GULF WAR ILLNESS

Gulf War and Health: Treatment for Chronic Multisymptom Illness.

National Academy of Sciences **Review**

Mil Med. 2017 Jan;182(1):1449-1450. doi: 10.7205/MILMED-D-16-00325.

Foreword: Despite our overwhelming victory of the Persian Gulf War in 1991 more than 25 years ago, it is troubling that many of its veterans continue to have disturbing and disabling symptoms associated with that experience. Research has not been able to establish a unifying pathophysiological explanation for these symptoms, yet it is undeniable that these symptoms are occurring. This article summarizes a report from the Institute of Medicine of the National Academies of Sciences, Engineering, and Medicine that reviews the literature relating to various modalities to treat these perplexing symptoms. The report makes it clear that no single approach is best; rather the approach needs to be individualized, integrated, comprehensive, and team based. The report calls for additional training for clinicians at the Department of Veterans Affairs to help these veterans and for additional research especially aimed at improving therapeutic methods. Readers are encouraged to read this report to enrich their understanding of the complexities of the military combat experience. —Frederick Erdtmann, MD,MPH, Former Director, Board on the Health of Select Populations, National Academies of Sciences, Engineering, and Medicine

CHRONIC FATIGUE SYNDROME

1. Identifying Key Symptoms Differentiating Myalgic Encephalomyelitis and Chronic Fatigue Syndrome from Multiple Sclerosis.

   Ohanian D, Brown A, Sunnquist M, Furst J, Nicholson L, Klebek L, Jason LA.

   Neurology (ECronicon). 2016;4(2):41-45.

   It is unclear what key symptoms differentiate Myalgic Encephalomyelitis (ME) and Chronic Fatigue syndrome (CFS) from Multiple Sclerosis (MS). The current study compared self-report symptom data of patients with ME or CFS with those with MS. The self-report data is from the DePaul Symptom Questionnaire, and participants were recruited to take the questionnaire online. Data were analyzed using a machine learning technique called decision trees. Five symptoms best differentiated the groups. The best discriminating symptoms were from the immune domain (i.e., flu-like symptoms and tender lymph nodes), and the trees correctly categorized MS from ME or CFS 81.2% of the time, with those with ME or CFS having more severe symptoms. Our findings support the use of machine learning to further explore the unique nature of these different chronic diseases.

CHRONIC FATIGUE SYNDROME (Continued)

2. Metabolic profiling of a myalgic encephalomyelitis/chronic fatigue syndrome discovery cohort reveals disturbances in fatty acid and lipid metabolism.

Germain A, Ruppert D, Levine SM, Hanson MR.

Mol Biosyst. 2017 Jan 6. doi: 10.1039/c6mb00600k. [Epub ahead of print]

Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) remains a continuum spectrum disease without biomarkers or simple objective tests, and therefore relies on a diagnosis from a set of symptoms to link the assortment of brain and body disorders to ME/CFS. Although recent studies show various affected pathways, the underlying basis of ME/CFS has yet to be established. In this pilot study, we compare plasma metabolic signatures in a discovery cohort, 17 patients and 15 matched controls, and explore potential metabolic perturbations as the aftermath of the complex interactions between genes, transcripts and proteins. This approach to examine the complex array of symptoms and underlying foundation of ME/CFS revealed 74 differentially accumulating metabolites, out of 361 ($P < 0.05$), and 35 significantly altered after statistical correction ($Q < 0.15$). The latter list includes several essential energy-related compounds which could theoretically be linked to the general lack of energy observed in ME/CFS patients. Pathway analysis points to a few pathways with high impact and therefore potential disturbances in patients, mainly taurine metabolism and glycerophospholipid metabolism, combined with primary bile acid metabolism, as well as glyoxylate and dicarboxylate metabolism and a few other pathways, all involved broadly in fatty acid metabolism. Purines, including ADP and ATP, pyrimidines and several amino acid metabolic pathways were found to be significantly disturbed. Finally, glucose and oxaloacetate were two main metabolites affected that have a major effect on sugar and energy levels. Our work provides a prospective path for diagnosis and understanding of the underlying mechanisms of ME/CFS.

