GULF WAR ILLNESS

Characterising the gut microbiome in veterans with Gulf War Illness: a protocol for a longitudinal, prospective cohort study.

Keating JA[1], Shaughnessy C[2], Baubie K[1], Kates AE[1,2], Putman-Buehler N[2], Watson L[2], Dominguez N[2], Watson K[1], Cook DB[1,3], Rabago D[4], Suen G[5], Gangnon R[6], Safdar N[1,2].

BMJ Open. **2019 Aug 19**;9(8):e031114. doi: 10.1136/bmjopen-2019-031114. PMCID: PMC6707676. PMID: 31431446.

INTRODUCTION: Approximately 25%-35% of the 1991 Gulf War Veteran population report symptoms consistent with Gulf War Illness (GWI), a chronic, multi-symptom illness characterised by fatigue, pain, irritable bowel syndrome and problems with cognitive function. GWI is a disabling problem for Gulf War Veterans, and there remains a critical need to identify innovative, novel therapies. Gut microbiota perturbation plays a key role in the symptomatology of other chronic multi-symptom illnesses, including myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS). Given similarities between ME/CFS and GWI and the presence of gastrointestinal disorders in GWI patients, Veterans with GWI may also have gut abnormalities like those seen with ME/CFS. In this longitudinal cohort study, we are comparing the diversity (structure) and the metagenomes (function) of the gut microbiome between Gulf War Veterans with and without GWI. If we find differences in Veterans with GWI, the microbiome could be a target for therapeutic intervention to alleviate GWI symptoms.

METHODS AND ANALYSIS: Participants answer questions about diet, exercise and lifestyle factors. Participants also complete a questionnaire (based on the Kansas case definition of GWI) regarding their medical history and symptoms; we use this questionnaire to group participants into GWI versus healthy control cohorts. We plan to enrol 52 deployed Gulf War Veterans: 26 with GWI and 26 healthy controls. Participants provide stool and saliva samples weekly for an 8-week period for microbiome analyses. Participants also provide blood samples at the beginning and end of this period, which we will use to compare measures of inflammation markers between the groups.

ETHICS AND DISSEMINATION: The protocol was approved by the University of Wisconsin-Madison Health Sciences Institutional Review Board and the William S. Middleton Memorial Veterans Hospital Research and Development Committee. Results of this study will be submitted for publication in a peer-reviewed journal.

CHRONIC FATIGUE SYNDROME

Suggested pathology of systemic exertion intolerance disease: Impairment of the E_3 subunit or crossover of swinging arms of the E_2 subunit of the pyruvate dehydrogenase complex decreases regeneration of cofactor dihydrolipoic acid of the E_2 subunit.

Bohne VJB[1], Bohne Ø[2].

Med Hypotheses. **2019 Sep**;130:109260. doi: 10.1016/j.mehy.2019.109260. PMID: 31383326. Epub 2019 Jun 14.

Systemic Exertion Intolerance Disease (SEID) or myalgic encephalomyelitis (ME) or chronic fatigue syndrome (CFS) has an unknown aetiology, with no known treatment and a prevalence of approximately 22 million individuals (2%) in Western countries. Although strongly suspected, the role of lactate in pathology is unknown, nor has the nature of the two most central symptoms of the condition - post exertional malaise and fatigue. The proposed mechanism of action of pyruvate dehydrogenase complex (PDC) plays a central role in maintaining energy production with cofactors alpha-lipoic acid (LA) and its counterpart dihydrolipoic acid (DHLA), its regeneration suggested as the new rate limiting factor. Decreased DHLA regeneration due to impairment of the E_3 subunit or crossover of the swinging arms of the E_2 subunit of PDC have been suggested as a cause of ME/CFS/SEID resulting in instantaneous fluctuations in lactate levels and instantaneous offset of the DHLA/LA ratio and defining the condition as an LA deficiency with chronic instantaneous hyperlactataemia with explicit stratification of symptoms. While instantaneous hyperlactataemia has been suggested to account for the PEM, the fatigue was explained by the downregulated throughput of pyruvate and consequently lower production of ATP with the residual enzymatic efficacy of the E_3 subunit or crossover of the E_2 as a proposed explanation of the fatigue severity. Functional diagnostics and visualization of instantaneous elevations of lactate and DHLA has been suggested. Novel treatment strategies have been implicated to compensate for chronic PDC impairment and hyperlactataemia. This hypothesis potentially influences the current understanding and treatment methods for any type of hyperlactataemia, fatigue, ME/CFS/SEID, and conditions associated with PDC impairment.

