies that any predisposing genetic mutation must be common. A database search for common damaging mutations in human enzymes produces 208 hits, including IDO2 with four such mutations. Non-functional IDO2, combined with well-established substrate inhibition of IDO1 and kinetic asymmetry of the large neutral amino acid transporter, LAT1, yielded a mathematical model of tryptophan metabolism that displays both physiological and pathological steady-states. Escape from the pathological one requires an exogenous perturbation. This model also identifies a critical point in cytosolic tryptophan abundance beyond which descent into the pathological steady-state is inevitable. If, however, means can be discovered to return cytosolic tryptophan below the critical point, return to the normal physiological steady-state is assured. Testing this hypothesis for any cell type requires only labelled tryptophan, a means to measure cytosolic tryptophan and kynurenine, and the standard tools of tracer kinetics.

CHRONIC FATIGUE SYNDROME (Continued)

A perspective on causation of the chronic fatigue syndrome by considering its nosology.

White PD[1].

J Eval Clin Pract. **2019 Aug 1**. doi: 10.1111/jep.13240. PMID: 31373106. [Epub ahead of print]

The causes of chronic fatigue syndrome (CFS) remain unknown, with many failures to replicate new findings. This may be because the condition is hard to diagnose, difficult to classify, or because of its heterogeneous nature. Authors have problems in differentiating CFS from myalgic encephalomyelitis (ME), which leads many to label it as a hybrid CFS/ME or ME/CFS. Attempts to validate the many published criterion-based definitions have ended in failure. The International Classification of Diseases provide several different descriptions to choose from, although the latest 11th edition has narrowed this down. This paper describes conventional attempts to define and classify the illness, suggesting that this may be what leads to a failure to replicate putative causes. The approach to CFS/ME may require a shift in the assumption that the illness is homogeneous. An alternative approach is provided by studies suggesting that the condition is heterogeneous. CONCLUSION: The way forward may be to be over-inclusive regarding the diagnosis as a first step, while subdividing the condition into likely subgroups as a means of finding valid and reliable associations with potential causes. Studies of aetiology must involve prospective designs since cross-sectional studies cannot inform either aetiology or pathophysiology.

HEADACHE and MIGRAINE

Repetitive Peripheral Magnetic Stimulation (rPMS) in Subjects With Migraine-Setup Presentation and Effects on Skeletal Musculature.

Renner T[1], Sollmann N[2,3], Trepte-Freisleder F[1], Albers L[1], Mathonia NM[1], Bonfert MV[1], König H[1], Klose B[1], Krieg SM[4], Heinen F[1], Gerstl L[1], Landgraf MN[1].

Front Neurol. **2019 Jul 16**;10:738. doi: 10.3389/fneur.2019.00738. PMCID: PMC6646581. PMID: 31379706. eCollection 2019.

Purpose: Repetitive peripheral magnetic stimulation (rPMS) has been successfully applied recently in migraineurs to alleviate migraine symptoms. Symptom relief has been achieved by stimulating myofascial trigger points (mTrPs) of the trapezius muscles, which are considered part of the trigemino-cervical complex (TCC). However, effects on musculature have not been assessed in detail, and the specificity of effects to muscles considered part of the TCC yet has to be elucidated. Against this background, this study presents the setup of rPMS in migraine and evaluates effects on skeletal musculature.

Materials and Methods: Thirty-seven adults (mean age: 25.0 ± 4.1 years, 36 females) suffering from migraine and presenting mTrPs according to physical examination underwent rPMS either to mTrPs in the trapezius muscles (considered part of the TCC; n = 19) or deltoid muscles (considered not part of the TCC; n = 18) during six sessions over the course of 2 weeks. Standardized questionnaires were filled in to assess any adverse events and experience with rPMS as well as satisfaction and benefits from stimulation. Algometry was performed to evaluate changes in pressure pain thresholds (PPTs).

