GULF WAR ILLNESS

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

CHRONIC FATIGUE SYNDROME

Cellular Immune Function in Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS).

Cliff JM[1], King EC[1], Lee JS[1], Sepúlveda N[1,2], Wolf AS[1], Kingdon C[3], Bowman E[3], Dockrell HM[1], Nacul L[3], Lacerda E[3], Riley EM[1].

Front Immunol. **2019 Apr 16**;10:796. doi: 10.3389/fimmu.2019.00796. PMCID: PMC6477089. PMID: 31057538. eCollection 2019.

Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) is a debilitating condition with unknown aetiology, Myalgic encephalomyelitis unclear pathophysiology and with no diagnostic test or biomarker available. Many patients report their ME/CFS began after an acute infection, and subsequent increased frequency of infections, such as colds or influenza, is common. These factors imply an altered immunological status exists in ME/CFS, in at least a proportion of patients, yet previous studies of peripheral immunity have been discrepant and inconclusive. The UK ME/CFS Biobank, which has collected blood samples from nearly 300 clinically-confirmed ME/CFS patients, enables large-scale studies of immunological function in phenotypically well-characterised participants. In this study, herpes virus serological status and T cell, B cell, NK cell and monocyte populations were investigated in 251 ME/CFS patients, including 54 who were severely affected, and compared with those from 107 healthy participants and with 46 patients with Multiple Sclerosis. There were no differences in seroprevalence for six human herpes viruses between ME/CFS and healthy controls, although seroprevalence for the Epstein-Barr virus was higher in multiple sclerosis patients. Contrary to previous reports, no significant differences were observed in NK cell numbers, subtype proportions or *in vitro* responsiveness between ME/CFS patients and healthy control participants. In contrast, the T cell compartment was altered in ME/CFS, with increased proportions of effector memory $CD8^+$ T cells and decreased proportions of terminally differentiated effector $CD8^+$ T cells. Conversely, there was a significantly increased proportion of mucosal associated invariant T cells (MAIT) cells, especially in severely affected ME/CFS patients. These abnormalities demonstrate that an altered immunological state does exist in ME/CFS, particularly in severely affected people. This may simply reflect ongoing or recent infection, or may indicate future increased susceptibility to infection. Longitudinal studies of ME/CFS patients are needed to help to determine cause and effect and thus any potential benefits of immuno-modulatory treatments for ME/CFS.

Searching for Serum Antibodies to Neuronal Proteins in Patients With Myalgic Encephalopathy/ Chronic Fatigue Syndrome.

Giannoccaro MP[1], Cossins J[2], Sørland K[3], Fluge Ø[3], Vincent A[2].

Clin Ther. **2019 Apr 30**. pii: S0149-2918(19)30163-8. doi: 10.1016/j.clinthera.2019.04.001. PMID: 31053295. [Epub ahead of print]

PURPOSE: A role for the immune system in causing myalgic encephalopathy/chronic fatigue syndrome (ME/CFS) is long suspected, but few studies have looked for specific autoantibodies that might contribute to the symptoms. Our aim was to look for evidence of antibodies to neuronal proteins in patients with ME/CSF.

METHODS: Sera samples from 50 patients and 50 healthy individuals were sent coded to the Neuroimmunology Laboratory in Oxford. Screening for antibody binding to neuronal tissue was performed on brain tissue and neuronal cultures. Specific serum antibodies were assessed by antigen-specific cell-based assays and radioimmunoassays. After antibody testing, the associations between seropositive status and clinical data were investigated.

FINDINGS: Overall, 8 patients and 11 participants were found to have some serum immunoreactivity toward neuronal or neuromuscular junction proteins, but only 1 patient and 2 participants had specific serum antibodies. Nevertheless, seropositive status in patients with ME was associated with shorter duration since onset and a more severe disease.

IMPLICATIONS: The results indicate no overall increased frequency of antibodies to neuronal proteins in ME/CSF and no evidence of a specific antibody that might be causative or contribute to clinical features in patients. However, the association of seropositive status with shorter duration of disease and more severe symptoms suggests a possible role of antibodies at onset in some patients and should be the focus of future studies.

CHRONIC FATIGUE SYNDROME (Continued)

A nanoelectronics-blood-based diagnostic biomarker for myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS).

