Orthopädie am St. Lambertiplatz
dr. med robert bethke, MHBA
Facharzt für Orthopädie und Unfallchirurgie, Diplom-Osteopath (DAAO)
Akupunktur · Sportmedizin · Chirotherapie · Notfallmedizin
Osteopathie · Kindermanualtherapie · Funktionelle Medizin

St. Lambertiplatz 6
21335 Lüneburg
Tel. 04131 - 430 31
Fax 04131 - 40 51 00
www.praxis-dr-bethke.de
info@praxis-dr-bethke.de

Studienauswahl zum Thema

chronic fatique syndrome (CFS) – leaky gut – mitochondriale Dysfunktion

Stand: 20.02.20221

Veröffentlichung 1[1]:

The emerging role of autoimmunity in myalgic encephalomyelitis/chronic fatigue syndrome (ME/cfs) - PubMed (nih.gov)

In: Molecular Neurobiology. 2014 Apr;49(2):741-56.
doi: 10.1007/s12035-013-8553-0. Epub 2013 Sep 26.

„Abstract

The World Health Organization classifies myalgic encephalomyelitis/chronic fatigue syndrome (ME/cfs) as a nervous system disease. Together with other diseases under the G93 heading, ME/cfs shares a triad of abnormalities involving elevated oxidative and nitrosative stress (O&NS), activation of immuno-inflammatory pathways, and mitochondrial dysfunctions with depleted levels of adenosine triphosphate (ATP) synthesis. There is also abundant evidence that many patients with ME/cfs (up to around 60 %) may suffer from autoimmune responses. A wide range of reported abnormalities in ME/cfs are highly pertinent to the generation of autoimmunity. Here we review the potential sources of autoimmunity which are observed in people with ME/cfs. The increased levels of pro-inflammatory cytokines, e.g., interleukin-1 and tumor necrosis factor-α, and increased levels of nuclear factor-κB predispose to an autoimmune environment. Many cytokine abnormalities conspire to produce a predominance of effector B cells and autoreactive T cells. The common observation of reduced natural killer cell function in ME/cfs is a source of disrupted homeostasis and prolonged effector T cell survival. B cells may be pathogenic by playing a role in autoimmunity independent of their ability to produce antibodies. The chronic or recurrent viral infections seen in many patients with ME/cfs can induce autoimmunity by mechanisms involving molecular mimicry and bystander activation. Increased bacterial translocation, as observed in ME/cfs, is known to induce chronic inflammation and autoimmunity. Low ATP production and mitochondrial dysfunction is a source of autoimmunity by inhibiting apoptosis and stimulating necrotic cell death. Self-epitopes may be damaged by exposure to prolonged O&NS, altering their immunogenic profile and become a target for the host's immune system. Nitric oxide may induce many faces of autoimmunity stemming from elevated mitochondrial membrane hyperpolarization and blockade of the methionine cycle with subsequent hypomethylation of DNA. Here we also outline options for treatment involving rituximab and endotherapia.“

1 Hinweis: Zu Vereinfachung sind die Abstracts – soweit vorhanden – mitabgedruckt und die Kernaussagen fett-dargestellt.

Veröffentlichung 2:
A neuro-immune model of Myalgic Encephalomyelitis/Chronic fatigue syndrome - PubMed (nih.gov)

In: Metabolic Brain Disease. 2013 Dec;28(4):523-40.
doi: 10.1007/s11011-012-9324-8. Epub 2012 Jun 21.

„Abstract

This paper proposes a neuro-immune model for Myalgic Encephalomyelitis/Chronic fatigue syndrome (ME/CFS**). A wide range of immunological and neurological abnormalities have been reported in people suffering from ME/CFS. They include abnormalities in proinflammatory cytokines, raised production of nuclear factor-κB, mitochondrial dysfunctions, autoimmune responses, autonomic disturbances and brain pathology. Raised levels of oxidative and nitrosative stress (O&NS), together with reduced levels of antioxidants are indicative of an immuno-inflammatory pathology. A number of different pathogens have been reported either as triggering or maintaining factors.** Our model proposes that initial infection and immune activation caused by a number of possible pathogens leads to a state of chronic peripheral immune activation driven by activated O&NS pathways that lead to progressive damage of self epitopes even when the initial infection has been cleared. Subsequent activation of autoreactive T cells conspiring with O&NS pathways cause further damage and provoke chronic activation of immuno-inflammatory pathways. The subsequent upregulation of proinflammatory compounds may activate microglia via the vagus nerve. Elevated proinflammatory cytokines together with raised O&NS conspire to produce mitochondrial damage. The subsequent ATP deficit together with inflammation and O&NS are responsible for the landmark symptoms of ME/CFS, including post-exertional malaise. Raised levels of O&NS subsequently cause progressive elevation of autoimmune activity facilitated by molecular mimicry, bystander activation or epitope spreading. These processes provoke central nervous system (CNS) activation in an attempt to restore immune homeostatsis. This model proposes that the antagonistic activities of the CNS response to peripheral inflammation, O&NS and chronic immune activation are responsible for the remitting-relapsing nature of ME/CFS. Leads for future research are suggested based on this neuro-immune model.“

Anmerkung: Ein Grund für eine gründliche Labordiagnostik! Weiterhin finden sich hier Erklärungsansätze für die Erkrankung.

Veröffentlichung 3:

Mitochondrial dysfunctions in myalgic encephalomyelitis/chronic fatigue syndrome explained by activated immuno-inflammatory, oxidative and nitrosative stress pathways - PubMed (nih.gov)

In: Metabolic Brain Disease. 2014 Mar;29(1):19-36.
doi: 10.1007/s11011-013-9435-x. Epub 2013 Sep 10.

