GULF WAR ILLNESS

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

CHRONIC FATIGUE SYNDROME

Differential diagnosis between "chronic fatigue" and "chronic fatigue syndrome".

Son CG[1].

Integr Med Res. **2019 Jun**;8(2):89-91. doi: 10.1016/j.imr.2019.04.005. PMCID: PMC6522773. PMID: 31193269. Epub 2019 Apr 12.

Fatigue is a common complaint experienced by most of subjects during lifetime, which affects approximately 30–50% of general population as point prevalence.1 According to the fatigue-lasting duration, it is classified as acute (<1 month), prolonged (>1 month, <6 months), and chronic fatigue (≥6 months), respectively. Acute fatigue is generally disappears after taking a rest or treating the causative diseases, while uncontrolled prolonged and chronic fatigue limit the physical and social activities.2 Especially, medically unexplained chronic fatigue is a debilitating status, such as idiopathic chronic fatigue (ICF) and chronic fatigue syndrome (CFS).

On the other hand, to distinguish CFS from chronic fatigue or ICF is very important in clinical practice. The reason is that although patients present fatigue symptom as their main complaint in subjects suffering from chronic fatigue or CFS, CFS is considered as to being in totally different pathologic illness.3 In 2015, US Institute of Medicine (IOM) reported diagnostic criteria for CFS as follows; three mandatory symptoms, a substantial impairment in activities accompanied by fatigue persisting for more than 6 months, post-exertional malaise (PEM) and unrefreshing sleep, and one optional symptom among cognitive impairment or orthostatic intolerance.4 Unlike chronic fatigue, CFS has characteristics of brain and CNS symptom and is counted as a complex, multisystem neuroimmune disease. As commonly referred to myalgic encephalomyelitis (ME)/CFS together, brain inflammation is frequently implied in pathology of CFS.5

Above facts brought a necessity of new name which distinguishes CFS from chronic fatigue, without the word “fatigue”. IOM therefore recommended “systemic exertion intolerance disease (SEID)” instead of CFS. The changed conception of CFS is summarized in Fig. 1. The accumulated evidences may indicate the possibility that CFS is not a part of chronic fatigue-related diseases but rather an isolated and different disease with chronic fatigue.6, 7 The major differences may come from the pathogenesis related to neuroinflammation in brain of CFS patients.8, 9

[See full text, references, and figures for this article excerpt in Integrative Medicine Research.]

HEADACHE and MIGRAINE

Genetic Risk Score for Coronary Disease Identifies Predispositions to Cardiovascular and Noncardiovascular Diseases.

Ntalla I[1], Kanoni S[1], Zeng L[2], Giannakopoulou O[1], Danesh J[3], Watkins H[4], Samani NJ[5], Deloukas P[6], Schunkert H[7]; UK Biobank CardioMetabolic Consortium CHD Working Group.

J Am Coll Cardiol. **2019 Jun 18**;73(23):2932-2942. doi: 10.1016/j.jacc.2019.03.512. PMID: 31196449.

BACKGROUND: The taxonomy of cardiovascular (CV) diseases is divided into a broad spectrum of clinical entities. Many such diseases coincide in specific patient groups and suggest shared predisposition.

OBJECTIVES: This study focused on coronary artery disease (CAD) and investigated the genetic relationship to CV and non-CV diseases with reported CAD comorbidity.

METHODS: This study examined 425,196 UK Biobank participants to determine a genetic risk score (GRS) based on 300 CAD associated variants (CAD-GRS). This score was associated with 22 traits, including risk factors, diseases secondary to CAD, as well as comorbid and non-CV conditions. Sensitivity analyses were performed in individuals free from CAD or stable angina diagnosis.

RESULTS: Hypercholesterolemia (odds ratio [OR]: 1.27; 95% CI: 1.26 to 1.29) and hypertension (OR: 1.11; 95% CI: 1.10 to 1.12) were strongly associated with the CAD-GRS, which indicated that the score contained variants predisposing to these conditions. However, the CAD-GRS was also significant in patients with CAD who were free of CAD risk factors (OR: 1.37; 95% CI: 1.30 to 1.44). The study observed significant associations between the CAD-GRS and peripheral arterial disease (OR: 1.28; 95% CI: 1.23 to 1.32), abdominal aortic aneurysms (OR: 1.28; 95% CI: 1.20 to 1.37), and stroke (OR: 1.08; 95% CI: 1.05 to 1.10), which remained significant in sensitivity analyses that suggested shared genetic predisposition. The score was also associated with heart failure (OR: 1.25; 95% CI: 1.22 to 1.29), atrial fibrillation (OR: 1.08; 95% CI: 1.05 to 1.10), and premature death (OR: 1.04; 95% CI: 1.02 to 1.06). These associations were abolished in sensitivity analyses that indicated that they were secondary to prevalent CAD. Finally, an inverse association was observed between the score and migraine headaches (OR: 0.94; 95% CI: 0.93 to 0.96).