HEADACHE and MIGRAINE

Lasmiditan for acute treatment of migraine in patients with cardiovascular risk factors: post-hoc analysis of pooled results from 2 randomized, double-blind, placebo-controlled, phase 3 trials.

Shapiro RE[1], Hochstetler HM[2], Dennehy EB[3,4], Khanna R[3], Doty EG[3], Berg PH[3], Starling AJ[5].

J Headache Pain. **2019 Aug 29**;20(1):90. doi: 10.1186/s10194-019-1044-6. PMID: 31464581.

BACKGROUND: In addition to the increased risk for cardiovascular (CV) disease and CV events associated with migraine, patients with migraine can also present with a number of CV risk factors (CVRFs). Existing treatment options can be limited due to contraindications, increased burden associated with monitoring, or patient avoidance of side effects. Safe and effective migraine treatment options are needed for patients with migraine and a history of CV or cerebrovascular disease or with increased risk for CV events. This analysis was designed to evaluate the safety and efficacy of oral lasmiditan, a selective serotonin 5-hydroxytryptamine 1F receptor agonist, in acute treatment of migraine attacks in patients with CVRFs.

METHODS: SAMURAI and SPARTAN were similarly designed, Phase 3, randomized, double-blind, placebo-controlled trials in adults treating a single migraine attack with lasmiditan 50, 100, or 200 mg. Both studies included patients with CVRFs, and SPARTAN allowed patients with coronary artery disease, clinically significant arrhythmia, or uncontrolled hypertension. Efficacy and safety of lasmiditan in subgroups of patients with differing levels of CVRFs are reported. For efficacy analyses, logistic regression was used to assess treatment-by-subgroup interactions. For safety analyses, Cochran-Mantel-Haenszel test of general association evaluated treatment comparisons; Mantel-Haenszel odds ratio assessed significant treatment effects.

RESULTS: In this pooled analysis, a total of 4439 patients received ≥1 dose of study drug. A total of 3500 patients (78.8%) had ≥1 CVRF, and 1833 patients (41.3%) had ≥2 CVRFs at baseline. Both trials met the primary endpoints of headache pain freedom and most bothersome symptom freedom at 2 h. The presence of CVRFs did not affect efficacy results. There was a low frequency of likely CV treatment-emergent adverse events (TEAEs) overall (lasmiditan, 30 [0.9%]; placebo, 5 [0.4%]). There was no statistical difference in the frequency of likely CV TEAEs in either the absence or presence of any CVRFs. The only likely CV TEAE seen across patients with ≥1, ≥ 2, ≥ 3, or ≥ 4 CVRFs was palpitations.

CONCLUSIONS: When analyzed by the presence of CVRFs, there was no statistical difference in lasmiditan efficacy or the frequency of likely CV TEAEs. Despite the analysis being limited by a single-migraine-attack design, the lack of differences in efficacy and safety with increasing numbers of CVRFs indicates that lasmiditan might be considered in the treatment algorithm for patients with CVRFs. Future studies are needed to assess long-term efficacy and safety.

TRIAL REGISTRATION: ClinicalTrials.gov NCT02439320 (SAMURAI), registered 18 March 2015 and ClinicalTrials.gov NCT02605174 (SPARTAN), registered 11 November 2015.

Primary Headaches and Sleep Disturbances: A Cause or a Consequence?

Andrijauskis D, Ciauskaite J, Vaitkus A, Pajediene E.

J Oral Facial Pain Headache. **2019 Aug 27**. doi: 10.11607/ofph.2405. PMID: 31465033. [Epub ahead of print]

AIMS: To evaluate the possible relationship between sleep disturbances and primary headaches.

METHODS: This prospective study was carried out in a random group of patients with active primary headaches (case group) and a control group. Patients with active primary headaches were further stratified into two groups: patients with migraine and patients with tension-type headache (TTH). Participants were questioned using the following standardized tests: Insomnia Severity Index (ISI), Pittsburgh Sleep Quality Index (PSQI), Epworth Sleepiness Scale (ESS), Berlin Sleep Apnea Questionnaire (BSAQ), and a custom-made headache questionnaire. The results of the questionnaires were compared among patients with TTH, patients with migraine, and age- and sex-matched controls.