„Abstract

Myalgic encephalomyelitis/chronic fatigue syndrome (ME/cfs) is classified by the World Health Organization as a disorder of the central nervous system. ME/cfs is an neuro-immune disorder accompanied by chronic low-grade inflammation, increased levels of oxidative and nitrosative stress (O&NS), O&NS-mediated damage to fatty acids, DNA and proteins, autoimmune reactions directed against neoantigens and brain disorders. **Mitochondrial dysfunctions have been found in ME/cfs**,

e.g. lowered ATP production, impaired oxidative phosphorylation and mitochondrial damage. This paper reviews the pathways that may explain mitochondrial dysfunctions in ME/cfs. Increased levels of pro-inflammatory cytokines, such as interleukin-1 and tumor necrosis factor-α, and elastase, and increased O&NS may inhibit mitochondrial respiration, decrease the activities of the electron transport chain and mitochondrial membrane potential, increase mitochondrial membrane permeability, interfere with ATP production and cause mitochondrial shutdown. The activated O&NS pathways may additionally lead to damage of mitochondrial DNA and membranes thus decreasing membrane fluidity. Lowered levels of antioxidants, zinc and coenzyme Q10, and ω3 polyunsaturated fatty acids in ME/cfs may further aggravate the activated immuno-inflammatory and O&NS pathways. Therefore, it may be concluded that immuno-inflammatory and O&NS pathways may play a role in the mitochondrial dysfunctions and consequently the bioenergetic abnormalities seen in patients with ME/cfs. Defects in ATP production and the electron transport complex, in turn, are associated with an elevated production of superoxide and hydrogen peroxide in mitochondria creating adaptive and synergistic damage. **It is argued that mitochondrial dysfunctions, e.g. lowered ATP production, may play a role in the onset of ME/cfs symptoms, e.g. fatigue and post exertional malaise, and may explain in part the central metabolic abnormalities observed in ME/cfs, e.g. glucose hypometabolism and cerebral hypoperfusion.**"

Veröffentlichung 4:

Why myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) may kill you: disorders in the inflammatory and oxidative and nitrosative stress (IO&NS) pathways may explain cardiovascular disorders in ME/CFS - PubMed (nih.gov)

In: Neuroendocrinology Letters. 2009;30(6):677-93.

„Abstract

There is evidence that disorders in inflammatory and oxidative and nitrosative (IO&NS) pathways and a lowered antioxidant status are important pathophysiological mechanisms underpinning myalgic encephalomyelitis / chronic fatigue syndrome (ME/CFS). **Important precipitating and perpetuating factors for ME/CFS are (amongst others) bacterial and viral infections; bacterial translocation due to an increased gut permeability; and psychological stress.** Recently, Jason et al (2006) reported that the mean age of patients with myalgic encephalomyelitis/chronic fatigue syndrome dying from heart failure, i.e. 58.7 years, is significantly lower than the age of those dying from heart failure in the general US population, i.e. 83.1 years. These findings implicate that ME/CFS is a risk factor to cardio-vascular disorder. This review demonstrates that disorders in various IO&NS pathways provide explanations for the earlier mortality due to cardiovascular disorders in ME/CFS. These pathways are: a) chronic low grade inflammation with extended production of nuclear factor kappa B and COX-2 and increased levels of tumour necrosis factor alpha; b) increased O&NS with increased peroxide levels, and phospholipid oxidation including oxidative damage to phosphatidylinositol; c) decreased levels of specific antioxidants, i.e. coenzyme Q10, zinc and dehydroepiandrosterone-sulphate**; d) bacterial translocation as a result of leaky gut;** e) decreased omega-3 polyunsatutared fatty acids (PUFAs), and increased omega-6 PUFA and saturated fatty acid levels; and f) the presence of viral and bacterial infections and psychological stressors. The mechanisms whereby each of these factors may contribute towards cardio-vascular disorder in ME/CFS are discussed. **ME/CFS is a multisystemic metabolic-inflammatory disorder**. The aberrations in IO&NS pathways may increase the risk for cardiovascular disorders."

<u>Anmerkungen:</u> Hier wird – neben anderen – der Zusammenhang zwischen leaky gut und chronic fatique syndrome hergestellt.

Veröffentlichung 5:

Chronic fatigue syndrome: Harvey and Wessely's (bio)psychosocial model versus a bio(psychosocial) model based on inflammatory and oxidative and nitrosative stress pathways - PubMed (nih.gov)

In: BMC Med. 2010 Jun 15;8:35.
doi: 10.1186/1741-7015-8-35.

„Abstract

Background: In a recently published paper, Harvey and Wessely put forward a 'biopsychosocial' explanatory model for myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS), which is proposed to be applicable to (chronic) fatigue even when apparent medical causes are present.

Methods: Here, we review the model proposed by Harvey and Wessely, which is the rationale for behaviourally oriented interventions, such as cognitive behaviour therapy (CBT) and graded exercise therapy (GET), and compare this model with a biological model, in which inflammatory, immune, oxidative and nitrosative (IO&NS) pathways are key elements.

Discussion: Although human and animal studies have established that the pathophysiology of ME/CFS includes IO&NS pathways, these abnormalities are not included in the model proposed by Harvey and Wessely. Activation of IO&NS pathways is known to induce fatigue and somatic (F&S) symptoms and can be induced or maintained by viral and bacterial infections, physical and psychosocial stressors, or organic disorders such as (auto)immune disorders. Studies have shown that ME/CFS and major depression are both clinical manifestations of shared IO&NS pathways, and that both disorders can be discriminated by specific symptoms and unshared or differentiating pathways. Interventions with CBT/GET are potentially harmful for many patients with ME/CFS, since the underlying pathophysiological abnormalities may be intensified by physical stressors.

Conclusions: **In contrast to Harvey and Wessely's (bio)psychosocial model for ME/CFS a bio(psychosocial) model based upon IO&NS abnormalities is likely more appropriate to this complex disorder. In clinical practice, we suggest physicians should also explore the IO&NS pathophysiology by applying laboratory tests that examine the pathways involved**.“

<u>Anmerkungen:</u> Hier mal eine wissenschaftliche Arbeit, die das chronic fatique syndrom nicht (nur) unter psychiatrischem-psychologischen Aspekt betrachtet, sondern eher eine organische Ursache postuliert. Damit lässt sich u.a. die umfangreiche Labordiagnostik begründen.

Veröffentlichung 6:

Fecal metagenomic profiles in subgroups of patients with myalgic encephalomyelitis/chronic fatigue syndrome - PubMed (nih.gov)

In: Microbiome. 2017 Apr 26;5(1):44. doi: 10.1186/s40168-017-0261-y.

„Abstract

Background: Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) is characterized by unexplained persistent fatigue, commonly accompanied by cognitive dysfunction, sleeping disturbances, orthostatic intolerance, fever, lymphadenopathy, and irritable bowel syndrome (IBS). The extent to which the gastrointestinal microbiome and peripheral inflammation are associated with ME/CFS remains unclear. We pursued rigorous clinical characterization, fecal bacterial metagenomics, and plasma immune molecule analyses in 50 ME/CFS patients and 50 healthy controls frequency-matched for age, sex, race/ethnicity, geographic site, and season of sampling.