3. Treatment and management of Chronic Fatigue Syndrome/Myalgic Encephalomyelitis: all roads lead to Rome.

Castro-Marrero J, Sáez-Francàs N, Santillo D, Alegre J.

Br J Pharmacol. 2017 Jan 4. doi: 10.1111/bph.13702. [Epub ahead of print] **Review**.

This comprehensive review explores the current evidence on benefits and harms of therapeutic interventions in Chronic Fatigue Syndrome/Myalgic Encephalomyelitis (CFS/ME) and makes recommendations. CFS/ME is a complex, multi-system, chronic medical condition whose pathophysiology remains unknown. No established diagnostic tests exist; nor are any FDA-approved drugs available for treatment. Because of the range of symptoms of CFS/ME, treatment approaches vary widely. Studies undertaken have heterogeneous designs and are limited by sample size, length of follow-up, applicability and methodological quality. The use of rintatolimod and rituximab as well as counselling, behavioural and rehabilitation therapy programs may be of benefit for CFS/ME, but the evidence of their effectiveness is still limited. Similarly, adaptive pacing appears to offer some benefits, but the results are debatable: so is the use of nutritional supplements, which may be of value to CFS/ME patients with lab-proven deficiencies. To summarize, then, the recommended treatment strategies should include proper administration of nutritional supplements in CFS/ME patients with demonstrated deficiencies and personalized pacing programs to relieve symptoms and improve performance of daily activities, but a larger RCT evaluation is required to confirm these preliminary observations. At present no firm conclusions can be drawn because the few RCTs undertaken to date have been small-scale, with a high risk of bias, and have used different case definitions. Further RCTs are now urgently needed with rigorous experimental designs and appropriate data analysis, focusing particularly on the comparison of outcomes measures according to clinical presentation, patient characteristics, case criteria and degree of disability (i.e., severely ill ME cases or bedridden).

HEADACHE MIGRAINE

1. Plasma Levels of Cyclooxygenase-2 (COX-2) and Visfatin During Different Stages and Different Subtypes of Migraine Headaches.

   Li C, Zhu Q, He Q, Wang J, Wang F, Zhang H.

   Med Sci Monit. 2017 Jan 3;23:24-28.

BACKGROUND The aim of this study was to determine the plasma levels of cyclooxygenase-2 (COX-2) and visfatin in different stages and different subtypes of migraine headaches compared to a control group to elucidate the pathological mechanisms involved.

MATERIAL AND METHODS We recruited a case-control cohort of 182 adult migraine patients and 80 age-matched and gender-matched healthy controls. The migraine patients were divided into two groups: the headache-attack-period group (Group A, n=77) and the headache-free-period group (Group B, n=105). The two groups were further divided into subgroups according to whether they had aura symptoms. Solid phase double antibody sandwich enzyme-linked immunosorbent assay (ELISA) was used to measure the plasma levels of COX-2 and visfatin. Statistical analysis was performed using SPSS 17.0.

RESULTS The plasma levels of COX-2 and visfatin in the headache-attack-period group were significantly higher than in the headache-free-period group and the control group; there were no significant differences between the headache-free group and the control group. There were no significant differences in plasma levels of COX-2 and visfatin between the subgroups: headache-attack-period with aura subgroup and the headache-attack-period without aura sub group.

CONCLUSIONS COX-2 and visfatin participated in the pathogenesis of migraine headaches. The presence of aura had no effect on the serum levels of COX-2 and visfatin.

2. Episodic status migrainosus: A novel migraine subtype.

   Singh TD, Cutrer FM, Smith JH.

   Cephalalgia. 2017 Jan 1:333102416686341. doi: 10.1177/0333102416686341. [Epub ahead of print]

OBJECTIVE: To report a case series of a novel migraine subtype, which we term as episodic status migrainosus (ESM), characterized by attacks of migraine exclusively lasting more than 72 hours. We hypothesized that this would represent a novel nosologic entity, possibly an unstable migraine phenotype with a high conversion rate to chronic migraine (CM).

METHODS: We conducted a retrospective review of patients diagnosed with status migrainosus at the Mayo Clinic, Rochester, between January 2005 and December 2015. All the records were then manually reviewed for patients with migraine headaches exclusively lasting more than 72 hours.