RESULTS: Of the 143 participants, 22.4% had TTH, 30.8% were diagnosed with migraine, and 46.9% did not have a diagnosed headache disorder. Patients with TTH were more likely to have insomnia (ISI score > 7) than patients with migraine (75% vs 50%, respectively) or controls (75% vs 37.3%, respectively) (P = .002). Frequency of poor sleep quality (global PSQI score ≥ 6) was significantly highest in the TTH group (87.5%), while the migraine and control groups had better sleep quality (47.7% and 43.3%, respectively) (P = .0001). TTH patients were more likely to have insufficient sleep (sleep efficiency < 85%) (53.1%) than those with migraine (25%) or the control group (29.9%) (P = .025).

CONCLUSION: Patients who suffered from TTH were more likely to have insomnia than patients with migraine or controls. Nearly all patients with TTH had poor sleep quality, which was also observed in approximately half of the individuals in the migraine and control groups. Three-quarters of patients in the TTH group and more than half in the migraine group indicated inadequate sleep as a trigger factor for headache.

HEADACHE and MIGRAINE (Continued)

Serum Vitamin B12 and Methylmalonic Acid Status in Migraineurs: A Case-Control Study.

Togha M[1], Razeghi Jahromi S[2], Ghorbani Z[3], Martami F[1,3], Seifishahpar M[1,2].

Headache. **2019 Aug 31**. doi: 10.1111/head.13618. PMID: 31471907. [Epub ahead of print]

BACKGROUND: Although the exact pathophysiological mechanistic pathways that result in the initiation of migraine attacks remain unclear, there are some proposed mechanisms including neurogenic inflammation, trigeminovascular system activation, vascular dysfunction, and augmented release of nitric oxide (NO) and homocysteine (Hcy). Vitamin B12 is thought to be involved in important pathways that seem to be related to the pathogenesis of migraine including scavenging against NO and prevention of hyperhomocysteinemia. Therefore, the aim of the current study was to evaluate the serum vitamin B12 and methylmalonic acid (MMA) status in a group of migraine patients compared to healthy controls.

METHODS: After the recruitment of cases and controls, demographic data and migraine characteristics (including the number of headache days, severity of headaches, and duration of each attack in hours) were recorded. Serum vitamin B12 and MMA levels were measured using the enzyme-linked immunosorbent assay technique.

RESULTS: Seventy migraine patients and 70 healthy subjects were enrolled in this case control study. The serum levels of B12 were found to be significantly lower in migraine patients than in healthy subjects (512 ± 300 vs 667 ± 351 pg/mL, P = .007); whereas migraineurs had higher levels of MMA than controls (1.39 [0.59,4.01] vs 1.01 [0.49,1.45] μg/dL, P = .027). In the fully adjusted multiple regression model, those in the highest vs the lowest serum B12 quartile had 80% decrease in the odds of having migraine ([OR = 0.20, 95% CI = 0.05-0.73], [P for trend = .008]); while, patients in the highest quartile of MMA had more than 5 times increased risk of having migraine ([OR = 5.44, 95% CI = 1.49-19.87] [P for trend = .002]). There was no association between serum B12 and MMA levels and headache characteristics.

CONCLUSION: Taken together, these findings suggest that participants with lower vitamin B12 and higher MMA levels that considered as lower functional activity of B12 had higher odds of migraine.

A randomized trial of telemedicine for migraine management.

Friedman DI[1,2], Rajan B[3], Seidmann A[4].

Cephalalgia. **2019 Aug 26**:333102419868250. doi: 10.1177/0333102419868250. PMID: 31450969. [Epub ahead of print]

OBJECTIVE: To determine whether synchronous video-based telemedicine visits with specialists are feasible and to evaluate clinical effectiveness, patient perceptions, and other benefits of telemedicine visits for follow-up migraine care in a tertiary headache center.

DESIGN: A one-year, randomized clinical trial.