Results: Topological analysis revealed associations between IBS co-morbidity, body mass index, fecal bacterial composition, and bacterial metabolic pathways but not plasma immune molecules. IBS co-morbidity was the strongest driving factor in the separation of topological networks based on bacterial profiles and metabolic pathways. Predictive selection models based on bacterial profiles supported findings from topological analyses indicating that ME/CFS subgroups, defined by IBS status, could be distinguished from control subjects with high predictive accuracy. Bacterial taxa predictive of ME/CFS patients with IBS were distinct from taxa associated with ME/CFS patients without IBS. Increased abundance of unclassified Alistipes and decreased Faecalibacterium emerged as the top biomarkers of ME/CFS with IBS; while increased unclassified Bacteroides abundance and decreased Bacteroides vulgatus were the top biomarkers of ME/CFS without IBS. Despite findings of differences in bacterial taxa and metabolic pathways defining ME/CFS subgroups, decreased metabolic pathways associated with unsaturated fatty acid biosynthesis and increased atrazine degradation pathways were independent of IBS co-morbidity. Increased vitamin B6 biosynthesis/salvage and pyrimidine ribonucleoside degradation were the top metabolic pathways in ME/CFS without IBS as well as in the total ME/CFS cohort. In ME/CFS subgroups, symptom severity measures including pain, fatigue, and reduced motivation were correlated with the abundance of distinct bacterial taxa and metabolic pathways.

Conclusions: Independent of IBS, ME/CFS is associated with dysbiosis and distinct bacterial metabolic disturbances that may influence disease severity. However, our findings indicate that dysbiotic features that are uniquely ME/CFS-associated may be masked by disturbances arising from the high prevalence of IBS co-morbidity in ME/CFS. These insights may enable more accurate diagnosis and lead to insights that inform the development of specific therapeutic strategies in ME/CFS subgroups."

<u>Anmerkungen:</u> Hier wird der Zusammenhang zwischen CFS und Darm diskutiert. Damit besteht die Indikation zur durchführten Labordiagnostik.

Veröffentlichung 7:

Myalgic encephalomyelitis, chronic fatigue syndrome: An infectious disease - PubMed (nih.gov)

In: Medical Hypotheses. 2015 Dez;85(6):765-73.
doi: 10.1016/j.mehy.2015.10.011. Epub 2016 Okt 19

"Abstract

The etiology of myalgic encephalomyelitis also known as chronic fatigue syndrome or ME/CFS has not been established. Controversies exist over whether it is an organic disease or a psychological disorder and even the existence of ME/CFS as a disease entity is sometimes denied. Suggested causal hypotheses have included psychosomatic disorders, infectious agents, immune dysfunctions,

autoimmunity, metabolic disturbances, toxins and inherited genetic factors. **Clinical, immunological and epidemiological evidence supports the hypothesis that: ME/CFS is an infectious disease; the causal pathogen persists in patients**; the pathogen can be transmitted by casual contact; host factors determine susceptibility to the illness; and there is a population of healthy carriers, who may be able to shed the pathogen. ME/CFS is endemic globally as sporadic cases and occasional cluster outbreaks (epidemics). Cluster outbreaks imply an infectious agent. An abrupt flu-like onset resembling an infectious illness occurs in outbreak patients and many sporadic patients. Immune responses in sporadic patients resemble immune responses in other infectious diseases. Contagion is shown by finding secondary cases in outbreaks, and suggested by a higher prevalence of ME/CFS in sporadic patients' genetically unrelated close contacts (spouses/partners) than the community. Abortive cases, sub-clinical cases, and carrier state individuals were found in outbreaks. **The chronic phase of ME/CFS does not appear to be particularly infective**. Some healthy patient-contacts show immune responses similar to patients' immune responses, suggesting exposure to the same antigen (a pathogen). The chronicity of symptoms and of immune system changes and the occurrence of secondary cases suggest persistence of a causal pathogen. Risk factors which predispose to developing ME/CFS are: a close family member with ME/CFS; inherited genetic factors; female gender; age; rest/activity; previous exposure to stress or toxins; various infectious diseases preceding the onset of ME/CFS; and occupational exposure of health care professionals. The hypothesis implies that ME/CFS patients should not donate blood or tissue and usual precautions should be taken when handling patients' blood and tissue. No known pathogen has been shown to cause ME/CFS. Confirmation of the hypothesis requires identification of a causal pathogen. Research should focus on a search for unknown and known pathogens. Finding a causal pathogen could assist with diagnosis; help find a biomarker; enable the development of anti-microbial treatments; suggest preventive measures; explain pathophysiological findings; and reassure patients about the validity of their symptoms.“

<u>Anmerkungen:</u> Auch hier neben der Diskussion der Erkrankungsursache wieder eine Begründung zur exakten und umfangereichen Labordiagnostik!

Veröffentlichung 8:

The effect of myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) severity on cellular bioenergetic function - PubMed (nih.gov)

In: PLOS ONE (Public Library of Science). 2020 Apr 10;15(4):e0231136.
doi: 10.1371/journal.pone.0231136. eCollection 2020.

„Abstract

Myalgic encephalomyelitis/ Chronic fatigue syndrome (ME/CFS) has been associated with abnormalities in mitochondrial function. In this study we have analysed previous bioenergetics data in peripheral blood mononuclear cells (PBMCs) using new techniques in order to further elucidate differences between ME/CFS and healthy control cohorts. We stratified our ME/CFS cohort into two individual cohorts representing moderately and severely affected patients in order to determine if disease severity is associated with bioenergetic function in PBMCs. **Both ME/CFS cohorts showed reduced mitochondrial function when compared to a healthy control cohort**. **This shows that disease severity does not correlate with mitochondrial function and even those with a moderate form of the disease show evidence of mitochondrial dysfunction**. Equations devised by another

research group have enabled us to calculate ATP-linked respiration rates and glycolytic parameters. Parameters of glycolytic function were calculated by taking into account respiratory acidification. This revealed severely affected ME/CFS patients to have higher rates of respiratory acidification and showed the importance of accounting for respiratory acidification when calculating parameters of glycolytic function. Analysis of previously published glycolysis data, after taking into account respiratory acidification, showed severely affected patients have reduced glycolysis compared to moderately affected patients and healthy controls. Rates of ATP-linked respiration were also calculated and shown to be lower in both ME/CFS cohorts. This study shows that severely affected patients have mitochondrial and glycolytic impairments, which sets them apart from moderately affected patients who only have mitochondrial impairment. This may explain why these patients present with a more severe phenotype."

