GULF WAR ILLNESS

Metabolic features of Gulf War illness.

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BACKGROUND: More than 230,000 veterans-about 1/3 of US personnel deployed in the 1990-1991 Persian Gulf War-developed chronic, multi-symptom health problems now called "Gulf War illness" (GWI), for which mechanisms and objective diagnostic signatures continue to be sought.

METHODS: Targeted, broad-spectrum serum metabolomics was used to gain insights into the biology of GWI. 40 male participants, included 20 veterans who met both Kansas and CDC diagnostic criteria for GWI and 20 nonveteran controls without similar symptoms that were 1:1 matched to GWI cases by age, sex, and ethnicity. Serum samples were collected and archived at -80° C prior to testing. 358 metabolites from 46 biochemical pathways were measured by hydrophilic interaction liquid chromatography and tandem mass spectrometry.

RESULTS: Veterans with GWI, compared to healthy controls, had abnormalities in 8 of 46 biochemical pathways interrogated. Lipid abnormalities accounted for 78% of the metabolic impact. Fifteen ceramides and sphingomyelins, and four phosphatidylcholine lipids were increased. Five of the 8 pathways were shared with the previously reported metabolic phenotype of males with Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS). However, 4 of the 5 shared pathways were regulated in opposite directions; key pathways that were up-regulated in GWI were down-regulated in ME/CFS. The single pathway regulated in the same direction was purines, which were decreased.

CONCLUSIONS: Our data show that despite heterogeneous exposure histories, a metabolic phenotype of GWI was clearly distinguished from controls. Metabolomic differences between GWI and ME/CFS show that common clinical symptoms like fatigue can have different chemical mechanisms and different diagnostic implications. Larger studies will be needed to validate these findings.

Oligodendrocyte involvement in Gulf War Illness.

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Glia. 2019 Nov;67(11):2107-2124. doi: 10.1002/glia.23668. PMID: 31339622. Epub **2019 Jul 24**.

Low level sarin nerve gas and other anti-cholinesterase agents have been implicated in Gulf War illness (GWI), a chronic multi-symptom disorder characterized by cognitive, pain and fatigue symptoms that continues to afflict roughly 32% of veterans from the 1990-1991 Gulf War. How disrupting cholinergic synaptic transmission could produce chronic illness is unclear, but recent research indicates that acetylcholine also mediates communication between axons and oligodendrocytes. Here we investigated the hypothesis that oligodendrocyte development is disrupted by Gulf War agents, by experiments using the sarin-surrogate acetylcholinesterase inhibitor, diisopropyl fluorophosphate (DFP). The effects of corticosterone, which is used in some GWI animal models, were also investigated. The data show that DFP decreased both the number of mature and dividing oligodendrocytes in the rat prefrontal cortex (PFC), but differences were found between PFC and corpus callosum. The differences seen between the PFC and corpus callosum likely reflect the higher percentage of proliferating oligodendroglia in the adult PFC. In cell culture, DFP also decreased oligodendrocyte survival through a non-cholinergic mechanism. Corticosterone promoted maturation of oligodendrocytes, and when used in combination with DFP it had protective effects by increasing the pool of mature oligodendrocytes and decreasing proliferation. Cell culture studies indicate direct effects of both DFP and corticosterone on OPCs, and by comparison with in vivo results, we conclude that in addition to direct effects, systemic effects and interruption of neuron-glia interactions contribute to the detrimental effects of GW agents on oligodendrocytes. Our results demonstrate that oligodendrocytes are an important component of the pathophysiology of GWI.

CHRONIC FATIGUE SYNDROME

Rethinking ME/CFS Diagnostic Reference Intervals via Machine Learning, and the Utility of Activin B for Defining Symptom Severity.

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Diagnostics (Basel). **2019 Jul 19**;9(3). pii: E79. doi: 10.3390/diagnostics9030079. PMID: 31331036.