RESULTS: Fifty patients were screened and 45 entered the study (43 women, two men). Out of 96 scheduled visits, 89 were successfully conducted using telemedicine. Eighteen patients (out of 22) in the telemedicine cohort and 12 patients (out of 23) in the in-office cohort completed the study. In this small study, clinical outcomes, namely improvement in MIDAS, number of headache days, and average severity at 12 months for participants in the telemedicine group, were not different from those in the in-office group. Convenience was rated higher and visit times were shorter in the telemedicine group.

CONCLUSIONS: In this cohort of patients with severe migraine-related disability, telemedicine was a feasible mode of treatment and an effective alternative to in-office visits for follow-up migraine care. Physician productivity could be higher with telemedicine, and patients may get better access because of its convenience.

TRIAL REGISTRATION: This study is listed on ClinicalTrials.gov (NCT01706003).

HEADACHE and MIGRAINE (Continued)

Complementary and Integrative Health Treatments for Migraine.

Patel PS[1], Minen MT.

J Neuroophthalmol. **2019 Sep**;39(3):360-369. doi: 10.1097/WNO.0000000000000841. PMID: 31403967.

BACKGROUND: Migraine is a chronic disabling neurologic condition that can be treated with a combination of both pharmacologic and complementary and integrative health options.

EVIDENCE ACQUISITION: With the growing interest in the US population in the use of nonpharmacologic treatments, we reviewed the evidence for supplements and behavioral interventions used for migraine prevention.

RESULTS: Supplements reviewed included vitamins, minerals, and certain herbal preparations. Behavioral interventions reviewed included cognitive behavioral therapy, biofeedback, relaxation, the third-wave therapies, acupuncture, hypnosis, and aerobic exercise.

CONCLUSIONS: This article should provide an appreciation for the wide range of nonpharmacologic therapies that might be offered to patients in place of or in addition to migraine-preventive medications.

CHRONIC PAIN

Comorbidity Profiles Identified in Older Primary Care Patients Who Attempt Suicide.

Morin RT[1], Li Y[1,2], Mackin RS[1,3], Whooley MA[4], Conwell Y[5], Byers AL[1,6].

J Am Geriatr Soc. **2019 Aug 30**. doi: 10.1111/jgs.16126. PMID: 31469184. [Epub ahead of print]

OBJECTIVES: To identify comorbidity profiles of older patients last seen in primary care before a suicide attempt and assess attempt and clinical factors (eg, means and lethality of attempt) associated with these profiles.

DESIGN: Cohort study and latent class analysis using Department of Veterans Affairs (VA) national data (2012-2014).

SETTING: All VA medical centers in the United States.

PARTICIPANTS: A total of 2131 patients 65 years and older who were last seen by a primary care provider before a first documented suicide attempt.

MEASUREMENTS: Fatal suicide attempt and means were identified using the National Suicide Data Repository. Nonfatal attempt was defined using the National Suicide Prevention Applications Network. Medical and psychiatric diagnoses and other variables were determined from electronic medical records.

RESULTS: Patients (mean age = 74.4 y; 98.2% male) were clustered into five classes based on medical and psychiatric diagnoses: Minimal Comorbidity (23.2%); Chronic Pain-Osteoarthritis (30.1%); Depression-Chronic Pain (22.9%); Depression-Medical Comorbidity (16.5%); and High Comorbidity (7.3%). The patients in the Minimal Comorbidity and Chronic Pain-Osteoarthritis classes were most likely to attempt fatally compared with classes with a higher burden of comorbidities. Overall, 61% of the sample attempted fatally, and 82.5% of suicide decedents used firearms.

CONCLUSION: This study provides evidence that most comorbidity profiles (>50%) in primary care patients attempting suicide were characterized by minimal depression diagnoses and fatal attempts, mostly with firearms. These findings suggest that more than a depression diagnosis contributes to risk and that conversations about firearm safety by medical providers may play an important role in suicide intervention and prevention.

CHRONIC PAIN (Continued)

Academic Detailing to Improve Opioid Safety: Implementation Lessons from a Qualitative Evaluation.

Midboe AM[1], Wu J[1], Erhardt T[1], Carmichael JM[2], Bounthavong M[3], Christopher MLD[4], Gale RC[1].

Pain Med. **2018 Sep 1**;19(suppl_1):S46-S53. doi: 10.1093/pm/pny085. PMID: 30203010.