Esfandyarpour R[1], Kashi A[2], Nemat-Gorgani M[2,3], Wilhelmy J[3], Davis RW[4,3].

Proc Natl Acad Sci U S A. **2019 Apr 29**. pii: 201901274. doi: 10.1073/pnas.1901274116. PMID: 31036648. [Epub ahead of print]

There is not currently a well-established, if any, biological test to diagnose myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS). The molecular aberrations observed in numerous studies of ME/CFS blood cells offer the opportunity to develop a diagnostic assay from blood samples. Here we developed a nanoelectronics assay designed as an ultrasensitive assay capable of directly measuring biomolecular interactions in real time, at low cost, and in a multiplex format. To pursue the goal of developing a reliable biomarker for ME/CFS and to demonstrate the utility of our platform for point-of-care diagnostics, we validated the array by testing patients with moderate to severe ME/CFS patients and healthy controls. The ME/CFS samples' response to the hyperosmotic stressor observed as a unique characteristic of the impedance pattern and dramatically different from the response observed among the control samples. We believe the observed robust impedance modulation difference of the samples in response to hyperosmotic stress can potentially provide us with a unique indicator of ME/CFS. Moreover, using supervised machine learning algorithms, we developed a classifier for ME/CFS patients capable of identifying new patients, required for a robust diagnostic tool.

Myalgia and chronic fatigue syndrome following immunization: macrophagic myofasciitis and animal studies support linkage to aluminum adjuvant persistency and diffusion in the immune system.

Gherardi RK[1], Crépeaux G[2], Authier FJ[3].

Autoimmun Rev. **2019 May 3**. pii: S1568-9972(19)30109-0. doi: 10.1016/j.autrev.2019.05.006. PMID: 31059838. [Epub ahead of print]

Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) is a multifactorial and poorly undersood disabling disease. We present epidemiological, clinical and experimental evidence that ME/CFS constitutes a major type of adverse effect of vaccines, especially those containing poorly degradable particulate aluminum adjuvants. Evidence has emerged very slowly due to the multiplicity, lack of specificity, delayed onset, and frequent medical underestimation of ME/CFS symptoms. It was supported by an epidemiological study comparing vaccinated vs unvaccinated militaries that remained undeployed during Gulf War II. Affected patients suffer from cognitive dysfunction affecting attention, memory and inter-hemispheric connexions, well correlated to brain perfusion defects and associated with a stereotyped and distinctive pattern of cerebral glucose hypometabolism. Deltoid muscle biopsy performed to investigate myalgia typically yields macrophagic myofasciitis (MMF), a histological biomarker assessing longstanding persistency of aluminum agglomerates within innate immune cells at site of previous immunization. MMF is seemingly linked to altered mineral particle detoxification by the xeno/autophagy machinery. Comparing toxicology of different forms of aluminum and different types of exposure is misleading and inadequate and small animal experiments have turned old dogma upside down. Instead of being rapidly solubilized in the extracellular space, injected aluminum particles are quickly captured by immune cells and transported to distant organs and the brain where they elicit an inflammatory response and exert selective low dose long-term neurotoxicity. Clinical observations and experiments in sheep, a large animal like humans, confirmed both systemic diffusion and neurotoxic effects of aluminum adjuvants. Post-immunization ME/CFS represents the core manifestation of "autoimmune/inflammatory syndrome induced by adjuvants" (ASIA).

CHRONIC FATIGUE SYNDROME (Continued)

A Novel Mutation in Slc2a4 as a Mouse Model of Fatigue.

de Groot MHM[1,2], Castorena CM[3], Cox KH[1], Kumar V[1], Mohawk JA[1,2], Ahmed NI[3], Takahashi JS[1,2].