<u>Anmerkungen:</u> Diese Studie zeigt, warum mitochondriale Parameter bei CFS untersucht werden müssen. Trotzdem zeigt diese Untersuchung, dass bei CFS mitochondriale Parameter untersucht werden müssen.

Veröffentlichung 9:

Neuroinflammation in Patients with Chronic Fatigue Syndrome/Myalgic Encephalomyelitis: An ^{11}C-(R)-PK11195 PET Study - PubMed (nih.gov)

In: The Journal of Nuclear Medicine. 2014 Jun;55(6):945-50.
doi: 10.2967/jnumed.113.131045. Epub 2014 Mar 24.

„Abstract

Chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME) is a disease characterized by chronic, profound, disabling, and unexplained fatigue. Although it is hypothesized that brain inflammation is involved in the pathophysiology of CFS/ME, there is no direct evidence of neuroinflammation in patients with CFS/ME. Activation of microglia or astrocytes is related to neuroinflammation. (11)C-(R)-(2-chlorophenyl)-N-methyl-N-(1-methylpropyl)-3-isoquinoline-carboxamide ((11)C-(R)-PK11195) is a ligand of PET for a translocator protein that is expressed by activated microglia or astrocytes. We used (11)C-(R)-PK11195 and PET to investigate the existence of neuroinflammation in CFS/ME patients.

Methods: Nine CFS/ME patients and 10 healthy controls underwent (11)C-(R)-PK11195 PET and completed questionnaires about fatigue, fatigue sensation, cognitive impairments, pain, and depression. To measure the density of translocator protein, nondisplaceable binding potential (BP(ND)) values were determined using linear graphical analysis with the cerebellum as a reference region.

Results: The BP(ND) values of (11)C-(R)-PK11195 in the cingulate cortex, hippocampus, amygdala, thalamus, midbrain, and pons were 45%-199% higher in CFS/ME patients than in healthy controls. In CFS/ME patients, the BP(ND) values of (11)C-(R)-PK11195 in the amygdala, thalamus, and midbrain positively correlated with cognitive impairment score, the BP(ND) values in the cingulate cortex and thalamus positively correlated with pain score, and the BP(ND) value in the hippocampus positively correlated with depression score.

Conclusion: Neuroinflammation is present in widespread brain areas in CFS/ME patients and was associated with the severity of neuropsychologic symptoms. Evaluation of neuroinflammation in CFS/ME patients may be essential for understanding the core pathophysiology and for developing objective diagnostic criteria and effective medical treatments."

<u>Anmerkungen:</u> Diskussion der Erkrankungsursachen.

Veröffentlichung 10:

Current Research Provides Insight into the Biological Basis and Diagnostic Potential for Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) - PubMed (nih.gov)

In: Diagnostics (Basel). 2019 Jul 10;9(3):73.
doi: 10.3390/diagnostics9030073.

„Abstract

Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) is a severe fatigue illness that occurs most commonly following a viral infection, but other physiological triggers are also implicated. It has a profound long-term impact on the life of the affected person. ME/CFS is diagnosed primarily by the exclusion of other fatigue illnesses, but the availability of multiple case definitions for ME/CFS has complicated diagnosis for clinicians. There has been ongoing controversy over the nature of ME/CFS, but a recent detailed report from the Institute of Medicine (Academy of Sciences, USA) concluded that ME/CFS is a medical, not psychiatric illness. Importantly, aspects of the biological basis of the ongoing disease have been revealed over the last 2-3 years that promise new leads towards an effective clinical diagnostic test that may have a general application. **Our detailed molecular studies with a preclinical study of ME/CFS patients, along with the complementary research of others, have reported an elevation of inflammatory and immune processes, ongoing neuro-inflammation, and decreases in general metabolism and mitochondrial function for energy production in ME/CFS**, **which contribute to the ongoing remitting/relapsing etiology of the illness**. These biological changes have generated potential molecular biomarkers for use in diagnostic ME/CFS testing."

<u>Anmerkungen:</u> Diese Studie widerlegt die These, dass keine Ursachen für CFS vorliegen würden und deshalb die umfangreich durchgeführte Diagnostik nicht medizinisch indiziert gewesen wäre.

Veröffentlichung 11:

Evidence for the existence of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) with and without abdominal discomfort (irritable bowel) syndrome - PubMed (nih.gov)

In: Neuroendocrinology Letters. 2014;35(6):445-53.

„Abstract

Background: There is evidence that Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) is accompanied by gastro-intestinal symptoms; and IgA and IgM responses directed against lipopolysaccharides (LPS) of commensal bacteria, indicating bacterial translocation.

Methods: This study was carried out to examine gastro-intestinal symptoms in subjects with ME/CFS versus those with chronic fatigue (CF). The two groups were dissected by dichotomizing those

fulfilling and not fulfilling Fukuda's critera. In these groups, we examined the association between gastro-intestinal symptoms and the IgA and IgM responses directed against commensal bacteria.

Results: Using cluster analysis performed on gastro-intestinal symptoms we delineated that the cluster analysis-generated diagnosis of abdominal discomfort syndrome (ADS) was significantly higher in subjects with ME/CFS (59.6%) than in those with CF (17.7%). The diagnosis of ADS was strongly associated with the diagnosis of irritable bowel syndrome (IBS). There is evidence that ME/CFS consists of two subgroups, i.e. ME/CFS with and without ADS. Factor analysis showed four factors, i.e. 1) inflammation-hyperalgesia; 2) fatigue-malaise; 3) gastro-intestinal symptoms/ADS; and 4) neurocognitive symptoms. The IgA and IgM responses to LPS of commensal bacteria were significantly higher in ME/CFS patients with ADS than in those without ADS.

Conclusions: **The findings show that ADS is a characteristic of a subset of patients with ME/CFS and that increased bacterial translocation (leaky gut) is associated with ADS symptoms.** This study has defined a pathway phenotype, i.e bacterial translocation, that is related to ME/CFS and ADS/IBS and that may drive systemic inflammatory processes.“

Anmerkungen: Zusammenhang zwischen leaky gut und CFS!