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

Objective: Academic detailing (AD) is a promising intervention to address the growing morbidity and mortality associated with opioids. While AD has been shown to be effective in improving provider prescribing practices across a range of conditions, it is unclear how best to implement AD. The present study was designed to identify key lessons for implementation based on a model AD program in the Veterans Health Administration (VA).

Design: Qualitative process evaluation using semistructured interviews.

Setting: Seven VA health care systems in the Sierra Pacific region.

Subjects: Current and former academic detailers (N = 10) and VA providers with varying exposure to AD (high, low, or no; N = 20).

Methods: Semistructured interviews were audio-recorded and transcribed. We used a team-based, mixed inductive and deductive approach guided by the Consolidated Framework for Implementation Research.

Results: Key lessons identified by academic detailers and providers coalesced around key themes: 1) one-on-one sessions customized to the provider's patient population are most useful; 2) leadership plays a critical role in supporting providers' participation in AD programs; 3) tracking academic detailer and provider performance is important for improving performance for both groups; 4) academic detailers play a key role in motivating provider behavior change and thus training in Motivational Interviewing is highly valuable; and 5) academic detailers noted that networking is important for sharing implementation strategies and resources.

Conclusions: Identifying and incorporating these key lessons into the implementation of complex interventions like AD are critical to facilitating uptake of evidence-based interventions addressing the opioid epidemic.

Physical activity, sedentary behaviour, physical fitness, and cognitive performance in women with fibromyalgia who engage in reproductive and productive work: the al-Ándalus project.

Álvarez-Gallardo IC[1,2], Estévez-López F[3], Torres-Aguilar XC[4], Segura-Jiménez V[5,6], Borges-Cosic M[4], Soriano-Maldonado A[7,8], Camiletti-Moirón D[5,6], García-Rodríguez IC[4], Munguía-Izquierdo D[9,10], Sierras-Robles Á[11], Delgado-Fernández M[4], Girela-Rejón MJ[12].

Clin Rheumatol. **2019 Aug 29**. doi: 10.1007/s10067-019-04750-8. PMID: 31468225. [Epub ahead of print]

INTRODUCTION/OBJECTIVES: Reproductive labour refers to activities and tasks directed at caregiving and domestic roles, such as cleaning, cooking, and childcare. Productive labour refers to activities that involve economic remuneration. The aim of the present study was to analyse physical activity, sedentary behaviour, physical fitness, and cognitive performance in women with fibromyalgia who engaged, or did not engage, in productive work.

METHOD: This cross-sectional study comprised 276 women with fibromyalgia from Andalusia (southern of Spain). Levels of physical activity (light, moderate, and vigorous) and sedentary behaviour were measured by an accelerometer. Physical fitness and cognitive performance were measured with a battery of performance-based tests.

RESULTS: More hours/week of homemaker-related tasks were associated with higher time spend in light physical activity and lower sedentary behaviour ($P < 0.001$ and $P < 0.05$, respectively). Furthermore, in comparison with those who only engaged in reproductive labour, women with fibromyalgia who engaged in productive work showed lower levels of sedentary behaviour and higher levels of light and moderate physical activity, physical fitness (except muscular strength), and cognitive performance (all, $P < 0.05$).

CONCLUSIONS: Altogether, our findings suggest that productive work is consistently related to better physical and cognitive functioning in women with fibromyalgia. If future research corroborates causality of our findings, then, to maintain women with fibromyalgia engaging in productive work may be strived for not only because of societal or economic reasons but also for better health. However, we should keep in mind that people with fibromyalgia have a chronic condition, and therefore, adaptations at the workplace are imperative. Key Points • Women with fibromyalgia, who spend more time in reproductive labour, have higher levels of light physical activity and lower sedentary behaviour; however, it is associated with poorer general health (as lower physical fitness or cognitive performance). • Household tasks are often seen as a responsibility associated with the gender roles that women with fibromyalgia perform, despite the feelings of incapacity they cause. Policies focused on reducing reproductive labour demands for fibromyalgia patients (i.e. social help on housework or childcare) might facilitate the inclusion of daily active behaviours. • People with fibromyalgia who engage in productive work seem to have better health outcomes than those who have not; however, we cannot forget that adaptations and flexibility at the workplace are imperative.

