GULF WAR ILLNESS

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

CHRONIC FATIGUE SYNDROME

Genetic Predisposition for Immune System, Hormone, and Metabolic Dysfunction in Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: A Pilot Study.

Perez M[1], Jaundoo R[2,3], Hilton K[1], Del Alamo A[1,3], Gemayel K[1], Klimas NG[1,3,4], Craddock TJA[1,2,3,5], Nathanson L[1,3].

Front Pediatr. **2019 May 24**;7:206. doi: 10.3389/fped.2019.00206. eCollection 2019. PMCID: PMC6542994. PMID: 31179255.

Introduction: Myalgic Encephalomyelitis/ Chronic Fatigue Syndrome (ME/CFS) is a multifactorial illness of unknown etiology with considerable social and economic impact. To investigate a putative genetic predisposition to ME/CFS we conducted genome-wide single-nucleotide polymorphism (SNP) analysis to identify possible variants.

Methods: 383 ME/CFS participants underwent DNA testing using the commercial company 23andMe. The deidentified genetic data was then filtered to include only non-synonymous and nonsense SNPs from exons and microRNAs, and SNPs close to splice sites. The frequencies of each SNP were calculated within our cohort and compared to frequencies from the Kaviar reference database. Functional annotation of pathway sets containing SNP genes with high frequency in ME/CFS was performed using over-representation analysis via ConsensusPathDB. Furthermore, these SNPs were also scored using the Combined Annotation Dependent Depletion (CADD) algorithm to gauge their deleteriousness.

Results: 5693 SNPs were found to have at least 10% frequency in at least one cohort (ME/CFS or reference) and at least two-fold absolute difference for ME/CFS. Functional analysis identified the majority of SNPs as related to immune system, hormone, metabolic, and extracellular matrix organization. CADD scoring identified 517 SNPs in these pathways that are among the 10% most deleteriousness substitutions to the human genome.

Patients with fibromyalgia and chronic fatigue syndrome show increased hsCRP compared to healthy controls.

Groven N[1], Fors EA[2], Klæbo Reitan S[3].

Brain Behav Immun. **2019 Jun 6**. pii: S0889-1591(19)30208-9. doi: 10.1016/j.bbi.2019.06.010. PMID: 31176728. [Epub ahead of print]

Chronic Fatigue Syndrome (CFS) and Fibromyalgia (FM) are both chronic disorders that have a devastating effect on the lives of the affected patients and their families. Both conditions have overlapping clinical features that partly resemble those of inflammatory disorders. The etiology is still not understood, and it is suggested that the immune system might be a contributing factor. So far, the results are inconclusive. The purpose of this study was to compare the two conditions and investigate the level of the inflammatory marker high-sensitivity CRP (hsCRP) in CFS and FM patients compared to healthy controls. Female participants aged 18-60 years were enrolled in this study. The group consisted of 49 CFS patients, 57 FM patients, and 54 healthy controls. hsCRP levels were significantly higher for both the CFS and the FM groups compared to healthy controls when adjusting for age, smoking, and BMI ($p < .001$). There was no difference between the two patient groups. The level of hsCRP was affected by BMI but not by age and smoking. Patients with CFS and FM have higher concentrations of hsCRP compared to healthy controls. This remains significant even after adjusting for BMI. CFS and FM cannot be distinguished from each other on the basis of hsCRP in our study.

CHRONIC FATIGUE SYNDROME (Continued)

Abnormal blood lactate accumulation during repeated exercise testing in myalgic encephalomyelitis/chronic fatigue syndrome.

Lien K[1,2], Johansen B[3], Veierød MB[4], Haslestad AS[1] , Bøhn SK[1], Melsom MN[5], Kardel KR[1], Iversen PO[1,6].

Physiol Rep. **2019 Jun**;7(11):e14138. doi: 10.14814/phy2.14138. PMCID: PMC6546966.