Genes Brain Behav. **2019 May 6**:e12578. doi: 10.1111/gbb.12578. PMID: 31059591. [Epub ahead of print]

Chronic fatigue is a debilitating disorder with widespread consequences, but effective treatment strategies are lacking. Novel genetic mouse models of fatigue may prove invaluable for studying its underlying physiological mechanisms and for testing treatments and interventions. In a screen of voluntary wheel-running behavior in N-ethyl-N-nitrosourea mutagenized C57BL/6J mice, we discovered two lines with low body weights and aberrant wheel-running patterns suggestive of a fatigue phenotype. Affected progeny from these lines had lower daily activity levels and exhibited low amplitude circadian rhythm alterations. Their aberrant behavior was characterized by frequent interruptions and periods of inactivity throughout the dark phase of the light-dark cycle and increased levels of activity during the rest or light phase. Expression of the behavioral phenotypes in offspring of strategic crosses was consistent with a recessive inheritance pattern. Mapping of phenotypic abnormalities showed linkage with a single locus on chromosome 1, and whole exome sequencing identified a single point mutation in the Slc2a4 gene encoding the GLUT4 insulin-responsive glucose transporter. The single nucleotide change (A to T, which we named "twiggy") was in the distal end of exon 10 and resulted in a premature stop (Y440*). Additional metabolic phenotyping confirmed that these mice recapitulate phenotypes found in GLUT4 knockout mice. However, to our knowledge, this is the first time a mutation in this gene has been shown to result in extensive changes in general behavioral patterns. These findings suggest that GLUT4 may be involved in circadian behavioral abnormalities and could provide insights into fatigue in humans.

The 'cognitive behavioural model' of chronic fatigue syndrome: Critique of a flawed model.

Geraghty K[1], Jason L[2], Sunnquist M[2], Tuller D[3], Blease C[4], Adeniji C[1].

Health Psychol Open. **2019 Apr 23**;6(1):2055102919838907. doi: 10.1177/2055102919838907. PMCID: PMC6482658. PMID: 31041108.

Chronic fatigue syndrome/myalgic encephalomyelitis is a debilitating illness that greatly impacts the lives of sufferers. A cognitive behavioural model attempts to explain illness onset and continuance with a hypothesis that the illness is perpetuated by patients' irrational beliefs and avoidance behaviours. This theory underpins the promotion of cognitive behavioural therapy, a treatment that aims to change beliefs and behaviours. This article reports on a detailed review of the cognitive behavioural model. Our review finds that the model lacks high-quality evidential support, conflicts with accounts given by most patients and fails to account for accumulating biological evidence of pathological and physiological abnormalities found in patients. There is little scientific credibility in the claim that psycho-behavioural therapies are a primary treatment for this illness.

Advances in ME/CFS: Past, Present, and Future.

Friedman KJ[1].

Front Pediatr. **2019 Apr 18**;7:131. doi: 10.3389/fped.2019.00131. PMCID: PMC6482157. PMID: 31058116. eCollection 2019.

The forerunner of what is today termed myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) was described by the U.S. Public Health Service in 1934. At the present time, we still do not know its cause and/or how to detect it by routine clinical laboratory tests. In consequence, the pathological nature of ME/CFS has been overlooked and the disease has been stigmatized by being mislabeled as psychosomatic or somatoform illness. Such misperceptions of the disease have led to insufficient research exploration of the disease and minimal to absent patient care. A 2015 Institute of Medicine report on the illness declared ME/CFS a disease affecting up to 2.5 million Americans and chastised the U.S. government for doing little to research the disease and to support its patients. Clinicians who currently treat this disease declare it to be more devastating than HIV/AIDS. A comparison of the histories of the two diseases, an examination of the current status of the two diseases, and a listing of the accomplishments that would be needed for ME/CFS to achieve the same level of treatment and care as currently experienced by patients with HIV/AIDS is provided.

HEADACHE and MIGRAINE

Erenumab in chronic migraine: Patient-reported outcomes in a randomized double-blind study.

Lipton RB[1], Tepper SJ[2], Reuter U[2], Silberstein S[2], Stewart WF[2], Nilsen J[2], Leonardi DK[2], Desai P[2], Cheng S[2], Mikol DD[2], Lenz R[2].

Neurology. **2019 May 7**;92(19):e2250-e2260. doi: 10.1212/WNL.0000000000007452. PMCID: PMC6537129. PMID: 30996060. Epub 2019 Apr 17.

OBJECTIVE: To determine the effect of erenumab, a human monoclonal antibody targeting the calcitonin gene-related peptide receptor, on health-related quality of life (HRQoL), headache impact, and disability in patients with chronic migraine (CM).