RESULTS: We identified 18 patients with ESM, with a female predominance (15(83.3%)) and a median age of onset of 16.5 (IQR 13-19) years. The median monthly attack frequency was two (IQR 1-3), with each attack lasting a median duration of seven (IQR 4-12.5) days. Stress was the most commonly reported precipitant (11 (61.1%)). Migraine with aura was common (10 (55.6%)), as was comorbid depression (10 (55.6%)). Fifteen (83.3%) patients developed CM at a median of 7.8 (IQR 2.6-21.9) years from their first attack. There was no significant association between the time to the development of chronic migraine with either attack frequency or duration and relevance.

CONCLUSIONS: We report the existence of a novel migraine subtype, episodic status migrainosus. This migraine subtype appears to have similar clinical characteristics to episodic migraine with or without aura, except for a notably high tendency to progress to chronic migraine.

HEADACHE MIGRAINE (Continued)

3. A double- blind, randomized, and placebo-controlled clinical trial with omega-3 polyunsaturated fatty acids (OPFA ω-3) for the prevention of migraine in chronic migraine patients using amitriptyline.

   Soares AA, Louçana PM, Nasi EP, Sousa KM, Sá OM, Silva-Néto RP.

   Nutr Neurosci. 2017 Jan 5:1-5. doi: 10.1080/1028415X.2016.1266133. [Epub ahead of print]

OBJECTIVE: To determine the prophylactic effect of OPFAϖ-3 in migraine.

SUBJECTS AND METHODS: This was a prospective, experimental, controlled, double-blind, and with comparison groups study. Sixty patients diagnosed with chronic migraine, according to the criteria of the International Classification of Headache Disorders, Third Edition (beta version) (ICHD-3β), were prophylactically treated with amitriptyline. They were divided into two equal groups: in group 1, prophylaxis was associated with OPFAϖ-3 and in group 2 with placebo. After 60 days, both groups were assessed by a second researcher.

RESULTS: Of the 60 patients with chronic migraine, only 51 patients (15 men and 36 women) completed the treatment. The group that received OPFAϖ-3 consisted of 27 (52.9%) patients (six men and 21 women), while the control group was equal to 24 (47.1%) patients (nine men and 15 women). These differences were not significant ($\chi^2 = 1.428$; $P = 0.375$). In 66.7% (18/27) of the patients who used OPFAϖ-3, there was a reduction of more than 80.0% per month in the number of days of headache, while in the control group, the same improvement occurred in 33.3% (8/24) of patients. This difference was significant ($\chi^2 = 5.649$; $P = 0.036$).

CONCLUSIONS: Polyunsaturated omega 3 fatty acids (OPFAϖ-3) are useful for prophylaxis of migraine attacks.

4. Genome-wide analysis of blood gene expression in migraine implicates immune-inflammatory pathways.

   Gerring ZF, Powell JE, Montgomery GW, Nyholt DR.

   Cephalalgia. 2017 Jan 1:333102416686769. doi: 10.1177/0333102416686769. [Epub ahead of print]

BACKGROUND: Typical migraine is a frequent, debilitating and painful headache disorder with an estimated heritability of about 50%. Although genome-wide association (GWA) studies have identified over 40 single nucleotide polymorphisms associated with migraine, further research is required to determine their biological role in migraine susceptibility. Therefore, we performed a study of genome-wide gene expression in a large sample of 83 migraine cases and 83 non-migraine controls to determine whether altered expression levels of genes and pathways could provide insights into the biological mechanisms underlying migraine.

METHODS: We assessed whole blood gene expression data for 17994 expression probes measured using IlluminaHT-12 v4.0 BeadChips. Differential expression was assessed using multivariable logistic regression. Gene expression probes with a nominal p value < 0.05 were classified as differentially expressed. We identified modules of co-regulated genes and tested them for enrichment of differentially expressed genes and functional pathways using a false discovery rate <0.05.

RESULTS: Association analyses between migraine and probe expression levels, adjusted for age and gender, revealed an excess of small p values, but there was no significant single-probe association after correction for multiple testing. Network analysis of pooled expression data identified 10 modules of co-expressed genes. One module harboured a significant number of differentially expressed genes and was strongly enriched with immune-inflammatory pathways, including multiple pathways expressed in microglial cells.