Post-exertional malaise and delayed recovery are hallmark symptoms of myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS). Studies on repeated cardiopulmonary exercise testing (CPET) show that previous exercise negatively affects oxygen uptake (VO_2) and power output (PO) in ME/CFS. Whether this affects arterial lactate concentrations ([La_a]) is unknown. We studied 18 female patients (18-50 years) fulfilling the Canadian Consensus Criteria for ME/CFS and 15 healthy females (18-50 years) who underwent repeated CPETs 24 h apart ($CPET_1$ and $CPET_2$) with [La_a] measured every 30th second. VO_2 at peak exercise (VO_{2peak}) was lower in patients than in controls on $CPET_1$ ($P < 0.001$) and decreased in patients on $CPET_2$ ($P < 0.001$). However, the difference in VO_{2peak} between CPETs did not differ significantly between groups. [La_a] per PO was higher in patients during both CPETs ($P_{interaction} < 0.001$), but increased in patients and decreased in controls from $CPET_1$ to $CPET_2$ ($P_{interaction} < 0.001$). Patients had lower VO_2 ($P = 0.02$) and PO ($P = 0.002$) at the gas exchange threshold (GET, the point where CO_2 production increases relative to VO_2), but relative intensity (%VO_{2peak}) and [La_a] at GET did not differ significantly from controls on $CPET_1$. Patients had a reduction in VO_2 ($P = 0.02$) and PO ($P = 0.01$) at GET on $CPET_2$, but no significant differences in %VO_{2peak} and [La_a] at GET between CPETs. Controls had no significant differences in VO_2, PO or %VO_{2peak} at GET between CPETs, but [La_a] at GET was reduced on $CPET_2$ ($P = 0.008$). In conclusion, previous exercise deteriorates physical performance and increases [La_a] during exercise in patients with ME/CFS while it lowers [La_a] in healthy subjects.

Orthostatic intolerance in chronic fatigue syndrome.

Garner R[1], Baraniuk JN[2].

J Transl Med. **2019 Jun 3**;17(1):185. doi: 10.1186/s12967-019-1935-y. PMCID: PMC6547462. PMID: 31159884.

BACKGROUND: Orthostatic intolerance (OI) is a significant problem for those with chronic fatigue syndrome (CFS). We aimed to characterize orthostatic intolerance in CFS and to study the effects of exercise on OI.

METHODS: CFS (n = 39) and control (n = 25) subjects had recumbent and standing symptoms assessed using the 20-point, anchored, ordinal Gracely Box Scale before and after submaximal exercise. The change in heart rate (ΔHR ≥ 30 bpm) identified Postural Orthostatic Tachycardia Syndrome (POTS) before and after exercise, and the transient, exercise-induced postural tachycardia Stress Test Activated Reversible Tachycardia (START) phenotype only after exercise.

RESULTS: Dizziness and lightheadedness were found in 41% of recumbent CFS subjects and in 72% of standing CFS subjects. Orthostatic tachycardia did not account for OI symptoms in CFS. ROC analysis with a threshold ≥ 2/20 on the Gracely Box Scale stratified CFS subjects into three groups: No OI (symptoms < 2), Postural OI (only standing symptoms ≥ 2), and Persistent OI (recumbent and standing symptoms ≥ 2).

CONCLUSIONS: Dizziness and Lightheadedness symptoms while recumbent are an underreported finding in CFS and should be measured when doing a clinical evaluation to diagnose orthostatic intolerance. POTS was found in 6 and START was found in 10 CFS subjects. Persistent OI had symptoms while recumbent and standing, highest symptom severity, and lability in symptoms after exercise. Trial registration The trial was registered at the following: https://clinicaltrials.gov/ct2/show/NCT03567811.

CHRONIC FATIGUE SYNDROME (Continued)

Chronic fatigue is characterized by a relative lack of abnormalities in biological markers.

Wyller VBB[1].