METHODS: In this double-blind, placebo-controlled study, 667 adults with CM were randomized (3:2:2) to placebo or erenumab (70 or 140 mg monthly). Exploratory endpoints included migraine-specific HRQoL (Migraine-Specific Quality-of-Life Questionnaire [MSQ]), headache impact (Headache Impact Test-6 [HIT-6]), migraine-related disability (Migraine Disability Assessment [MIDAS] test), and pain interference (Patient-Reported Outcomes Measurement Information System [PROMIS] Pain Interference Scale short form 6b).

RESULTS: Improvements were observed for all endpoints in both erenumab groups at month 3, with greater changes relative to placebo observed at month 1 for many outcomes. All 3 MSQ domains were improved from baseline with treatment differences for both doses exceeding minimally important differences established for MSQ-role function-restrictive (≥3.2) and MSQ-emotional functioning (≥7.5) and for MSQ-role function-preventive (≥4.5) for erenumab 140 mg. Changes from baseline in HIT-6 scores at month 3 were -5.6 for both doses vs -3.1 for placebo. MIDAS scores at month 3 improved by -19.4 days for 70 mg and -19.8 days for 140 mg vs -7.5 days for placebo. Individual-level minimally important difference was achieved by larger proportions of erenumab-treated participants than placebo for all MSQ domains and HIT-6. Lower proportions of erenumab-treated participants had MIDAS scores of severe (≥21) or very severe (≥41) or PROMIS scores ≥60 at month 3.

CONCLUSIONS: Erenumab-treated patients with CM experienced clinically relevant improvements across a broad range of patient-reported outcomes.

CLINICALTRIALSGOV IDENTIFIER: **NCT02066415**.

CLASSIFICATION OF EVIDENCE: This study provides Class II evidence that for patients with CM, erenumab treatment improves HRQoL, headache impact, and disability.

Aberrant interactions of cortical networks in chronic migraine: A resting-state fMRI study.

Coppola G[1], Di Renzo A[1], Petolicchio B[1], Tinelli E [1], Di Lorenzo C[1], Parisi V[2], Serrao M[1], Calistri V[1], Tardioli S[1], Cartocci G[1], Schoenen J[1], Caramia F[1], Di Piero V[1], Pierelli F[1].

Neurology. **2019 May 3**. pii: 10.1212/WNL.0000000000007577. doi: 10.1212/WNL.0000000000007577. PMID: 31053665. [Epub ahead of print]

OBJECTIVE: We investigated resting-state (RS)-fMRI using independent component analysis (ICA) to determine the functional connectivity (FC) between networks in chronic migraine (CM) patients and their correlation with clinical features.

METHODS: Twenty CM patients without preventive therapy or acute medication overuse underwent 3T MRI scans and were compared to a group of 20 healthy controls (HC). We used MRI to collect RS data in 3 selected networks, identified using group ICA: the default mode network (DMN), the executive control network (ECN), and the dorsal attention system (DAS).

RESULTS: Compared to HC, CM patients had significantly reduced functional connectivity between the DMN and the ECN. Moreover, in patients, the DAS showed significantly stronger FC with the DMN and weaker FC with the ECN. The higher the severity of headache, the increased the strength of DAS connectivity, and the lower the strength of ECN connectivity.

CONCLUSION: These results provide evidence for large-scale reorganization of functional cortical networks in chronic migraine. They suggest that the severity of headache is associated with opposite connectivity patterns in frontal executive and dorsal attentional networks.

HEADACHE and MIGRAINE (Continued)

Static and dynamic functional connectivity differences between migraine and persistent post-traumatic headache: A resting-state magnetic resonance imaging study.

Dumkrieger G[1], Chong CD[1], Ross K[2], Berisha V[3], Schwedt TJ[1].

Cephalalgia. **2019 May** 1:333102419847728. doi: 10.1177/0333102419847728. PMID: 31042064. [Epub ahead of print]

INTRODUCTION: Although migraine and persistent post-traumatic headache often share phenotypic characteristics, few studies have interrogated the pathophysiological differences underlying these headache types. While there is now some indication of differences in brain structure between migraine and persistent post-traumatic headache, differences in brain function have not been adequately investigated. The objective of this study was to compare static and dynamic functional connectivity patterns in migraine versus persistent post-traumatic headache using resting-state magnetic resonance imaging.