CONCLUSIONS: These data suggest immune-inflammatory pathways play an important role in the pathogenesis, manifestation, and/or progression of migraine in some patients. Furthermore, gene-expression associations are measurable in whole blood, suggesting the analysis of blood gene expression can inform our understanding of the biological mechanisms underlying migraine, identify biomarkers, and facilitate the discovery of novel pathways and thus determine new targets for drug therapy.

CHRONIC PAIN

1. Intraoperative ketamine reduces immediate postoperative opioid consumption after spinal fusion surgery in chronic pain patients with opioid dependency: A randomized, blinded trial.

   Nielsen RV, Fomsgaard JS, Siegel H, Martusevicius R, Nikolajsen L, Dahl JB, Mathiesen O.

   Pain. 2017 Jan 6. doi: 10.1097/j.pain.0000000000000782. [Epub ahead of print]

Perioperative handling of surgical patients with opioid dependency represents an important clinical problem. Animal studies suggest that ketamine attenuates central sensitization and hyperalgesia and thereby reduces postoperative opioid tolerance. We hypothesized that intraoperative ketamine would reduce immediate postoperative opioid consumption compared to placebo in chronic pain patients with opioid dependency undergoing lumbar spinal fusion surgery. Primary outcome was morphine consumption 0-24 h postoperatively. Secondary outcomes were acute pain at rest and during mobilization 2-24 h postoperatively (VAS), adverse events and persistent pain 6 months postoperatively. One hundred and fifty patients were randomly assigned to intraoperative S-ketamine bolus 0.5 mg/kg and infusion 0.25 mg/kg/h or placebo. Postoperatively patients received their usual opioids, paracetamol and IV Patient Controlled Analgesia (PCA) with morphine. In the final analyses 147 patients were included. PCA IV morphine consumption 0-24 hours postoperatively was significantly reduced in the ketamine group compared to the placebo group: 79 (47) vs 121 (53) mg IV, mean difference 42 mg (95% CI -59 to -25), P<0.001. Sedation was significantly reduced in the ketamine group 6 and 24 h postoperatively. There were no significant differences regarding acute pain, nausea, vomiting, hallucinations or nightmares. Back pain at 6 months postoperatively compared to preoperative pain was significantly more improved in the ketamine group compared to the placebo group, P=0.005. In conclusion, intraoperative ketamine significantly reduced morphine consumption 0-24 h after lumbar fusion surgery in opioid dependent patients. The trend regarding less persistent pain 6 months postoperatively needs further investigation.

2. Analgesic and Anti-Inflammatory Effects of the Novel Semicarbazide-Sensitive Amine-Oxidase Inhibitor SzV-1287 in Chronic Arthritis Models of the Mouse.

   Horváth Á, Menghis A, Botz B, Borbély É, Kemény Á, Tékus V, Csepregi JZ, Mócsai A, Juhász T, Zákány R, Bogdán D, Mátyus P, Keeble J, Pintér E, Helyes Z.

   Sci Rep. 2017 Jan 9;7:39863. doi: 10.1038/srep39863.

Semicarbazide-sensitive amine oxidase (SSAO) catalyses oxidative deamination of primary amines. Since there is no data about its function in pain and arthritis mechanisms, we investigated the effects of our novel SSAO inhibitor SzV-1287 in chronic mouse models of joint inflammation. Effects of SzV-1287 (20 mg/kg i.p./day) were investigated in the K/BxN serum-transfer and complete Freund's adjuvant (CFA)-evoked active immunization models compared to the reference SSAO inhibitor LJP-1207. Mechanonociception was assessed by aesthesiometry, oedema by plethysmometry, clinical severity by scoring, joint function by grid test, myeloperoxidase activity by luminescence, vascular leakage by fluorescence in vivo imaging, histopathological changes by semiquantitative evaluation, and cytokines by Luminex assay. SzV-1287 significantly inhibited hyperalgesia and oedema in both models. Plasma leakage and keratinocyte chemoattractant production in the tibiotarsal joint, but not myeloperoxidase activity was significantly reduced by SzV-1287 in K/BxN-arthritis. SzV-1287 did not influence vascular and cellular mechanisms in CFA-arthritis, but significantly decreased histopathological alterations. There was no difference in the anti-hyperalgesic and anti-inflammatory actions of SzV-1287 and LJP-1207, but only SzV-1287 decreased CFA-induced tissue damage. Unlike SzV-1287, LJP-1207 induced cartilage destruction, which was confirmed in vitro. SzV-1287 exerts potent analgesic and anti-inflammatory actions in chronic arthritis models of distinct mechanisms, without inducing cartilage damage.