Brain Behav Immun. **2019 Jun 4**. pii: S0889-1591(19)30575-6. doi: 10.1016/j.bbi.2019.05.043. PMID: 31173846. [Epub ahead of print]

I thank Michiel Tack for the comments on our recent paper (Kristiansen et al., 2019), in which we reported large differences in a range of bodily symptoms between post-infectious fatigue and non-fatigue subjects, but only subtle differences in neuroendocrine and immune markers. Mr. Tack maintains that the latter finding is weakened by three methodological limitations.

Firstly, I agree that defining fatigue caseness by a cut-off score of 4 on the Chalder Fatigue Questionnaire (CFQ) leads to inclusion of subjects with only minor bodily complaints. However, association analyses within the same cohort of post-infectious adolescents using CFQ as a continuous variable (avoiding the problem of dichotomizing the study population in a fatigued and a non-fatigued group) have revealed results very similar to the ones reported by Kristiansen et al. (Pedersen et al., 2019). Furthermore, the association between fatigue and level of activity was rather poor. Thus, I doubt weather addition of behavioral consequences to define substantial fatigue – as suggested by Mr. Tack – will increase validity.

Secondly, I agree that the relatively low numbers of participants adhering to case definitions of CFS/ME increases the risk of type II-errors for the subgroup-analyses. However, despite lower statistical power, we did observe a significant higher score for the majority of symptom variables as compared to the entire group of fatigued individuals. Thus, the discrepancy between the experience of severe bodily complaints and the relative lack of corresponding bodily alterations appears to be even more pronounced within the CFS/ME subgroups. Also, it should be noted that a similar number of patients in previous studies has been sufficient to detect autonomic alterations (Wyller et al., 2011), which – in light of the present results – might be regarded a consequence of deconditioning.

Thirdly, I agree that a more thorough assessment of post-exertional malaise (PEM) would have been beneficial. However, no validated inventory was available when our study was launched, and based on recent findings, it seems reasonable to assume that a single question addressing the main element of PEM (fatigue after exertion) serves as a good proxy for a composite PEM score (Holtzman et al., 2019).

The field of chronic fatigue and CFS/ME is characterized by scientific controversies. Research has documented the debilitating symptoms of chronic fatigue and CFS/ME, while at the same time failed to discover specific and reproducible abnormalities in underlying biological mechanisms. This apparent paradox might explain the continuous claim from some stakeholders to continue the search for “objective” biological markers of disease. However, such claim might in itself lead to methodological problems, as it tends to prevent hypotheses falsification: If an assumed abnormality of biological mechanisms (such as immune disturbances) is not found, it is always possible to explain the absence of findings with a *post hoc* supposition of methodological limitations.

[See full text, references, and supplementary data for this excerpt in Brain, Behavior, and Immunity.]

HEADACHE and MIGRAINE

FDA approves first treatment for episodic cluster headache that reduces the frequency of attacks

FDA News Release, June 04, 2019

The U.S. Food and Drug Administration today approved Emgality (galcanezumab-gnlm) solution for injection for the treatment of episodic cluster headache in adults.

“Emgality provides patients with the first FDA-approved drug that reduces the frequency of attacks of episodic cluster headache, an extremely painful and often debilitating condition,” said Eric Bastings, M.D., deputy director of the Division of Neurology Products in the FDA’s Center for Drug Evaluation and Research. “The FDA is committed to continuing to work with drug developers to bring treatments for unmet medical needs to patients.”

Cluster headache is a form of headache that produces extreme pain and tends to occur in clusters, often at the same time(s) of the day, for several weeks to months. The headaches are accompanied by symptoms that may include: bloodshot eyes, excessive tearing of the eyes, drooping of the eyelids, runny nose and/or nasal congestion and facial sweating. Some people experience restlessness and agitation. Cluster headache attacks may strike several times a day, generally lasting between 15 minutes and three hours.