METHODS: This case-control study interrogated the static functional connectivity and dynamic functional connectivity patterns of 59 a priori selected regions of interest involved in pain processing. Pairwise connectivity (region of interest to region of interest) differences between migraine (n = 33) and persistent post-traumatic headache (n = 44) were determined and compared to healthy controls (n = 36) with ANOVA and subsequent t-tests. Pearson partial correlations were used to explore the relationship between headache burden (headache frequency; years lived with headache) and functional connectivity and between pain intensity at the time of imaging and functional connectivity for migraine and persistent post-traumatic headache groups, separately.

RESULTS: Significant differences in static functional connectivity between migraine and persistent post-traumatic headache were found for 17 region pairs that included the following regions of interest: Primary somatosensory, secondary somatosensory, posterior insula, hypothalamus, anterior cingulate, middle cingulate, temporal pole, supramarginal gyrus, superior parietal, middle occipital, lingual gyrus, pulvinar, precuneus, cuneus, somatomotor, ventromedial prefrontal cortex, and dorsolateral prefrontal cortex. Significant differences in dynamic functional connectivity between migraine and persistent post-traumatic headache were found for 10 region pairs that included the following regions of interest: Secondary somatosensory, hypothalamus, middle cingulate, temporal pole, supramarginal gyrus, superior parietal, lingual gyrus, somatomotor, precentral, posterior cingulate, middle frontal, fusiform gyrus, parieto-occiptal, and amygdala. Although there was overlap among the regions demonstrating static functional connectivity differences and those showing dynamic functional connectivity differences between persistent post-traumatic headache and migraine, there was no overlap in the region pair functional connections. After controlling for sex and age, there were significant correlations between years lived with headache with static functional connectivity of the right dorsolateral prefrontal cortex with the right ventromedial prefrontal cortex in the migraine group and with static functional connectivity of right primary somatosensory with left supramarginal gyrus in the persistent post-traumatic headache group. There were significant correlations between headache frequency with static functional connectivity of left secondary somatosensory with right cuneus in the migraine group and with static functional connectivity of left middle cingulate with right pulvinar and right posterior insula with left hypothalamus in the persistent post-traumatic headache group. Dynamic functional connectivity was significantly correlated with headache frequency, after controlling for sex and age, in the persistent post-traumatic headache group for one region pair (right middle cingulate with right supramarginal gyrus). Dynamic functional connectivity was correlated with pain intensity at the time of imaging for the migraine cohort for one region pair (right posterior cingulate with right amygdala).

CONCLUSIONS: Resting-state functional imaging revealed static functional connectivity and dynamic functional connectivity differences between migraine and persistent post-traumatic headache for regions involved in pain processing. These differences in functional connectivity might be indicative of distinctive pathophysiology associated with migraine versus persistent post-traumatic headache.

Adherence to the 2008 IHS guidelines for controlled trials of drugs for the preventive treatment of chronic migraine in adults.

Deen M[1], Martinelli D[2,3], Pijpers J[4], Diener HC[5], Silberstein S[6], Ferrari MD[4], Ashina M[1], Tassorelli C[2,3], Yuan H[6].

Cephalalgia. **2019 May 1**:333102419847751. doi: 10.1177/0333102419847751. PMID: 31042062. [Epub ahead of print]

INTRODUCTION: Since the definition of chronic migraine as a new disease entity in 2004, numerous clinical trials have examined the efficacy of preventive treatments in chronic migraine. Our aim was to assess the adherence of these trials to the Guidelines of the International Headache Society published in 2008.

METHODS: We searched PubMed for controlled clinical trials investigating preventive treatment for chronic migraine in adults designed after the release of the Guidelines and published until December 2017. Trial quality was evaluated with a 13-item scoring system enlisting essential recommendations adapted from the Guidelines.

RESULTS: Out of 3352 retrieved records, we included 16 papers in the analysis dealing with pharmacological treatment of chronic migraine. The median score was 6.5 (range 2-13). All trials were randomized, the large majority (81.25%) were placebo-controlled and double-blinded (87.5%). Adherence was lowest on i) a priori definition of outcomes (31.25%), ii) primary endpoint definition (37.5%%) and iii) trial registration (37.5%).