Biomarker discovery applied to myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS), a disabling disease of inconclusive aetiology, has identified several cytokines to potentially fulfil a role as a quantitative blood/serum marker for laboratory diagnosis, with activin B a recent addition. We explored further the potential of serum activin B as a ME/CFS biomarker, alone and in combination with a range of routine test results obtained from pathology laboratories. Previous pilot study results showed that activin B was significantly elevated for the ME/CFS participants compared to healthy (control) participants. All the participants were recruited via CFS Discovery and assessed via the Canadian/International Consensus Criteria. A significant difference for serum activin B was also detected for ME/CFS and control cohorts recruited for this study, but median levels were significantly lower for the ME/CFS cohort. Random Forest (RF) modelling identified five routine pathology blood test markers that collectively predicted ME/CFS at ≥62% when compared via weighted standing time (WST) severity classes. A closer analysis revealed that the inclusion of activin B to the panel of pathology markers improved the prediction of mild to moderate ME/CFS cases. Applying correct WST class prediction from RFA modelling, new reference intervals were calculated for activin B and associated pathology markers, where 24-h urinary creatinine clearance, serum urea and serum activin B showed the best potential as diagnostic markers. While the serum activin B results remained statistically significant for the new participant cohorts, activin B was found to also have utility in enhancing the prediction of symptom severity, as represented by WST class.

HEADACHE and MIGRAINE

Hypocalcemia and Vitamin D Deficiency amongst Migraine Patients: A Nationwide Retrospective Study.

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Medicina (Kaunas). **2019 Jul 25**;55(8). pii: E407. doi: 10.3390/medicina55080407. PMID: 31349730.

Background and Objectives: Inadequate vitamin D and calcium intake have been linked to many health issues including chronic headaches. Some studies suggested an association between low vitamin D levels and increase the risk of frequent headaches in middle-aged and older men; however, no single study reported the role of these deficiencies in migraine patients. We aimed to investigate the association of hypocalcemia and vitamin D deficiency with migraine hospitalizations.

Materials and Methods: A population-based retrospective cross-sectional analysis of the Nationwide Inpatient Sample (NIS) (years 2003-2014) in migraine hospitalizations was performed. The prevalence, demographic characteristics and All Patient Refined Diagnosis Related Groups severity/disability association were compared in patients with hypocalcemia and vitamin D deficiency to those without deficiencies, using ICD-9-CM codes. Weighted analyses using Chi-Square, paired Student's t-test, and Cochran-Armitage trend test were performed. Survey logistic regression was performed to find an association between deficiencies and migraine hospitalizations and deficiency induced disability amongst migraineurs.

Results: Between years 2003 and 2014, of the total 446,446 migraine hospitalizations, 1226 (0.27%) and 2582 (0.58%) presented with hypocalcemia and vitamin D deficiency, respectively. In multivariable analysis, hypocalcemia [Odds Ratio (OR): 6.19; Confidence Interval (CI): 4.40-8.70; $p < 0.0001$] and vitamin D deficiency (OR: 3.12; CI: 2.38-4.08; $p < 0.0001$) were associated with markedly elevated odds of major/extreme loss of function. There was higher prevalence (3.0% vs. 1.5% vs. 1.6%; $p < 0.0001$) and higher odds of migraine among vitamin D deficiency (OR: 1.97; CI: 1.89-2.05; $p < 0.0001$) patients in comparison to patients with hypocalcemia (OR: 1.11; CI: 1.03-1.20; $p = 0.0061$) and no-deficiency, respectively.

Conclusions: In this study, we demonstrated a significant association between hypocalcemia and vitamin D deficiency with migraine attacks and deficiency induced loss of function among migraineurs. Early preventive measures may reduce the disability in migraineurs.

CHRONIC PAIN

Individual differences and health in chronic pain: are sex-differences relevant?

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Health Qual Life Outcomes. **2019 Jul 22**;17(1):128. doi: 10.1186/s12955-019-1182-1. PMID: 31331336.

BACKGROUND: Because psychological variables are known to intercorrelate, the goal of this investigation was to compare the unique association between several well-established psychological constructs in pain research and pain-related outcomes. Sex differences are considered because pain is experienced differently across sex groups.

METHODS: Participants were 456 consecutive chronic pain patients attending a tertiary pain clinic (mean age = 58.4 years, SD = 14.8, 63.6% women). The study design was cross-sectional. Psychological constructs included personality (NEO-Five Factor Inventory), irrational thinking (General Attitudes and Beliefs Scale), and coping (Social Problem Solving Inventory). Outcomes were pain severity and interference (Brief Pain Inventory) and physical, general, and mental health status (Short Form-36). To decide whether the bivariate analyses and the two-block, multivariate linear regressions for each study outcome (block 1 = age, sex, and pain severity; block 2 = psychological variables) should be conducted with the whole sample or split by sex, we first explored whether sex moderated the relationship between psychological variables and outcomes. An alpha level of 0.001 was set to reduce the risk of type I errors due to multiple comparisons.