The effectiveness of Emgality for the treatment of episodic cluster headache was demonstrated in a clinical trial that compared the drug to placebo in 106 patients. The trial measured the average number of cluster headaches per week for three weeks and compared the average changes from baseline in the Emgality and placebo groups. During the three-week period, patients taking Emgality experienced 8.7 fewer weekly cluster headache attacks than they did at baseline, compared to 5.2 fewer attacks for patients on placebo.

There is a risk of hypersensitivity reactions with Emgality use. If a serious hypersensitivity reaction occurs, treatment should be discontinued. Hypersensitivity reactions could occur days after administration and may be prolonged. The most common side effect reported by participants in the clinical trials was injection site reactions.

Emgality is given by patient self-injection. It was first approved by the FDA in September 2018 for the preventive treatment of migraine in adults. The FDA granted the approval of Emgality to Eli Lilly.

The FDA granted this application Priority Review and Breakthrough Therapy designation.

CHRONIC PAIN

Pain Quality by Location in Outpatients with Cancer.

Schlaeger JM[1], Weng LC[2], Huang HL[3], Tsai HH[2], Takayama M[4], Ngamkham S[5], Yao Y[6], Wilkie DJ[7].

Pain Manag Nurs. **2019 May 31**. pii: S1524-9042(18)30514-9. doi: 10.1016/j.pmn.2019.04.007. PMID: 31160180. [Epub ahead of print]

BACKGROUND: The McGill Pain Questionnaire (MPQ) pain quality descriptors have been analyzed to characterize the sensory, affective, and evaluative domains of pain, but have not been differentiated by pain location.

AIM: To examine MPQ pain quality descriptors by pain location in outpatients with lung or prostate cancer.

DESIGN: Cross sectional.

SETTINGS: Eleven oncology clinics or patients' homes.

SUBJECTS: 264 adult outpatients (80% male; mean age 62.2 ± 10.0 years, 85% White).

METHODS: Subjects completed a 100 mm visual analogue scale of pain intensity and MPQ clinic or home visit, marking sites where they had pain on a body outline and circling from 78 verbal descriptors those that described their pain. A researcher noted next to the descriptor spontaneous comments about sites feeling like a selected word and queried the subjects about any other words to obtain the site(s).

RESULTS: Pain quality descriptors were assigned to all 7 pain locations marked by ≥ 20% of 198 lung or 66 prostate cancer patients. Four pain locations were marked with pain quality descriptors significanlty ($p < .05$) more frequently for lung cancer (53% chest-aching, burning; 58% back-aching, stabbing; 48% head-aching, sharp; and 19% arms-aching, stabbing) than for prostate cancer, which had significantly more frequent pain locations in the abdomen (64%-aching, burning) and lower back/buttocks (55%-aching, burning).

CONCLUSIONS: This type of pain characterization is innovative and has the potential to help implement targeted treatments for patients with cancer and other chronic pain conditions.

CHRONIC PAIN (Continued)

A Bcr-Abl Inhibitor GNF-2 Attenuates Inflammatory Activation of Glia and Chronic Pain.

Song GJ[1,2], Rahman MH[3], Jha MK[3,4], Gupta DP[1,3], Park SH[1], Kim JH[3], Lee SH[5], Lee IK[6], Sim T[7,8], Bae YC[9], Lee WH[10], Suk K[3].

Front Pharmacol. **2019 May 20**;10:543. doi: 10.3389/fphar.2019.00543. PMCID: PMC6535676. PMID: 31164822. eCollection 2019.