CONCLUSIONS: A wide spectrum of CV conditions, including premature death, might develop consecutively or in parallel with CAD for the same genetic roots. In conditions like heart failure, the study found evidence that the CAD-GRS could be used to stratify patients with no or limited genetic overlap with CAD risk. Increased genetic predisposition to CAD was inversely associated with migraine headaches.

Guidelines of the International Headache Society for controlled trials of preventive treatment of chronic migraine in adults.

Tassorelli C[1,2], Diener HC[3], Dodick DW[4], Silberstein SD[5], Lipton RB[6], Ashina M[7], Becker WJ[8,9], Ferrari MD[10], Goadsby PJ[11], Pozo-Rosich P[12,13], Wang SJ[14]; International Headache Society Clinical Trials Standing Committee.

Cephalalgia. **2018 Apr**;38(5):815-832. doi: 10.1177/0333102418758283. PMID: 29504482 .Epub 2018 Mar 4.

[Note: Delayed posting in PubMed—Not previously listed in RAC Research Alerts.]

Background Quality clinical trials form an essential part of the evidence base for the treatment of headache disorders. In 1991, the International Headache Society Clinical Trials Standing Committee developed and published the first edition of the Guidelines for Controlled Trials of Drugs in Migraine. In 2008, the Committee published the first specific guidelines on chronic migraine. Subsequent advances in drug, device, and biologicals development, as well as novel trial designs, have created a need for a revision of the chronic migraine guidelines. Objective The present update is intended to optimize the design of controlled trials of preventive treatment of chronic migraine in adults, and its recommendations do not apply to trials in children or adolescents.

CHRONIC PAIN

Genome-wide association study of multisite chronic pain in UK Biobank.

Johnston KJA[1,2,3], Adams MJ[4], Nicholl BI[1], Ward J[1], Strawbridge RJ[1,5], Ferguson A[1], McIntosh AM[4], Bailey MES[3], Smith DJ[1].

PLoS Genet. **2019 Jun 13**;15(6):e1008164. doi: 10.1371/journal.pgen.1008164. PMID: 31194737. [Epub ahead of print]

Chronic pain is highly prevalent worldwide and represents a significant socioeconomic and public health burden. Several aspects of chronic pain, for example back pain and a severity-related phenotype 'chronic pain grade', have been shown previously to be complex heritable traits with a polygenic component. Additional pain-related phenotypes capturing aspects of an individual's overall sensitivity to experiencing and reporting chronic pain have also been suggested as a focus for investigation. We made use of a measure of the number of sites of chronic pain in individuals within the UK general population. This measure, termed Multisite Chronic Pain (MCP), is a complex trait and its genetic architecture has not previously been investigated. To address this, we carried out a large-scale genome-wide association study (GWAS) of MCP in ~380,000 UK Biobank participants. Our findings were consistent with MCP having a significant polygenic component, with a Single Nucleotide Polymorphism (SNP) heritability of 10.2%. In total 76 independent lead SNPs at 39 risk loci were associated with MCP. Additional gene-level association analyses identified neurogenesis, synaptic plasticity, nervous system development, cell-cycle progression and apoptosis genes as enriched for genetic association with MCP. Genetic correlations were observed between MCP and a range of psychiatric, autoimmune and anthropometric traits, including major depressive disorder (MDD), asthma and Body Mass Index (BMI). Furthermore, in Mendelian randomisation (MR) analyses a causal effect of MCP on MDD was observed. Additionally, a polygenic risk score (PRS) for MCP was found to significantly predict chronic widespread pain (pain all over the body), indicating the existence of genetic variants contributing to both of these pain phenotypes. Overall, our findings support the proposition that chronic pain involves a strong nervous system component with implications for our understanding of the physiology of chronic pain. These discoveries may also inform the future development of novel treatment approaches.

IRRITABLE BOWEL SYNDROME

No Updates this Week for Irritable Bowel Syndrome.

OTHER RESEARCH OF INTEREST

Sleep in the United States Military.

Good CH[1], Brager CPTAJ[2], Capaldi LTCVF[3], Mysliwiec COLV[4].