CHRONIC PAIN (Continued)

Machine Learning to Understand the Immune-Inflammatory Pathways in Fibromyalgia.

Andrés-Rodríguez L[1,2,3,4], Borràs X[1,4], Feliu-Soler A[5,6,7,8], Pérez-Aranda A[9,10,11], Rozadilla-Sacanell A[12], Arranz B[13], Montero-Marin J[3], García-Campayo J[3,14], Angarita-Osorio N[1,2], Maes M[15], Luciano JV[16,17,18].

Int J Mol Sci. **2019 Aug 29**;20(17). pii: E4231. doi: 10.3390/ijms20174231. PMID: 31470635.

Fibromyalgia (FM) is a chronic syndrome characterized by widespread musculoskeletal pain, and physical and emotional symptoms. Although its pathophysiology is largely unknown, immune-inflammatory pathways may be involved. We examined serum interleukin (IL)-6, high sensitivity C-reactive protein (hs-CRP), CXCL-8, and IL-10 in 67 female FM patients and 35 healthy women while adjusting for age, body mass index (BMI), and comorbid disorders. We scored the Fibromyalgia Severity Score, Widespread Pain Index (WPI), Symptom Severity Scale (SSS), Hospital Anxiety (HADS-A), and Depression Scale and the Perceived Stress Scale (PSS-10). Clinical rating scales were significantly higher in FM patients than in controls. After adjusting for covariates, IL-6, IL-10, and CXCL-8 were lower in FM than in HC, whereas hs-CRP did not show any difference. Binary regression analyses showed that the diagnosis FM was associated with lowered IL-10, quality of sleep, aerobic activities, and increased HADS-A and comorbidities. Neural networks showed that WPI was best predicted by quality of sleep, PSS-10, HADS-A, and the cytokines, while SSS was best predicted by PSS-10, HADS-A, and IL-10. Lowered levels of cytokines are associated with FM independently from confounders. Lowered IL-6 and IL-10 signaling may play a role in the pathophysiology of FM.

IRRITABLE BOWEL SYNDROME

Probiotics in Irritable Bowel Syndrome: An Up-to-Date Systematic Review.

Dale HF[1,2,3], Rasmussen SH[4], Asiller ÖÖ[4,5], Lied GA[4,6,7].

Nutrients. **2019 Sep 2**;11(9). pii: E2048. doi: 10.3390/nu11092048. PMCID: PMC6769995. PMID: 31480656.

Irritable bowel syndrome (IBS) is a frequent functional gastrointestinal disorder, and alterations in the gut microbiota composition contributes to symptom generation. The exact mechanisms of probiotics in the human body are not fully understood, but probiotic supplements are thought to improve IBS symptoms through manipulation of the gut microbiota. The aim of this systematic review was to assess the latest randomized controlled trials (RCTs) evaluating the effect of probiotic supplementation on symptoms in IBS patients. A literature search was conducted in Medline (PubMed) until March 2019. RCTs published within the last five years evaluating effects of probiotic supplements on IBS symptoms were eligible. The search identified in total 35 studies, of which 11 met the inclusion criteria and were included in the systematic review. Seven studies (63.6%) reported that supplementation with probiotics in IBS patients significantly improved symptoms compared to placebo, whereas the remaining four studies (36.4%) did not report any significant improvement in symptoms after probiotic supplementation. Of note, three studies evaluated the effect of a mono-strain supplement, whereas the remaining eight trials used a multi-strain probiotic. Overall, the beneficial effects were more distinct in the trials using multi-strain supplements with an intervention of 8 weeks or more, suggesting that multi-strain probiotics supplemented over a period of time have the potential to improve IBS symptoms.

OTHER RESEARCH OF INTEREST

High-precision plasma β-amyloid 42/40 predicts current and future brain amyloidosis.

Schindler SE[1], Bollinger JG[1], Ovod V[1], Mawuenyega KG[1], Li Y[1], Gordon BA[1], Holtzman DM[1], Morris JC[1], Benzinger TLS[1], Xiong C[1], Fagan AM[1], Bateman RJ[2].

Neurology. **2019 Aug 1**. pii: 10.1212/WNL.0000000000008081. doi: 10.1212/WNL.0000000000008081. PMID: 31371569. [Epub ahead of print]

OBJECTIVE: We examined whether plasma β-amyloid (Aβ)42/Aβ40, as measured by a high-precision assay, accurately diagnosed brain amyloidosis using amyloid PET or CSF p-tau181/Aβ42 as reference standards.