CHRONIC PAIN (Continued)

3. The analgesic effects of oxytocin in the peripheral and central nervous system.

   Xin Q, Bai B, Liu W.

   Neurochem Int. 2017 Jan 5. pii: S0197-0186(16)30332-1. doi: 10.1016/j.neuint.2016.12.021. [Epub ahead of print]

Pain is a ubiquitously unpleasant feeling among humans as well as many animal species often caused by actual and potential tissue damage. However, it is absolutely crucial for our survival in many ways. Acute pain can signal the presence of danger or life-threatenting events, which help escape noxious stimuli. By contrast, when pain becomes chronic or persistent, it becomes an encumbrance and exerts deleterious effects to the body and mind, often co-occured with anxiety and depression. Additionaly, chronic pain is more or less an economic burden for the patients because it requires immediate medical treatments and seriously hinders pepople in their work. To date, there has been a lack of breakthrough progress in the pain field, despite huge gains in basic science knowledge obtained using animal models, it is still difficult to develop many new clinically effective analgesic drugs to control pain with long-term effectiveness. Opioids and nonsteroidal anti-inflammatory drugs were introduced for pain management more than a century ago. Those drugs do have proven efficacy in the treatment of pain but the use of them are also significantly limited due to the multiple serious adverse effects (e.g., drug resistance, addiction and gastrointestinal bleeding). In the field of pain relief and treatment, there is a strong impetus to develop and establish novel analgesics that must be safer and more effective to offer significant pain relief for a wide variety of painful conditions. Preliminary evidence suggests that oxytocin might be the ideal candidate as a target for reducing the severity of pain. In this review, we present a summary of the total literature related to the effects of oxytocin on pain modulation in both animals and humans. Better understanding the fundamental physiopharmacology of the actions of oxytocin in pain may highlight novel mechanisms associated with analgesia.

4. Prevention of Chronic Post-Thoracotomy Pain in Rats by Intrathecal Resolvin D1 and D2: Effectiveness of perioperative and delayed drug delivery.

   Wang JC, Strichartz GR.

   J Pain. 2017 Jan 4. pii: S1526-5900(16)30371-6. doi: 10.1016/j.jpain.2016.12.012. [Epub ahead of print]

Thoracotomy results in a high frequency of chronic post-operative pain. Resolvins are endogenous molecules, synthesized and released by activated immune cells, effective against inflammatory and neuropathic pain. Different resolvins have differential actions on selective neuronal and glial receptors and enzymes. This paper examines the ability of intrathecal Resolvin D1 (RvD1) and Resolvin D2 (RvD2) to reduce chronic post-thoracotomy pain in rats. Thoracotomy, involving intercostal incision and rib retraction, resulted in a decrease in the mechanical force threshold to induce nocifensive behavior, an enlargement of the pain-sensitive area, and an increase in the fraction of rats showing nocifensive behavior, all for at least 5 weeks. The qualitative nature of the behavioral responses to tactile stimulation changed dramatically after thoracotomy, including the appearance of vigorous behaviors, such as turning, shuddering, and squealing, all absent in naive rats. Intrathecal delivery of RvD1 (30ng/30μL), at surgery or 4 days later, halved the spread of the mechano-sensitive area, lowered by 60% the percent of rats with tactile hypersensitivity, and reduced the drop in threshold for a nocifensive response, along with a reduction in the occurrence of vigorous nocifensive responses. RvD2's actions on threshold changes were statistically the same. These findings suggest that intrathecal resolvins, delivered pre-operatively or several days later, can prevent chronic post-operative hyperalgesia.

PERSPECTIVE: In studies of rats, the injection of the pro-resolving compounds of the Resolvin-D series into spinal fluid, before or just after thoracotomy surgery, prevents the occurrence of acute and chronic pain. If these chemicals, which have shown no side-effects, were used in humans it might greatly reduce chronic post-operative pain.

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