Neuropsychopharmacology. **2019 Jun 11**. doi: 10.1038/s41386-019-0431-7. PMID: 31185484. [Epub ahead of print]

The military lifestyle often includes continuous operations whether in training or deployed environments. These stressful environments present unique challenges for service members attempting to achieve consolidated, restorative sleep. The significant mental and physical derangements caused by degraded metabolic, cardiovascular, skeletomuscular, and cognitive health often result from insufficient sleep and/or circadian misalignment. Insufficient sleep and resulting fatigue compromises personal safety, mission success, and even national security. In the long-term, chronic insufficient sleep and circadian rhythm disorders have been associated with other sleep disorders (e.g., insomnia, obstructive sleep apnea, and parasomnias). Other physiologic and psychologic diagnoses such as post-traumatic stress disorder, cardiovascular disease, and dementia have also been associated with chronic, insufficient sleep. Increased co-morbidity and mortality are compounded by traumatic brain injury resulting from blunt trauma, blast exposure, and highly physically demanding tasks under load.
We present the current state of science in human and animal models specific to service members during- and post-military career. We focus on mission requirements of night shift work, sustained operations, and rapid re-entrainment to time zones. We then propose targeted pharmacological and non-pharmacological countermeasures to optimize performance that are mission- and symptom-specific. We recognize a critical gap in research involving service members, but provide tailored interventions for military health care providers based on the large body of research in health care and public service workers.

OTHER RESEARCH OF INTEREST (Continued)

Residual symptoms after natural remission of insomnia: associations with relapse over 4 years.

Ji X[1,2], Ivers H[1,3,4], Savard J[1,3,4], LeBlanc M[1,3], Morin CM[1,2].

Sleep. **2019 Jun 13**. pii: zsz122. doi: 10.1093/sleep/zsz122. PMID: 31192349. [Epub ahead of print]

STUDY OBJECTIVES: Chronic insomnia tends to "wax and wane" over lifetime. The presence of residual insomnia symptoms is common, especially among naturally remitted individuals. This study aims to examine the features of these residual symptoms and their potential association with future relapse.

METHODS: A population-based data set on the natural history of insomnia was used for this secondary analysis. Residual insomnia symptoms were investigated in those who had insomnia symptoms/syndrome at baseline and achieved full remission (according to predetermined diagnostic algorithm) within the following 1 year. Cox regressions were used to determine the hazard ratio (HR) of each residual symptom for predicting relapse in the next 4 years. The nature and severity of residual symptoms were examined with an extended version of the Insomnia Severity Index (ISI), which incorporates additional items on sleep quality and specific sleep-related daytime impairments (on daytime fatigue, cognitive functioning, mood, interpersonal relationship, and daily activities). In addition, the presence of depressive symptoms and medical conditions were controlled for in investigating risks of insomnia relapse.

RESULTS: A total of 434 participants were included in this study (age ranges from 18 to 94; 65.9% female); 248 of them had relapsed within 4 years. The response rate ranged from 78% to 83%. The most frequently reported residual symptoms with at least moderate severity (ISI items ≥2 on 0-4 ISI item scale) were poor "Quality of sleep" (39.2 %), followed by "difficulty maintaining sleep" (DMS; 27%). The most common residual daytime impairments related to insomnia were fatigue (24.7 %), mood disturbances (23%) and cognitive disturbances (22.6%). After controlling for baseline insomnia and depression severity and concurrent physical diseases, impairments of cognition (HR = 1.46), poor quality of sleep (HR = 1.43), disturbed mood (HR = 1.39), being female (HR = 1.36), DMS (HR = 1.35), and fatigue (HR = 1.24) were significantly associated with insomnia relapse in the next 4 years. Moreover, residual poor sleep quality and daytime insomnia symptoms were independent of DMS in predicting relapse. Subgroup regressions according to sex showed that for male participants, residual cognition impairments (HR = 1.98) was the most significant predictors of future relapse, whereas residual DMS (HR = 1.46) significantly predicted relapse for women only.

CONCLUSION: A wide range of residual symptoms exists in individuals with naturally remitted insomnia. Notably, residual DMS is the most common residual nighttime symptom and the only nighttime symptom associated with insomnia relapse. Additionally, perceived poor sleep quality and cognitive, mood, and somatic impairments attributed to sleep disturbances are also related to future relapse. Attention to these residual symptoms when initiating insomnia treatment is warranted to minimize future relapse.

OTHER RESEARCH OF INTEREST (Continued)

Vestibular dysfunction in acute traumatic brain injury.