DISCUSSION: Most clinical trials adhered to the recommendations of the IHS, whereas adherence to migraine-specific recommendations was lower. Greater awareness and adherence to the guidelines are essential to improve the quality of clinical trials, validity of publications and the generalizability of the results.

CHRONIC PAIN

Marked Increases in Resting-State MEG Gamma-Band Activity in Combat-Related Mild Traumatic Brain Injury.

Huang MX[1,2], Huang CW[3], Harrington DL[1,2], Nichols S[4], Robb-Swan A[1,2], Angeles-Quinto A[1,2], Le L[5], Rimmele C[5], Drake A[6], Song T [2], Huang JW[7], Clifford R[1,8,9], Ji Z[2], Cheng CK[10], Lerman I[1], Yurgil KA[1, 9,11], Lee RR[1,2], Baker DG[1,8,9].

Cereb Cortex. **2019 May 1**. pii: bhz087. doi: 10.1093/cercor/bhz087. PMID: 31041986. [Epub ahead of print]

Combat-related mild traumatic brain injury (mTBI) is a leading cause of sustained impairments in military service members and veterans. Recent animal studies show that GABA-ergic parvalbumin-positive interneurons are susceptible to brain injury, with damage causing abnormal increases in spontaneous gamma-band (30-80 Hz) activity. We investigated spontaneous gamma activity in individuals with mTBI using high-resolution resting-state magnetoencephalography source imaging. Participants included 25 symptomatic individuals with chronic combat-related blast mTBI and 35 healthy controls with similar combat experiences. Compared with controls, gamma activity was markedly elevated in mTBI participants throughout frontal, parietal, temporal, and occipital cortices, whereas gamma activity was reduced in ventromedial prefrontal cortex. Across groups, greater gamma activity correlated with poorer performances on tests of executive functioning and visuospatial processing. Many neurocognitive associations, however, were partly driven by the higher incidence of mTBI participants with both higher gamma activity and poorer cognition, suggesting that expansive upregulation of gamma has negative repercussions for cognition particularly in mTBI. This is the first human study to demonstrate abnormal resting-state gamma activity in mTBI. These novel findings suggest the possibility that abnormal gamma activities may be a proxy for GABA-ergic interneuron dysfunction and a promising neuroimaging marker of insidious mild head injuries.

Brain Electrical Activity Associated With Visual Attention and Reactive Motor Inhibition in Patients With Fibromyalgia.

González-Villar AJ[1], Arias M, Carrillo-de-la-Peña MT.

Psychosom Med. **2019 May**;81(4):380-388. doi: 10.1097/PSY.0000000000000677.

OBJECTIVE: Fibromyalgia (FM) is a generalized chronic pain condition associated with multiple cognitive impairments, including altered inhibitory processes. Inhibition is a key component of human executive functions and shares neural substrate with pain processing, which may explain the inhibitory deficits in FM. Here, we investigated the integrity of brain inhibitory mechanisms in these patients.

METHODS: We recorded the electroencephalographic activity of 27 patients with FM and 27 healthy controls (HCs) (all women) while they performed a reactive motor inhibition task (the stop-signal paradigm). We analyzed task-induced modulations in electrophysiological markers related to inhibition (N2, P3, and midfrontal theta oscillations) and visual attention (posterior alpha oscillations).

RESULTS: The FM group performed the task correctly, with no differences relative to HCs at the behavioral level. We did not find any between-group differences in N2 amplitude ($F(1,52) = 0.01$, $p = .93$), P3 amplitude ($F(1,52) = 3.46$; $p = .068$), or theta power ($F(1,52) = 0.05$; $p = .82$). However, modulation of posterior alpha power after presentation of either the go or stop stimuli was lower in patients than in HCs ($F(1,52) = 7.98$; $p = .007$).

CONCLUSIONS: N2, P3, theta power, and behavioral results indicate that the mechanisms of motor inhibition are sufficiently preserved to enable correct performance of the stop-signal task in patients with FM. Nevertheless, the lower modulation of alpha suggests greater difficulty in mobilizing and maintaining visual attentional resources, a result that may explain the cognitive dysfunction observed in FM.