METHODS: Using an immunoprecipitation and liquid chromatography-mass spectrometry assay, we measured Aβ42/Aβ40 in plasma and CSF samples from 158 mostly cognitively normal individuals that were collected within 18 months of an amyloid PET scan.

RESULTS: Plasma Aβ42/Aβ40 had a high correspondence with amyloid PET status (receiver operating characteristic area under the curve [AUC] 0.88, 95% confidence interval [CI] 0.82-0.93) and CSF p-tau181/Aβ42 (AUC 0.85, 95% CI 0.79-0.92). The combination of plasma Aβ42/Aβ40, age, and *APOE* ε4 status had a very high correspondence with amyloid PET (AUC 0.94, 95% CI 0.90-0.97). Individuals with a negative amyloid PET scan at baseline and a positive plasma Aβ42/Aβ40 (<0.1218) had a 15-fold greater risk of conversion to amyloid PET-positive compared to individuals with a negative plasma Aβ42/Aβ40 (p = 0.01).

CONCLUSIONS: Plasma Aβ42/Aβ40, especially when combined with age and *APOE* ε4 status, accurately diagnoses brain amyloidosis and can be used to screen cognitively normal individuals for brain amyloidosis. Individuals with a negative amyloid PET scan and positive plasma Aβ42/Aβ40 are at increased risk for converting to amyloid PET-positive. Plasma Aβ42/Aβ40 could be used in prevention trials to screen for individuals likely to be amyloid PET-positive and at risk for Alzheimer disease dementia.

CLASSIFICATION OF EVIDENCE: This study provides Class II evidence that plasma Aβ42/Aβ40 levels accurately determine amyloid PET status in cognitively normal research participants.

A Mechanical Brain Damage Framework Used to Model Abnormal Brain Tau Protein Accumulations of National Football League Players.

Horstemeyer MF[1,2,3], Berthelson PR[4,5], Moore J[6,4], Persons AK[6,4], Dobbins A[7], Prabhu RK[4,5].

Ann Biomed Eng. **2019 Aug 1**. doi: 10.1007/s10439-019-02294-1. PMID: 31372858. [Epub ahead of print]

A mechanics-based brain damage framework is used to model the abnormal accumulation of hyperphosphorylated p-tau associated with chronic traumatic encephalopathy within the brains of deceased National Football League (NFL) players studied at Boston University and to provide a framework for understanding the damage mechanisms. p-tau damage is formulated as the multiplicative decomposition of three independently evolving damage internal state variables (ISVs): nucleation related to number density, growth related to the average area, and coalescence related to the nearest neighbor distance. The ISVs evolve under different rates for three well known mechanical boundary conditions, which in themselves introduce three different rates making a total of nine scenarios, that we postulate are related to brain damage progression: (1) monotonic overloads, (2) cyclic fatigue which corresponds to repetitive impacts, and (3) creep which is correlated to damage accumulation over time. Different NFL player positions are described to capture the different types of damage progression. Skill position players, such as quarterbacks, are expected to exhibit a greater p-tau protein accumulation during low cycle fatigue (higher amplitude impacts with a lesser number), and linemen who exhibit a greater p-tau protein accumulation during high cycle fatigue (lower amplitude impacts with a greater number of impacts). This mechanics-based damage framework presents a foundation for developing a multiscale model for traumatic brain injury that combines mechanics with biology.

OTHER RESEARCH OF INTEREST (Continued)

Stimulation-induced side effects after Deep Brain Stimulation - a systematic review.

Zarzycki MZ[1], Domitrz I[1].

Acta Neuropsychiatr. **2019 Aug 27**:1-24. doi: 10.1017/neu.2019.35. PMID: 31452489. [Epub ahead of print]

OBJECTIVE: Deep Brain Stimulation (DBS) was approved by Food and Drug Administration for Parkinson's Disease, essential tremor, primary generalized or segmental dystonia and obsessive-compulsive disorder treatment. The exact mechanism of DBS remains unclear which causes side effects. The aim of this review was to assess variables causing stimulation-induced chronic psychiatric/ personality-changing side effects.