Results: All stimulation sessions were successfully performed without adverse events, with 84.2% of subjects of the trapezius group and 94.4% of subjects of the deltoid group describing rPMS as comfortable (p = 0.736). Muscular pain or tension improved in 73.7% of subjects of the trapezius group and in 61.1% of subjects of the deltoid group (p = 0.077). PPTs of the trapezius muscles clearly increased from the first to the last stimulation sessions-regardless of the stimulated muscle (rPMS to the trapezius or deltoid muscles). However, depending on the examined muscles the increase of PPTs differed significantly (subjects with stimulation of trapezius muscles: p = 0.021; subjects with stimulation of deltoid muscles: p = 0.080).

Conclusion: rPMS is a comfortable method in migraineurs that can improve local muscular pain or tension. Furthermore, it is able to increase directly and indirectly the PPTs of the trapezius muscles (considered part of the TCC) when applied over mTrPs, supporting the role of the TCC in migraineurs.

HEADACHE and MIGRAINE (Continued)

Linking Traumatic Brain Injury, Sleep Disruption and Post-Traumatic Headache: a Potential Role for Glymphatic Pathway Dysfunction.

Piantino J[1], Lim MM[2,3,4], Newgard CD[5], Iliff J[6,7].

Curr Pain Headache Rep. **2019 Jul 29**;23(9):62. doi: 10.1007/s11916-019-0799-4. PMID: 31359173.

PURPOSE OF THE REVIEW: Traumatic brain injury (TBI) is a major public health concern in the USA and worldwide. Sleep disruption and headaches are two of the most common problems reported by patients after TBI. In this manuscript, we review the current knowledge regarding the relation between post-traumatic sleep disruption and headaches. We also describe the role of the glymphatic system as a potential link between TBI, sleep, and headaches.

RECENT FINDINGS: Recent studies show a reciprocal relation between post-traumatic sleep disruption and headaches: patients with sleep disruption after TBI report more headaches, and post-traumatic headaches are a risk factor for developing disrupted sleep. Despite this clinical association, the exact mechanisms linking post-traumatic sleep disruption and headaches are not well understood. The glymphatic pathway, a newly described brain-wide network of perivascular spaces that supports the clearance of interstitial solutes and wastes from the brain, is active primarily during sleep, and becomes dysfunctional after TBI. We propose a model where changes in glymphatic function caused by TBI and post-traumatic sleep disruption may impair the clearance of neuropeptides involved in the pathogenesis of post-traumatic headaches, such as CGRP. The relation between TBI, post-traumatic sleep disruption, and post-traumatic headaches, although well documented in the literature, remains poorly understood. Dysfunction of the glymphatic system caused by TBI offers a novel and exiting explanation to this clinically observed phenomenon. The proposed model, although theoretical, could provide important mechanistic insights to the TBI-sleep-headache association.

Vitamin D in migraine headache: a comprehensive review on literature.

Ghorbani Z[1,2], Togha M[2], Rafiee P[3], Ahmadi ZS[4], Rasekh Magham R[5], Haghighi S[2], Razeghi Jahromi S[6], Mahmoudi M[7,8,9].

Neurol Sci. **2019 Aug 3**. doi: 10.1007/s10072-019-04021-z. PMID: 31377873. [Epub ahead of print]

INTRODUCTION: As a primary headache, migraine has been established as the first leading disability cause worldwide in the subjects who aged less than 50 years. A variety of dietary supplements have been introduced for migraine complementary treatment. As an anti-inflammatory and antioxidant agent, vitamin D is one of these agents which has been of interest in recent years. Although higher prevalence of vitamin D deficiency/insufficiency has been highlighted among migraineurs compared to controls, there is not any consensus in prescribing vitamin D in clinical practice. Therefore, in the current review, in addition to observational and case-control studies, we also included clinical trials concerning the effects of vitamin D supplementation on migraine/headache.

METHODS: Based on a PubMed/MEDLINE and ScienceDirect database search, this review study includes published articles up to June 2019 concerning the association between migraine/headache and vitamin D status or supplementation.