GNF-2 is an allosteric inhibitor of Bcr-Abl. It was developed as a new class of anti-cancer drug to treat resistant chronic myelogenous leukemia. Recent studies suggest that c-Abl inhibition would provide a neuroprotective effect in animal models of Parkinson's disease as well as in clinical trials. However, the role of c-Abl and effects of GNF-2 in glia-mediated neuroinflammation or pain hypersensitivity has not been investigated. Thus, in the present study, we tested the hypothesis that c-Abl inhibition by GNF-2 may attenuate the inflammatory activation of glia and the ensuing pain behaviors in animal models. Our results show that GNF-2 reduced lipopolysaccharide (LPS)-induced nitric oxide and pro-inflammatory cytokine production in cultured glial cells in a c-Abl-dependent manner. The small interfering ribonucleic acid (siRNA)-mediated knockdown of c-Abl attenuated LPS-induced nuclear factor kappa light chain enhancer of activated B cell (NF-κB) activation and the production of pro-inflammatory mediators in glial cell cultures. Moreover, GNF-2 administration significantly attenuated mechanical and thermal hypersensitivities in experimental models of diabetic and inflammatory pain. Together, our findings suggest the involvement of c-Abl in neuroinflammation and pain pathogenesis and that GNF-2 can be used for the management of chronic pain.

IRRITABLE BOWEL SYNDROME

How Patients with IBS Use Low FODMAP Dietary Information Provided by General Practitioners and Gastroenterologists: A Qualitative Study.

Trott N[1], Aziz I[2], Rej A[3], Surendran Sanders D[4].

Nutrients. **2019 Jun 11**;11(6). pii: E1313. doi: 10.3390/nu11061313. PMCID: PMC6627590. PMID: 31212668.

There is a lack of dietitians trained to deliver the low fermentable oligosaccharides, disaccharides, monosaccharides, and polyols (FODMAP) diet (LFD) for irritable bowel syndrome (IBS). Many patients receive nutritional information from general practitioners (GPs) or gastroenterologists (GEs). Since the LFD is dietitian-led, the aim of this research was to qualitatively explore the effects of GP- and GE-delivered LFD information, in IBS self-management. Semi-structured interviews were conducted in a purposive sample of 8 people with IBS (6 female), who used the LFD as their primary treatment. Interpretive Phenomenological Analysis (IPA) was used to develop themes on the lived experience of the participant's use of LFD information from GPs and GEs. This information was perceived as trustworthy but simplistic; often just "food lists" with little personalisation to meet individual needs and difficult to apply in "real life". The information required substantial interpretation and the familial and social effects of implementation were not addressed in the materials provided. Supplementary digital resources were regarded as more practical but the participants expressed concern in relation to the validity of these materials. The findings in this study support current clinical guidelines proposed by both the National Institute for Health and Care Excellence and the British Dietetic Association that the LFD should be considered a dietitian-led only intervention.

IRRITABLE BOWEL SYNDROME (Continued)

Role of brain imaging in disorders of brain-gut interaction: a Rome Working Team Report.

Mayer EA[1], Labus J[1], Aziz Q[2], Tracey I[3], Kilpatrick L[1], Elsenbruch S[4], Schweinhardt P[5], Oudenhove LV[6], Borsook D[7].

Gut. **2019 Sep**;68(9):1701-1715. doi: 10.1136/gutjnl-2019-318308. Epub 2019 Jun 7.

Imaging of the living human brain is a powerful tool to probe the interactions between brain, gut and microbiome in health and in disorders of brain-gut interactions, in particular IBS. While altered signals from the viscera contribute to clinical symptoms, the brain integrates these interoceptive signals with emotional, cognitive and memory related inputs in a non-linear fashion to produce symptoms. Tremendous progress has occurred in the development of new imaging techniques that look at structural, functional and metabolic properties of brain regions and networks. Standardisation in image acquisition and advances in computational approaches has made it possible to study large data sets of imaging studies, identify network properties and integrate them with non-imaging data. These approaches are beginning to generate brain signatures in IBS that share some features with those obtained in other often overlapping chronic pain disorders such as urological pelvic pain syndromes and vulvodynia, suggesting shared mechanisms. Despite this progress, the identification of preclinical vulnerability factors and outcome predictors has been slow. To overcome current obstacles, the creation of consortia and the generation of standardised multisite repositories for brain imaging and metadata from multisite studies are required.

OTHER RESEARCH OF INTEREST

No Updates this Week for Other Research of Interest.

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