Veröffentlichung 12:

Myalgic encephalomyelitis/chronic fatigue syndrome: From pathophysiological insights to novel therapeutic opportunities - PubMed (nih.gov)

In: Pharmacological Research. 2019 Okt;148:104450.
doi: 10.1016/j.phrs.2019.104450. Epub 2019 Sep 8.

„Abstract

Myalgic encephalomyelitis (ME) or chronic fatigue syndrome (CFS) is a common and disabling condition with a paucity of effective and evidence-based therapies, reflecting a major unmet need. Cognitive behavioural therapy and graded exercise are of modest benefit for only some ME/CFS patients, and many sufferers report aggravation of symptoms of fatigue with exercise. The presence of a multiplicity of pathophysiological abnormalities in at least the subgroup of people with ME/CFS diagnosed with the current international consensus "Fukuda" criteria, points to numerous potential therapeutic targets. **Such abnormalities include extensive data showing that at least a subgroup has a pro-inflammatory state, increased oxidative and nitrosative stress, disruption of gut mucosal barriers and mitochondrial dysfunction together with dysregulated bioenergetics**. In this paper, these pathways are summarised, and data regarding promising therapeutic options that target these pathways are highlighted; they include coenzyme Q10, melatonin, curcumin, molecular hydrogen and N-acetylcysteine. These data are promising yet preliminary, suggesting hopeful avenues to address this major unmet burden of illness.“

Anmerkungen: Noch ein Zusammenhang zwischen leaky gut und CFS!

Veröffentlichung 13:

Gut Microbiota, Bacterial Translocation, and Interactions with Diet: Pathophysiological Links between Major Depressive Disorder and Non-Communicable Medical Comorbidities - PubMed (nih.gov)

In: Psychotherapy and Psychosomatics. 2017;86(1):31-46.
doi: 10.1159/000448957. Epub 2016 Nov 25.

„Abstract

Background: Persistent low-grade immune-inflammatory processes, oxidative and nitrosative stress (O&NS), and hypothalamic-pituitary-adrenal axis activation are integral to the pathophysiology of major depressive disorder (MDD). The microbiome, intestinal compositional changes, and resultant bacterial translocation add a new element to the bidirectional interactions of the gut-brain axis; new evidence implicates these pathways in the patho-aetiology of MDD. In addition, abnormalities in the gut-brain axis are associated with several chronic non-communicable disorders, which frequently co-occur in individuals with MDD, including but not limited to irritable bowel syndrome (IBS), chronic fatigue syndrome (CFS), obesity, and type 2 diabetes mellitus (T2DM).

Methods: We searched the PubMed/MEDLINE database up until May 1, 2016 for studies which investigated intestinal dysbiosis and bacterial translocation (the 'leaky gut') in the pathophysiology of MDD and co-occurring somatic comorbidities with an emphasis on IBS, CFS, obesity, and T2DM.

Results: The composition of the gut microbiota is influenced by several genetic and environmental factors (e.g. diet). Several lines of evidence indicate that gut-microbiota-diet interactions play a significant pathophysiological role in MDD and related medical comorbidities. Gut dysbiosis and the leaky gut may influence several pathways implicated in the biology of MDD, including but not limited to immune activation, O&NS, and neuroplasticity cascades. However, methodological inconsistencies and limitations limit comparisons across studies.

Conclusions**: Intestinal dysbiosis and the leaky gut may constitute a key pathophysiological link between MDD and its medical comorbidities. This emerging literature opens relevant preventative and therapeutic perspectives.**“

Anmerkungen: Auch wenn diese Studie primär Richtung Depression geht, darf angenommen werden, dass die grundsätzlichen Mechanismen und Interaktion zwischen Darm und ZNS die Gleichen wie bei CFS sein dürften.

Veröffentlichung 14:

Normalization of leaky gut in chronic fatigue syndrome (CFS) is accompanied by a clinical improvement: effects of age, duration of illness and the translocation of LPS from gram-negative bacteria - PubMed (nih.gov)

In: Neuroendocrinology Letters. 2008 Dec;29(6):902-10.

„Abstract

Background: There is now evidence that an increased translocation of LPS from gram negative bacteria with subsequent gut-derived inflammation, i.e. induction of systemic inflammation and oxidative & nitrosative stress (IO&NS), is a new pathway in chronic fatigue syndrome (CFS).

Methods: The present study examines the serum concentrations of IgA and IgM to LPS of gram-negative enterobacteria, i.e. Hafnia Alvei; Pseudomonas Aeruginosa, Morganella Morganii, Pseudomonas Putida, Citrobacter Koseri, and Klebsielle Pneumoniae in CFS patients both before and after intake of natural anti-inflammatory and anti-oxidative substances (NAIOSs), such as glutamine, N-acetyl cysteine and zinc, in conjunction with a leaky gut diet during 10-14 months. We measured the above immune variables as well as the Fibromyalgia and Chronic Fatigue Syndrome Rating Scale in 41 patients with CFS before and 10-14 months after intake of NAIOSs.

Results: Subchronic intake of those NAIOSs significantly attenuates the initially increased IgA and IgM responses to LPS of gram negative bacteria. Up to 24 patients showed a significant clinical improvement or remission 10-14 months after intake of NAIOSs. A good clinical response is significantly predicted by attenuated IgA and IgM responses to LPS, the younger age of the patients, and a shorter duration of illness (< 5 years).

Discussion: The results show that normalization of the IgA and IgM responses to translocated LPS may predict clinical outcome in CFS. **The results support the view that a weakened tight junction barrier with subsequent gut-derived inflammation is a novel pathway in CFS and that it is a new target for drug development in CFS.** Meanwhile, CFS patients with leaky gut can be treated with specific NAIOSs and a leaky gut diet."

Veröffentlichung 15:

Eukaryotes in the gut microbiota in myalgic encephalomyelitis/chronic fatigue syndrome - PubMed (nih.gov)

In: PeerJ. 22.01.2018;6:e4282.
doi: 10.7717/peerj.4282. eCollection 2018.