RESULTS: The percentage of subjects with vitamin D deficiency and insufficiency among migraineurs and headache patients has been reported to vary between 45 and 100%. In a number of studies, vitamin D level was negatively correlated with frequency of headaches. The present findings show that supplementation with this vitamin in a dose of 1000-4000 IU/d could reduce the frequency of attacks in migraineurs.

CONCLUSION: It seems a high proportion of migraine patients might suffer from vitamin D deficiency/insufficiency. Further, the current evidence shows that in addition to routine drug therapy, vitamin D administration might reduce the frequency of attacks in migraineurs. However, these results have yet to be confirmed.

CHRONIC PAIN

No Updates this Week for Chronic Pain.

IRRITABLE BOWEL SYNDROME

No Updates this Week for Irritable Bowel Syndrome.

OTHER RESEARCH OF INTEREST

Comparing Outcomes of Women-Only and Mixed-Gender Intensive Posttraumatic Stress Disorder Treatment for Female Veterans.

Stefanovics EA[1,2], Rosenheck RA[1,2].

J Trauma Stress. **2019 Aug**;32(4):606-615. doi: 10.1002/jts.22417. PMID: 31361360. Epub 2019 Jul 30.

Although most female veterans treated in specialized intensive Veterans Health Administration (VHA) posttraumatic stress disorder (PTSD) programs receive services in settings in which over 95% of participants are men, two programs include only women. Whether outcomes for women with PTSD are superior in women-only programs has not been evaluated. National program evaluation data on 1,357 women veterans from 57 sites were collected at program entry and 4 months after discharge. With adjustment for differences in baseline characteristics, outcomes of women in two women-only programs (n = 469) were compared with those from 55 mixed-gender programs (n = 888), using mixed models with random effect for site. The primary outcome was total PTSD symptom level, with supplementary information on PTSD assessment subscales, substance use, and other outcomes. At program entry, female veterans in women-only programs had lower scores on measures of total PTSD symptoms, p = .013, d = -0.24, and on several subscales. Adjusting for these differences, there were no significant differences between program types in terms of PTSD total score or scores on secondary measures. In women-only programs, veterans had longer lengths of stay and were rated by their clinicians to have a higher level of commitment to therapy at discharge. Thus, women-only programs did not show superior outcomes; however, compared to participants in mixed-gender programs, those in women-only programs had longer lengths of stay, higher levels of commitment to therapy, and were more likely to participate in posttreatment outcome assessments following discharge.

Symptom frequency and development of a generic functional disorder symptom scale suitable for use in studies of patients with irritable bowel syndrome, fibromyalgia syndrome or chronic fatigue syndrome.

Hyland ME[1], Bacon AM[1], Lanario JW[1], Davies AF[2].

Chronic Dis Transl Med. **2019 Jun 24**;5(2):129-138. doi: 10.1016/j.cdtm.2019.05.003. PMCID: PMC6656911. PMID: 31367702. eCollection 2019 Jun.

Objectives: To describe the extent to which irritable bowel syndrome (IBS), fibromyalgia syndrome (FMS), and chronic fatigue syndrome (CFS) exhibit symptom overlap, and to validate a patient-derived, generic symptom questionnaire.

Methods: A patient-derived 61-item symptom-frequency questionnaire was completed by participants recruited through IBS, FMS and CFS self-help websites. Principal axis factor analysis with oblimin rotation was performed separately for those reporting an IBS, FMS or CFS diagnosis.

Results: Questionnaires were completed by 1751 participants of whom 851 reported more than one of the three diagnoses. Stomach pain on at least a weekly basis was reported by 79% of IBS, 52% of FMS, and 43% of CFS single diagnosis participants. Pain increasing the day after activity was reported by 32% of IBS, 94% of FMS, and 85% of CFS single diagnosis participants. Waking still tired at least once weekly was reported by 75% of IBS, 97% of FMS, and 95% of CFS single diagnosis participants. Exploratory factor analysis produced consistent results across all three diagnostic groups, the 61 items loading on 12 correlated factors with a single higher order factor on which all items loaded. Frequency analysis led to the rejection of one item (cold sores on or near lips), and freeform reporting by participants of additional symptoms identified an additional five, namely, restless legs, hair loss/brittle hair/thinning, dizziness/balance problems, blurred vision and urination problems.