CHRONIC PAIN (Continued)

Sez6 levels are elevated in cerebrospinal fluid of patients with inflammatory pain-associated conditions.

Roitman M[1], Edgington-Mitchell LE[2,3,4], Mangum J[5], Ziogas J[5], Adamides AA[6], Myles P[7], Choo-Bunnett H[8], Bunnett NW[8], Gunnersen JM[1].

Pain Rep. **2019 Mar 25**;4(2):e719. doi: 10.1097/PR9.0000000000000719. eCollection 2019 Mar-Apr. PMCID: PMC6455686. PMID: 31041421.

Introduction: Seizure-related protein 6 (Sez6) contributes to chronic pain development as *sez6* knockout mice show attenuated pain behaviours after peripheral nerve injury, compared with control mice. The type I transmembrane isoform of Sez6 is cleaved by the β-amyloid precursor protein cleavage enzyme 1 (BACE1), resulting in Sez6 extracellular domain shedding from the neuron surface.

Objectives: To determine whether this BACE1-shed form of Sez6 can be detected in the cerebrospinal fluid (CSF) and whether Sez6 levels in the CSF are altered in neuropathic pain or chronic inflammatory pain (IP).

Methods: We analysed the CSF samples collected during surgery from patients with chronic neuropathic pain (n = 8) or IP (n = 33), comparing them to the CSF samples from patients with suspected subarachnoid haemorrhage that was subsequently excluded (nonsurgical group, n = 5). Western blots were used to determine the relative Sez6 levels in the CSF from the different patient and nonsurgical comparison groups.

Results: The results show that BACE1-shed Sez6 can be readily detected in the CSF by Western blot and that the levels of Sez6 are significantly higher in the IP group than in the nonsurgical comparison group.

Conclusion: The association between elevated Sez6 levels in the CSF and IP is further evidence for persistent alterations in central nervous system activity in chronic IP conditions.

IRRITABLE BOWEL SYNDROME

Probiotics, prebiotics, and low FODMAP diet for irritable bowel syndrome - What is the current evidence?

Ooi SL[1], Correa D[1], Pak SC[2].

Complement Ther Med. **2019 Apr**;43:73-80. doi: 10.1016/j.ctim.2019.01.010. PMID: 30935559. Epub 2019 Jan 16.

Irritable bowel syndrome (IBS) is one of the most common functional gastrointestinal disorders worldwide. While the pathogenesis is not clearly understood, current research points to the role of the gut microbiome and alterations in the diversity of the microbiota. Probiotics, prebiotics, and low FODMAP diet are therapeutic means associated with modification of the gut microbiome for the alleviation of IBS symptoms. This narrative review assesses the current evidence on the efficacy of these treatment options based on findings from recent systematic reviews and meta-analyses published from October 2013 to October 2018. There is a general agreement in the 11 included systematic reviews and meta-analyses that probiotic therapy is safe and can be effective in improving overall IBS symptom scores and abdominal pain in the general IBS population. Nonetheless, conflicting findings remain and no recommendation on the specific species/strains or combination can be made. Short-term restriction of FODMAP in the diet can improve IBS symptoms as per the findings of 7 systematic reviews and meta-analyses, even though the quality of the evidence remains questionable. Inappropriate use of the low FODMAP diet can potentially impact health negatively. As such, a low FODMAP diet is only recommended as a second line treatment guided by qualified clinicians with specialized training. Despite preclinical studies of some prebiotics demonstrated the potential use in improving gut microbiome and intestinal inflammatory response, the beneficial effect of prebiotics for IBS remains theoretical. Two systematic reviews found no evidence to support the clinical use of prebiotics for IBS.

IRRITABLE BOWEL SYNDROME (Continued)

The potential probiotic Lactobacillus rhamnosus CNCM I-3690 strain protects the intestinal barrier by stimulating both mucus production and cytoprotective response.

Martín R[1], Chamignon C[1], Mhedbi-Hajri N[2], Chain F[1], Derrien M[2], Escribano-Vázquez U[1], Garault P[2], Cotillard A[2], Pham HP[3], Chervaux C[2], Bermúdez-Humarán LG[1], Smokvina T[4], Langella P[5].