„Abstract

Patients with myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) often suffer from gastrointestinal symptoms and many are diagnosed with irritable bowel syndrome (IBS). Previous studies, including from our laboratory, have demonstrated that the ME/CFS gut bacterial composition is altered and less diverse when compared to healthy individuals. Patients have increased biomarkers of inflammation and leaky gut syndrome. To further investigate dysbiosis in the ME/CFS gut microbiome, we sought to characterize the eukaryotes present in the gut of 49 individuals with ME/CFS and 39 healthy controls. Using 18S rRNA sequencing, we have identified eukaryotes in stool samples of 17 healthy individuals and 17 ME/CFS patients. Our analysis demonstrates a small, nonsignificant decrease in eukaryotic diversity in ME/CFS patients compared to healthy individuals. In addition, ME/CFS patients show a nonsignificant increase in the ratio of fungal phyla Basidiomycota to Ascomycota, which is consistent with ongoing inflammation in ME/CFS. We did not identify specific eukaryotic taxa that are associated with ME/CFS disease status."

Veröffentlichung 16:

Modification of Immunological Parameters, Oxidative Stress Markers, Mood Symptoms, and Well-Being Status in CFS Patients after Probiotic Intake: Observations from a Pilot Study - PubMed (nih.gov)

In: Oxidative Medicine and Cellular Longevity. 2019 Nov 23;2019:1684198. doi: 10.1155/2019/1684198. eCollection 2019.

„Abstract

The present study discusses about the effects of a combination of probiotics able to stimulate the immune system of patients affected by Chronic Fatigue Syndrome/Myalgic Encephalomyelitis (CFS/ME). To this purpose, patients diagnosed according to Fukuda's criteria and treated with probiotics were analyzed by means of clinical and laboratory evaluations, before and after probiotic administrations. Probiotics were selected considering the possible pathogenic mechanisms of ME/CFS syndrome, which has been associated with an impaired immune response, dysregulation of Th1/Th2 ratio, and high oxidative stress with exhaustion of antioxidant reserve due to severe mitochondrial dysfunction. Immune and oxidative dysfunction could be related with the gastrointestinal (GI) chronic low-grade inflammation in the lamina propria and intestinal mucosal surface associated with dysbiosis, leaky gut, bacterial translocation, and immune and oxidative dysfunction. **Literature data demonstrate that bacterial species are able to modulate the functions of the immune and oxidative systems and that the administration of some probiotics can improve mucosal barrier function, modulating the release of proinflammatory cytokines, in CFS/ME patients.** This study represents a preliminary investigation to verifying the safety and efficacy of a certain combination of probiotics in CFS/ME patients. **The results suggest that probiotics can modify the well-being status as well as inflammatory and oxidative indexes in CFS/ME patients.** No adverse effects were observed except for one patient, which displayed a flare-up of symptoms, although all inflammatory parameters (i.e., cytokines, fecal calprotectin, ESR, and immunoglobulins) were reduced after probiotic intake. The reactivation of fatigue symptoms in this patient, whose clinical history reported the onset of CFS/ME following mononucleosis, could be related to an abnormal stimulation of the immune system as suggested by a recent study describing an exaggerated immune activation associated with chronic fatigue.“

Anmerkungen: Diese Studie impliziert eine Darm-Immuntherapie mit Pro- und Präbiotika durchzuführen, wie es beim Patienten durchgeführt wurde.

Veröffentlichung 17:

Inflammatory and oxidative and nitrosative stress pathways underpinning chronic fatigue, somatization and psychosomatic symptoms - PubMed (nih.gov)

In: Current opinion in Psychiatry. 2009 Jan;22(1):75-83.
doi: 10.1097/yco.0b013e32831a4728.

„Abstract

Purpose of review: The aim of this paper is to review recent findings on inflammatory and oxidative and nitrosative stress (IO&NS) pathways in chronic fatigue and somatization disorder.

Recent findings: Activation of IO&NS pathways is the key phenomenon underpinning chronic fatigue syndrome (CFS): intracellular inflammation, with an increased production of nuclear factor kappa beta (NFkappabeta), cyclo-oxygenase-2 (COX-2) and inducible NO synthase (iNOS); and damage caused by O&NS to membrane fatty acids and functional proteins. **These IO&NS pathways are induced by a number of trigger factors, for example psychological stress, strenuous exercise, viral infections and an increased translocation of LPS from gram-bacteria (leaky gut).** The 'psychosomatic' symptoms experienced by CFS patients are caused by intracellular inflammation (aches and pain, muscular tension, fatigue, irritability, sadness, and the subjective feeling of infection); damage caused by O&NS (aches and pain, muscular tension and fatigue); and gut-derived inflammation (complaints of irritable bowel). Inflammatory pathways (monocytic activation) are also detected in somatizing disorder.

Summary: 'Functional' symptoms, as occurring in CFS and somatization, have a genuine organic cause, that is activation of peripheral and central IO&NS pathways and gut-derived inflammation. The development of new drugs, aimed at treating those disorders, should target these IO&NS pathways.“

Veröffentlichung 18:

Normalization of the increased translocation of endotoxin from gram negative enterobacteria (leaky gut) is accompanied by a remission of chronic fatigue syndrome - PubMed (nih.gov)

In: Neuroendocrinology Letters. 2007 Dec;28(6):739-44.

„Abstract

There is now evidence that chronic fatigue syndrome (CFS) is accompanied by an increased translocation of endotoxins from gram-negative enterobacteria through the gut wall, as demonstrated by increased prevalences and median values for serum IgM and IgA against the endotoxins of gram-negative enterobacteria. This condition can also be described as increased gut permeability or leaky gut and indicates intestinal mucosal dysfunction (IMD). Here we report a case of a 13 year old girl with CFS who showed very high values for serum IgM against the LPS of some enterobacteria and signs of oxidative and nitrosative stress, activation of the inflammatory response system, and IgG3 subclass deficiency. **Upon treatment with specific antioxidants and a "leaky gut diet", which both aim to treat increased gut permeability, and immunoglobins intravenously, the increased translocation of the LPS of gram negative enterobacteria normalized and this normalization was accompanied by a complete remission of the CFS symptoms**.“

Veröffentlichung 19:

Recognizing the Leaky Gut as a Trans-diagnostic Target for Neuroimmune Disorders Using Clinical Chemistry and Molecular Immunology Assays - PubMed (nih.gov)

In: Current Topics in Medicinal Chemistry. 2018;18(19):1641-1655.
doi: 10.2174/1568026618666181115100610.