Conclusions: IBS, FMS and CFS are polysymptomatic spectrum disorders with a wide range of overlapping symptoms, many of which are unrelated to diagnostic criteria. Frequency analysis and factor analysis confirm the validity of using the same questionnaire across different diagnostic categories. The 65-item general symptom questionnaire (GSQ-65) is a valid generic symptom scale suitable for assessing the many different symptoms of people with IBS, FMS and CFS.

OTHER RESEARCH OF INTEREST (Continued)

The Role of Inflammation in Depression and Fatigue.

Lee CH[1], Giuliani F[1,2].

Front Immunol. **2019 Jul 19**;10:1696. doi: 10.3389/fimmu.2019.01696. eCollection 2019. PMCID: PMC6658985. PMID: 31379879.

Depression and fatigue are conditions responsible for heavy global societal burden, especially in patients already suffering from chronic diseases. These symptoms have been identified by those affected as some of the most disabling symptoms which affect the quality of life and productivity of the individual. While many factors play a role in the development of depression and fatigue, both have been associated with increased inflammatory activation of the immune system affecting both the periphery and the central nervous system (CNS). This is further supported by the well-described association between diseases that involve immune activation and these symptoms in autoimmune disorders, such as multiple sclerosis and immune system activation in response to infections, like sepsis. Treatments for depression also support this immunopsychiatric link. Antidepressants have been shown to decrease inflammation, while higher levels of baseline inflammation predict lower treatment efficacy for most treatments. Those patients with higher initial immune activation may on the other hand be more responsive to treatments targeting immune pathways, which have been found to be effective in treating depression and fatigue in some cases. These results show strong support for the hypothesis that depression and fatigue are associated with an increased activation of the immune system which may serve as a valid target for treatment. Further studies should focus on the pathways involved in these symptoms and the development of treatments that target those pathways will help us to better understand these conditions and devise more targeted treatments.

Beyond the antibodies: serum metabolomic profiling of myasthenia gravis.

Blackmore D[1], Siddiqi Z[2], Li L[3], Wang N[3], Maksymowych W[4].

Metabolomics. **2019 Aug 1**;15(8):109. doi: 10.1007/s11306-019-1571-9. PMID: 31372762.

INTRODUCTION: Myasthenia gravis (MG) is a chronic, potentially debilitating autoimmune disease characterized by weakness and rapid fatigue of the voluntary muscles that worsens on exertion. Left untreated, MG symptoms may cause significant morbidity or even death. To date, no robust biological marker is available to follow the course of the disease. Therefore, new diagnostic approaches and biological markers are essential not only for improved diagnosis of the disease but for improved outcomes.

OBJECTIVES: The present study applied a two-control, multi-label metabolomics profiling approach as a potential strategy for the identification of biomarkers unique to myasthenia gravis (MG).

METHODS: Metabolic analyses using acid- and dansyl-labelled serum from seropositive MG (n = 46), rheumatoid arthritis (RA) (n = 23) and healthy controls (HC) (n = 49) were performed on samples from adult patients presenting to the University of Alberta Hospital neuromuscular and rheumatology clinics. Comparisons between patients with MG vs. HC, and RA vs. HC were made using univariate and multivariate statistics.

RESULTS: Serum biomarker patterns were statistically significantly different between groups. Principal component analysis (PCA) and partial least squares discriminant analysis (PLS-DA) models exhibited considerable distinction between all groups. Metabolites were then filtered to remove peak pairs common to both disease cohorts. Combined metabolite panels revealed clear separation between MG and HC for both library-matched (AUROC: 0.92 ± 0.03) and highest AUC patients (AUROC: 0.94 ± 0.05).

CONCLUSION: In patients presenting to the clinic with seropositive MG, metabolomic profiling is capable of distinguishing patients with disease from those without. These results provide an important first step towards a potential biomarker for improving MG identification.

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