Sci Rep. **2019 Apr 1**;9(1):5398. doi: 10.1038/s41598-019-41738-5.

The gut barrier plays an important role in human health. When barrier function is impaired, altered permeability and barrier dysfunction can occur, leading to inflammatory bowel diseases, irritable bowel syndrome or obesity. Several bacteria, including pathogens and commensals, have been found to directly or indirectly modulate intestinal barrier function. The use of probiotic strains could be an important landmark in the management of gut dysfunction with a clear impact on the general population. Previously, we found that Lactobacillus rhamnosus CNCM I-3690 can protect intestinal barrier functions in mice inflammation model. Here, we investigated its mechanism of action. Our results show that CNCM I-3690 can (i) physically maintain modulated goblet cells and the mucus layer and (ii) counteract changes in local and systemic lymphocytes. Furthermore, mice colonic transcriptome analysis revealed that CNCM I-3690 enhances the expression of genes related to healthy gut permeability: motility and absorption, cell proliferation; and protective functions by inhibiting endogenous proteases. Finally, SpaFED pili are clearly important effectors since an L. rhamnosus ΔspaF mutant failed to provide the same benefits as the wild type strain. Taken together, our data suggest that CNCM I-3690 restores impaired intestinal barrier functions via anti-inflammatory and cytoprotective responses.

OTHER RESEARCH OF INTEREST

Effectiveness and Acceptability of Cognitive Behavior Therapy Delivery Formats in Adults With Depression: A Network Meta-analysis.

Cuijpers P[1], Noma H[2], Karyotaki E[2], Cipriani A[3,4], Furukawa TA[5].

JAMA Psychiatry. **2019 Apr 17**. doi: 10.1001/jamapsychiatry.2019.0268. PMCID: PMC6583673. PMID: 30994877. [Epub ahead of print]

Importance: Cognitive behavior therapy (CBT) has been shown to be effective in the treatment of acute depression. However, whether CBT can be effectively delivered in individual, group, telephone-administered, guided self-help, and unguided self-help formats remains unclear.

Objective: To examine the most effective delivery format for CBT via a network meta-analysis.

Data Sources: A database updated yearly from PubMed, PsycINFO, Embase, and the Cochrane Library. Literature search dates encompassed January 1, 1966, to January 1, 2018.

Study Selection: Randomized clinical trials of CBT for adult depression. The 5 treatment formats were compared with each other and the control conditions (waiting list, care as usual, and pill placebo).

Data Extraction and Synthesis: PRISMA guidelines were used when extracting data and assessing data quality. Data were pooled using a random-effects model. Pairwise and network meta-analyses were conducted.

Main Outcomes and Measures: Severity of depression and acceptability of the treatment formats.

Results: A total of 155 trials with 15 191 participants compared 5 CBT delivery formats with 2 control conditions. In half of the studies (78 [50.3%]), patients met the criteria for a depressive disorder; in the other half (77 [49.7%]), participants scored above the cutoff point on a self-report measure. The effectiveness of individual, group, telephone, and guided self-help CBT did not differ statistically significantly from each other. These formats were statistically significantly more effective than the waiting list (standardized mean differences [SMDs], 0.87-1.02) and care as usual (SMDs, 0.47-0.72) control conditions as well as the unguided self-help CBT (SMDs, 0.34-0.59). In terms of acceptability (dropout for any reason), individual (relative risk [RR] = 1.44; 95% CI, 1.09-1.89) and group (RR = 1.38; 95% CI, 1.06-1.80) CBT were significantly better than guided self-help. Guided self-help was also less acceptable than being on a waiting list (RR = 0.63; 95% CI, 0.52-0.75) and care as usual (RR = 0.72; 95% CI, 0.57-0.90). Sensitivity analyses supported the overall findings.

Conclusions and Relevance: For acute symptoms of depression, group, telephone, and guided self-help treatment formats appeared to be effective interventions, which may be considered as alternatives to individual CBT; although there were few indications of significant differences in efficacy between treatments with human support, guided self-help CBT may be less acceptable for patients than individual, group, or telephone formats.

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