„Abstract

Background: **Increased intestinal permeability with heightened translocation of Gramnegative bacteria, also known as "leaky gut", is associated with the pathophysiology of neuroimmune disorders, such as Major Depressive Disorder (MDD), Chronic Fatigue Syndrome (CSF) and (deficit) schizophrenia,** as well as with general medical disorders, including irritable bowel syndrome. This review aims to summarize clinical biochemistry and molecular immunology tests that may aid in the recognition of leaky gut in clinical practice.

Methods: We searched online libraries, including PubMed/MEDLINE, Google Scholar and Scopus, with the key words "diagnosis" or "biomarkers" and "leaky gut", "bacterial translocation", and "intestinal permeability" and focused on papers describing tests that may aid in the clinical recognition of leaky gut.

Results: To evaluate tight junction barrier integrity, serum IgG/IgA/IgM responses to occludin and zonulin and IgA responses to actomyosin should be evaluated. The presence of cytotoxic bacterial products in serum can be evaluated using IgA/IgM responses to sonicated samples of common Gram-negative gut commensal bacteria and assays of serum lipopolysaccharides (LPSs) and other bacterial toxins, including cytolethal distenting toxin, subunit B. Major factors associated with increased gut permeability, including gut dysbiosis and yeast overgrowth, use of NSAIDs and alcohol, food hypersensitivities (IgE-mediated), food intolerances (IgG-mediated), small bacterial overgrowth (SIBO), systemic inflammation, psychosocial stressors, some infections (e.g., HIV) and dietary patterns, should be assessed. Stool samples can be used to assay gut dysbiosis, gut inflammation and decreased mucosal defenses using assays of fecal growth of bacteria, yeast and fungi and stool assays of calprotectin, secretory IgA, β-defensin, α- antitrypsin, lysozyme and lactoferrin. Blood and breath tests should be used to exclude common causes of increased gut permeability, namely, food hypersensitivities and intolerances, SIBO, lactose intolerance and fructose malabsorption.

Discussion: Here, we propose strategies to recognize "leaky gut" in a clinical setting using the most adequate clinical chemistry and molecular immunology assays.“

Anmerkungen: Zusammenhang leaky gut zu CFS.

Veröffentlichung 20:

Leaky brain in neurological and psychiatric disorders: Drivers and consequences - PubMed (nih.gov)

In: Australian and New Zealand Journal of Psychiatry. 2018 Oct;52(10):924-948.
doi: 10.1177/0004867418796955.

„Abstract

Background: The blood-brain barrier acts as a highly regulated interface; its dysfunction may exacerbate, and perhaps initiate, neurological and neuropsychiatric disorders.

Methods: In this narrative review, focussing on redox, inflammatory and mitochondrial pathways and their effects on the blood-brain barrier, a model is proposed detailing mechanisms which might explain how increases in blood-brain barrier permeability occur and can be maintained with increasing inflammatory and oxidative and nitrosative stress being the initial drivers.

Results: Peripheral inflammation, which is causatively implicated in the pathogenesis of major psychiatric disorders, is associated with elevated peripheral pro-inflammatory cytokines, which in turn cause increased blood-brain barrier permeability. Reactive oxygen species, such as superoxide radicals and hydrogen peroxide, and reactive nitrogen species, such as nitric oxide and peroxynitrite, play essential roles in normal brain capillary endothelial cell functioning; however, chronically elevated oxidative and nitrosative stress can lead to mitochondrial dysfunction and damage to the blood-brain barrier. Activated microglia, redox control of which is mediated by nitric oxide synthases and nicotinamide adenine dinucleotide phosphate (NADPH) oxidases, secrete neurotoxic molecules such as reactive oxygen species, nitric oxide, prostaglandin, cyclooxygenase-2, quinolinic acid, several chemokines (including monocyte chemoattractant protein-1 [MCP-1], C-X-C motif chemokine ligand 1 [CXCL-1] and macrophage inflammatory protein 1α [MIP-1α]) and the pro-inflammatory cytokines interleukin-6, tumour necrosis factor-α and interleukin-1β, which can exert a detrimental effect on blood-brain barrier integrity and function. Similarly, reactive astrocytes produce neurotoxic molecules such as prostaglandin E2 and pro-inflammatory cytokines, which can cause a 'leaky brain'.

Conclusion: **Chronic inflammatory and oxidative and nitrosative stress is associated with the development of a 'leaky gut'. The following evidence-based approaches, which address the leaky gut and blood-brain barrier dysfunction, are suggested as potential therapeutic interventions for neurological and neuropsychiatric disorders**: melatonin, statins, probiotics containing Bifidobacteria and Lactobacilli, N-acetylcysteine, and prebiotics containing fructo-oligosaccharides and galacto-oligosaccharides.“

Anmerkungen: Wieder eine Literaturstelle zum Zusammenhang zwischen CFS (als Beispiel für eine „neurological and neuropsychiatric disorder“).

Veröffentlichung 21:

The Role of the Microbiota-Gut-Brain Axis and Antibiotics in ALS and Neurodegenerative Diseases - PubMed (nih.gov)

In: Mikroorganismen. 2020 23. Mai8(5):784.
doi: 10.3390/Mikroorganismen8050784.

„Abstract:

The human gut hosts a wide and diverse ecosystem of microorganisms termed the microbiota, which line the walls of the digestive tract and colon where they co-metabolize digestible and indigestible food to contribute a plethora of biochemical compounds with diverse biological functions. The influence gut microbes have on neurological processes is largely yet unexplored. **However, recent data regarding the so-called leaky gut, leaky brain syndrome suggests a potential link between the gut microbiota, inflammation and host co-metabolism that may affect neuropathology both locally and distally from sites where microorganisms are found.** The focus of this manuscript is to draw connection between the microbiota-gut-brain (MGB) axis, antibiotics and the use of "BUGS AS DRUGS" for neurodegenerative diseases, their treatment, diagnoses and management and to compare the effect of current and past pharmaceuticals and antibiotics for alternative mechanisms of action for brain and neuronal disorders, such as Alzheimer disease (AD), Amyotrophic Lateral Sclerosis (ALS), mood disorders, schizophrenia, autism spectrum disorders and others. It is a paradigm shift to suggest these diseases can be largely affected by unknown aspects of the

microbiota. Therefore, a future exists for applying microbial, chemobiotic and chemotherapeutic approaches to enhance translational and personalized medical outcomes. Microbial modifying applications, such as CRISPR technology and recombinant DNA technology, among others, echo a theme in shifting paradigms, which involve the gut microbiota (GM) and mycobiota and will lead to potential gut-driven treatments for refractory neurologic diseases."