RESULTS: The moderation analyses indicated no sex differences in the association between psychological variables and study outcomes (all interaction terms $p > .05$). Thus, further analyses were calculated with the whole sample. Specifically, the bivariate analyses revealed that psychological constructs were intercorrelated in the expected direction and mostly correlated with mental health and overall perceived health status. In the regressions, when controlling for age, sex, and pain severity, psychological factors as a block significantly increased the explained variance of physical functioning ($\Delta R2 = .037$, $p < .001$), general health ($\Delta R2 = .138$, $p < .001$), and mental health ($\Delta R2 = .362$, $p < .001$). However, unique associations were only obtained for mental health and neuroticism ($\beta = -0.30$, $p < .001$) and a negative problem orientation ($\beta = -0.26$, $p < .001$).

CONCLUSIONS: There is redundancy in the relationship between psychological variables and pain-related outcomes and the strength of this association is highest for mental health status. The association between psychological characteristics and health outcomes was comparable for men and women, which suggests that the same therapeutic targets could be selected in psychological interventions of pain patients irrespective of sex.

Effects of Exergames on Brain Dynamics in Women with Fibromyalgia: A Randomized Controlled Trial.

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J Clin Med. **2019 Jul 11**;8(7). pii: E1015. doi: 10.3390/jcm8071015. PMID: 31336706.

BACKGROUND: Exergames are non-immersive versions of virtual reality that involve physical exercise and have shown several benefits on physical fitness and quality of life in women with fibromyalgia. However, the effects on brain dynamics are still unknown.

AIM: the aim was to evaluate the effects of a 24-week exergame intervention on resting brain dynamics in women with fibromyalgia in a single-blinded, randomized controlled trial.

METHODS: Fifty-six women with fibromyalgia were assessed for eligibility; 55 fulfilled the inclusion criteria. The exercise group completed a 24-week exergame-based intervention that focused on mobility, postural control, upper and lower limb coordination, aerobic fitness, and strength. This group received two 60-min sessions per week. We measured electroencephalographic (EEG) signals from 19 channels. Participants were also divided into two subgroups according to the duration of their symptoms. The intervention was more effective in the group with a shorter duration of symptoms, showing between-group differences in F8, T5 and T4.

CONCLUSION: Exergames may lead to changes in brain dynamics that could be related to increased cerebral blood flow.

IRRITABLE BOWEL SYNDROME

Is Bacillus coagulans supplementation plus low FODMAP diet superior to low FODMAP diet in irritable bowel syndrome management?

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PURPOSE: The aim of this study was to assess the superiority of low fermentable oligosaccharides, disaccharides, monosaccharides, and polyols (FODMAPs) diet plus Bacillus coagulans supplementation to low FODMAP diet alone in the reduction of irritable bowel syndrome (IBS) symptoms.

METHODS: In this randomized clinical trial, fifty IBS patients who met Rome IV criteria for IBS were randomly assigned to receive a low FODMAP diet plus either a probiotic or a placebo capsule for 8 weeks. Probiotic capsules contained 10^9B. coagulans spores and 400 mg inulin, while placebo capsules consisted of 500 mg rice starch.

RESULTS: Significant improvements were observed in abdominal pain intensity and frequency, abdominal distension, satisfaction with bowel habits, quality of life, defecation consistency, and patient-reported severity score in both groups; however, only improvement in severity score was significantly higher in probiotic group compared with placebo group (P = 0.001). Moreover, the frequency of patients with clinical improvement in IBS-symptom severity scale (IBS-SSS) was significantly more in probiotic group compared to placebo group (P = 0.038).

CONCLUSION: Our results indicate that the addition of probiotic supplement containing B. coagulans to the low FODMAP diet might be superior to low FODMAP diet in alleviating IBS symptoms.

OTHER RESEARCH OF INTEREST

A randomized controlled efficacy trial of Mindfulness-Based Stress Reduction compared to an active control group and usual care for fibromyalgia: the EUDAIMON study.