Marcus HJ[1,2], Paine H[1], Sargeant M[2], Wolstenholme S[1], Collins K[1], Marroney N[1], Arshad Q[1,2], Tsang K[1], Jones B[1], Smith R[2], Wilson MH[1], Rust HM[1,2], Seemungal BM[3,4].

J Neurol. **2019 Jun 14**. doi: 10.1007/s00415-019-09403-z. PMID: 31201499. [Epub ahead of print]

Traumatic brain injury (TBI) is the commonest cause of disability in under-40-year-olds. Vestibular features of dizziness (illusory self-motion) or imbalance which affects 50% of TBI patients at 5 years, increases unemployment threefold in TBI survivors. Unfortunately, vestibular diagnoses are cryptogenic in 25% of chronic TBI cases, impeding therapy. We hypothesized that chronic adaptive brain mechanisms uncouple vestibular symptoms from signs. This predicts a masking of vestibular diagnoses chronically but not acutely. Hence, defining the spectrum of vestibular diagnoses in acute TBI should clarify vestibular diagnoses in chronic TBI. There are, however, no relevant acute TBI data. Of 111 Major Trauma Ward adult admissions screened (median 38-years-old), 96 patients (87%) had subjective dizziness (illusory self-motion) and/or objective imbalance were referred to the senior author (BMS). Symptoms included: feeling unbalanced (58%), headache (50%) and dizziness (40%). In the 47 cases assessed by BMS, gait ataxia was the commonest sign (62%) with half of these cases denying imbalance when asked. Diagnoses included BPPV (38%), acute peripheral unilateral vestibular loss (19%), and migraine phenotype headache (34%), another potential source of vestibular symptoms. In acute TBI, vestibular signs are common, with gait ataxia being the most frequent one. However, patients underreport symptoms. The uncoupling of symptoms from signs likely arises from TBI affecting perceptual mechanisms. Hence, the cryptogenic nature of vestibular symptoms in TBI (acute or chronic) relates to a complex interaction between injury (to peripheral and central vestibular structures and perceptual mechanisms) and brain-adaptation, emphasizing the need for acute prospective, mechanistic studies.

Scalp hair cortisol and testosterone levels in patients with sarcoidosis.

van Manen MJG[1], Wester VL[2], van Rossum EFC[2], van den Toorn LM[1], Dorst KY[3], de Rijke YB[3], Wijsenbeek MS[1].

PLoS One. **2019 Jun 14**;14(6):e0215763. doi: 10.1371/journal.pone.0215763. PMID: 31199799. eCollection 2019.

BACKGROUND: Patients with sarcoidosis often experience fatigue and psychological distress, but little is known about the etiology of these conditions. While serum and saliva steroid hormones are used to monitor acute steroid levels, scalp hair analysis is a relatively new method enabling measurement of long-term steroid levels, including hair cortisol reflecting chronic stress. We investigated whether scalp hair cortisol and testosterone levels differ between sarcoidosis patients both with and without fatigue and general population controls. Additionally, we studied if these hormones could serve as objective biomarkers for psychological distress in patients with sarcoidosis.

METHODS: We measured hair steroid levels using liquid chromatography-tandem mass spectrometry in glucocorticoid naïve sarcoidosis patients. Patients completed the Perceived Stress Scale, Fatigue Assessment Scale, Hospital Anxiety and Depression Scale and Short Form 36 (SF-36). Hair steroid levels from 293 participants of the population-based Lifelines cohort study served as controls.

RESULTS: Thirty-two patients (14 males) were included. Hair cortisol, but not testosterone, concentrations were significantly higher in patients with sarcoidosis than in general population controls (mean 6.6 versus 2.7 pg/mg, $p<0.001$). No differences were found in hair cortisol and testosterone levels between fatigued and non-fatigued patients with sarcoidosis. Hair cortisol of sarcoidosis patients correlated significantly with anxiety ($r = 0.47$, $p = 0.01$), depression ($r = 0.46$, $p = 0.01$), and SF-36 mental domain ($r = -0.38$, $p = 0.03$), but not with fatigue.

CONCLUSIONS: Patients with sarcoidosis have chronically higher levels of the stress hormone cortisol than the normal population, while testosterone levels in hair did not differ. Hair cortisol levels were positively related to subjective measures of psychological distress, but not to fatigue. Our study shows that hair cortisol is a promising non-invasive biomarker for psychological distress in patients with sarcoidosis.

TRIAL REGISTRATION: ClinicalTrials.gov: NCT03108547. Registered 31 March 2017, retrospectively registered.

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