METHODS: The analysis of scientific database (PubMed, Cochrane Library, EMBASE) was conducted. The included articles had to be research study or case report and DBS to be conducted in therapeutic purposes. The researches with mental disorders in patients' medical histories were excluded.

RESULTS: 17 articles were used in the review. In the group of movement disorders the characteristic of side effects was strongly related to the placement of the electrode implantation. Tiredness/ fatigue was correlated with DBS in thalamus. Implantations in subthalamic nucleus were mostly followed by affective side effects such as depression or suicide. The higher voltage of electrode was connected with more severe depression after implantation. The analysis of affective disorder contained only 3 articles – 2 about obsessive-compulsive disorder and 1 about depression. Forgetfulness and word-finding problems as activities connected with cognition may be an inevitable side effect if obsessive thoughts are to be inhibited.

CONCLUSION: DBS of subthalamic nucleus should be seen as the most hazardous place of implantation. As a result there is a strong need of "gold standards" based on the connectivity research and closer cooperation of scientists and clinicians.

Nonorgan manifestations of sarcoidosis.

Tavee J[1,2], Culver D[3].

Curr Opin Pulm Med. **2019 Sep**;25(5):533-538. doi: 10.1097/MCP.0000000000000597. PMID: 31365388.

PURPOSE OF REVIEW: The current review discusses the diagnosis and management of nonorgan-related symptoms that commonly arise in the setting of systemic sarcoidosis. Fatigue, small fiber neuropathy (SFN) and neuropsychological symptoms are highlighted.

RECENT FINDINGS: The debilitating effects of chronic nonorgan-based symptoms in sarcoidosis have led to recent studies focusing on incidence rates, contributing factors and potential therapeutic strategies. In a web-based survey of over 1000 sarcoidosis patients, the most common symptom was fatigue, which was reported by over 90% of participants, whereas memory loss and concentration problems were reported in 50%. SFN was also common, and may be diagnosed with tools such as skin biopsy measurement of intraepidermal nerve fibers and corneal confocal microscopy. In a recent cohort study of SFN patients, serologic evaluation demonstrated other contributing causes such as diabetes and vitamin B12 deficiency, which warrant-specific treatment. Finally, physical inactivity in patients with sarcoidosis correlated with lower quality-of-life (QOL) scores and possibly fatigue. Multidisciplinary programs that include physical therapy, patient education and psychological support were found to improve fatigue and mood disorders.

SUMMARY: Recognition of nonorgan-related symptoms and their impact on patient QOL is essential to optimal treatment of the sarcoidosis patient.

OTHER RESEARCH OF INTEREST (Continued)

Indications for treatment of sarcoidosis.

Nunes H[1,2], Jeny F[1,2], Bouvry D[1,2], Uzunhan Y[1,2], Valeyre D[1,2].

Curr Opin Pulm Med. **2019 Sep**;25(5):505-518. doi: 10.1097/MCP.0000000000000604. PMID: 31365385.

PURPOSE OF REVIEW: To describe the current knowledge on indications for sarcoidosis treatment.

RECENT FINDINGS: Despite the lack of evidence-based recommendations, the sarcoidosis community has adopted the concept of starting systemic anti-inflammatory treatment because of potential danger (risk of severe dysfunction on major organs or death) or unacceptable impaired quality of life (QoL). On the contrary, while QoL and functionality are patients' priorities, few studies have evaluated treatment effect on patient-reported outcomes. The awareness of long-term corticosteroids toxicities and consequences on QoL and the emergence of novel drugs have changed therapeutic management. Second-line therapy, mainly methotrexate and azathioprine, are indicated for corticosteroids sparing or corticosteroids-resistant sarcoidosis. TNF-α inhibitors are a useful third-line therapy in chronic refractory disease. In addition to organ-targeted treatment, efforts should also be taken for treating nonorgan-specific symptoms, such as physical training for fatigue, and various disease complications.

SUMMARY: Clinicians should offer a tailored treatment for each patient and ensure a holistic multidisciplinary approach, including pharmacological and nonpharmacological interventions. Patient-centered communication is critical to drive shared decisions, in particular for the tricky situation of isolated impaired QoL as the unique therapeutic indication. Once treatment is decided, clinicians should define a clear therapeutic plan, including goals and instruments to assess response.

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