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Fibromyalgia syndrome (FM) represents a great challenge for clinicians and researchers because the efficacy of currently available treatments is limited. The present study examined the efficacy of Mindfulness-Based Stress Reduction (MBSR) for reducing functional impairment as well as the role of mindfulness-related constructs as mediators of treatment outcomes for people with FM. 225 participants with FM were randomized into three study arms: MBSR plus treatment-as-usual (TAU), FibroQoL (multicomponent intervention for FM) plus TAU, and TAU alone. The primary endpoint was functional impact (measured with the Fibromyalgia Impact Questionnaire Revised), and secondary outcomes included "fibromyalginess", anxiety and depression, pain catastrophising, perceived stress and cognitive dysfunction. The differences in outcomes between groups at post-treatment assessment (primary endpoint) and 12-month follow-up were analyzed using linear mixed-effects models and mediational models through path analyses. MBSR was superior to TAU both at post-treatment (large effect sizes) and at follow-up (medium to large effect sizes), and MBSR was also superior to FibroQoL post-treatment (medium to large effect sizes), but long-term it was only modestly better (significant differences only in pain catastrophising and fibromyalginess). Immediately post-treatment, the NNT for 20% improvement in MBSR versus TAU and FibroQoL was 4.0 (95%CI= 2.1-6.5) and 5.0 (95%CI= 2.7-37.3). An unreliable NNT value of 9 (not computable 95%CI) was found for FibroQoL vs. TAU. Changes produced by MBSR in functional impact were mediated by psychological inflexibility and the mindfulness facet Acting with awareness. These findings are discussed in relation to previous studies of psychological treatments for FM.

OTHER RESEARCH OF INTEREST (Continued)

General theory of inflammation: patient self-administration of hydrocortisone safely achieves superior control of hydrocortisone-responding disorders by matching dosage with symptom intensity.

Irwin JB[1], Baldwin AL[2], Stenberg VI[3].

J Inflamm Res. **2019 Jun 13**;12:161-166. doi: 10.2147/JIR.S195165. PMCID: PMC6581742. PMID: 31354330. eCollection 2019.

Objective: To determine if patient self-administration of hydrocortisone will safely achieve superior symptom control for all hydrocortisone-responding disorders as it does for Addison's disease and rheumatoid arthritis.

Methods: Two thousand four hundred and twenty-eight participants with hydrocortisone-responding disorders were brought to a minimum symptom state using daily administered hydrocortisone tablets in a 24-week, open study. Thereafter, participants used 5-day, low-dose hydrocortisone regimens to quench subsequent disorder exacerbations (flares) to maintain the minimum symptom state. Stressors such as emotional traumas, infections, allergies, and injuries were minimized to reduce disorder intensity, hydrocortisone consumption, and participant discomfort.

Results: Two thousand fifteen participants, 601 with fibromyalgia, 579 with osteoarthritis, 246 with rheumatoid arthritis, 226 with undifferentiated arthritis, 75 with back pain, 51 with Parkinson's disease, 44 with polymyalgia rheumatica, 25 with neuropathy, 25 with chronic fatigue syndrome, 25 with dementia, 21 with migraine headache, 19 with multiple sclerosis, and 78 with other disorders completed the 24-week study to achieve a composite average symptom improvement of 76% with equal response rates. The participants averaged ingesting 12 mg of hydrocortisone per day. No significant adverse reactions were observed.

Conclusions: Patient self-administration of hydrocortisone safely achieves superior symptom control for 38 hydrocortisone-responding disorders at equal rates and symptom improvements to confirm and amplify an earlier double-blind study finding on rheumatoid arthritis. These results are consistent with the body having an inflammation control system and chronic inflammation being a disorder unto itself with differing symptoms sets dependent on its location.

Clinical Trials Government Identifier: NCT03558971.

Collective self-experimentation in patient-led research: How online health communities foster innovation.

Kempner J[1], Bailey J[2].

Soc Sci Med. **2019 Jun 12**:112366. doi: 10.1016/j.socscimed.2019.112366. PMID: 31345612. [Epub ahead of print]

Researchers across academia, government, and private industry increasingly value patient-led research for its ability to produce quick results from large samples of the population. This study examines the role played by self-experimentation in the production of health data collected in these projects. We ask: How does the collaborative context of online health communities, with their ability to facilitate far-reaching collaborations over time and space, transform the practice and epistemological foundations of engaging in n = 1 experimentation? We draw from a digital ethnography of an online patient-led research movement, in which participants engage in self-experiments to develop a protocol for using psilocybe-containing mushrooms as a treatment for cluster headache, an excruciating neurological disease for which there is little medical research and huge unmet treatment need. We find that the collectivizing features of the internet have collectivized self-experimentation. Group dynamics shape everything in "collective self-experimentation," from individual choices of intervention, reporting of outcomes, data analysis, determinations of efficacy, to embodiment. This study raises important questions about the role that individuals play in the creation of medical knowledge and the data that informs crowdsourced research.

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