Veröffentlichung 22:

Complementary and alternative medicine for patients with chronic fatigue syndrome: a systematic review - PubMed (nih.gov)

In: BMC Complementary Medicine and Therapies. 2011 Oct 7;11:87.
doi: 10.1186/1472-6882-11-87.

„Abstract

Background: Throughout the world, patients with chronic diseases/illnesses use complementary and alternative medicines (CAM). The use of CAM is also substantial among patients with diseases/illnesses of unknown aetiology. Chronic fatigue syndrome (CFS), also termed myalgic encephalomyelitis (ME), is no exception. Hence, a systematic review of randomised controlled trials of CAM treatments in patients with CFS/ME was undertaken to summarise the existing evidence from RCTs of CAM treatments in this patient population.

Methods: Seventeen data sources were searched up to 13th August 2011. All randomised controlled trials (RCTs) of any type of CAM therapy used for treating CFS were included, with the exception of acupuncture and complex herbal medicines; studies were included regardless of blinding. Controlled clinical trials, uncontrolled observational studies, and case studies were excluded.

Results: A total of 26 RCTs, which included 3,273 participants, met our inclusion criteria. The CAM therapy from the RCTs included the following: mind-body medicine, distant healing, massage, tuina and tai chi, homeopathy, ginseng, and dietary supplementation. Studies of qigong, massage and tuina were demonstrated to have positive effects, whereas distant healing failed to do so. Compared with placebo, homeopathy also had insufficient evidence of symptom improvement in CFS. Seventeen studies tested supplements for CFS. Most of the supplements failed to show beneficial effects for CFS, with the exception of NADH and magnesium.

Conclusions: **The results of our systematic review provide limited evidence for the effectiveness of CAM therapy in relieving symptoms of CFS.** However, we are not able to draw firm conclusions concerning CAM therapy for CFS due to the limited number of RCTs for each therapy, the small sample size of each study and the high risk of bias in these trials. Further rigorous RCTs that focus on promising CAM therapies are warranted."

Veröffentlichung 23:

Chronic fatigue syndrome (CFS): Suggestions for a nutritional treatment in the therapeutic approach - PubMed (nih.gov)

In: Biomedicine & Pharmacotherapy, 2019 Jan; 109:1000-1007.
doi: 10.1016/j.biopha.2018.10.076. Epub 2018 Nov 5.

„Abstract

Chronic fatigue syndrome (CFS) is known as a multi-systemic and complex illness, which induces fatigue and long-term disability in educational, occupational, social, or personal activities. The diagnosis of this disease is difficult, due to lacking a proper and suited diagnostic laboratory test, besides to its multifaceted symptoms. Numerous factors, including environmental and immunological issues, and a large spectrum of CFS symptoms, have recently been reported. In this review, we focus on the nutritional intervention in CFS, discussing the many immunological, environmental, and nutritional aspects currently investigated about this disease. Changes in immunoglobulin levels, cytokine profiles and B- and T- cell phenotype and declined cytotoxicity of natural killer cells, are commonly reported features of immune dysregulation in CFS. **Also, some nutrient deficiencies (vitamin C, vitamin B complex, sodium, magnesium, zinc, folic acid, l-carnitine, l-tryptophan, essential fatty acids, and coenzyme Q10) appear to be important in the severity and exacerbation of CFS symptoms. This review highlights a far-driven analysis of mineral and vitamin deficiencies among CFS patients.“**

Veröffentlichung 24:

Intravenous nutrient therapy: the "Myers' cocktail" - PubMed (nih.gov)

In: Alternative Medicine Review. 2002 Oct;7(5):389-403.

„Abstract

Building on the work of the late John Myers, MD, the author has used an intravenous vitamin-and-mineral formula for the treatment of a wide range of clinical conditions. The modified "Myers' cocktail," which consists of magnesium, calcium, B vitamins, and vitamin C, has been found to be effective against acute asthma attacks, migraines, fatigue (including chronic fatigue syndrome), fibromyalgia, acute muscle spasm, upper respiratory tract infections, chronic sinusitis, seasonal allergic rhinitis, cardiovascular disease, and other disorders. **This paper presents a rationale for the therapeutic use of intravenous nutrients, reviews the relevant published clinical research, describes the author's clinical experiences, and discusses potential side effects and precautions.“**

Veröffentlichung 25:

Effect of high dose vitamin C on Epstein-Barr viral infection - PubMed (nih.gov)

In: Medical Science Monitor. 2014 May 3;20:725-32.
doi: 10.12659/MSM.890423.

„Abstract

Background Many natural compounds were tested for the ability to suppress viral replication. The present manuscript details an analysis of high dose vitamin C therapy on patients with EBV infection. Material and Methods The data were obtained from the patient history database at the Riordan Clinic. Among people in our database who were treated with intravenous vitamin C (7.5 g to 50 g infusions) between 1997 and 2006, 178 patients showed elevated levels of EBV EA IgG (range 25 to 211 AU) and 40 showed elevated levels of EBV VCA IgM (range 25 to 140 AU). Most of these patients had a diagnosis of chronic fatigue syndrome, with the rest being diagnosed as having mononucleosis, fatigue, or EBV infection. Results Our data provide evidence that high dose intravenous vitamin C

therapy has a positive effect on disease duration and reduction of viral antibody levels. Plasma levels of ascorbic acid and vitamin D were correlated with levels of antibodies to EBV. We found an inverse correlation between EBV VCA IgM and vitamin C in plasma in patients with mononucleosis and CFS meaning that patients with high levels of vitamin C tended to have lower levels of antigens in the acute state of disease. In addition, a relation was found between vitamin D levels and EBV EA IgG with lower levels of EBV early antigen IgG for higher levels of vitamin D. Conclusions The clinical study of ascorbic acid and EBV infection showed the reduction in EBV EA IgG and EBV VCA IgM antibody levels over time during IVC therapy that is consistent with observations from the literature that millimolar levels of ascorbate hinder viral infection and replication in vitro."

Veröffentlichung 26:

A Systematic Review of Drug Therapies for Chronic Fatigue Syndrome/Myalgic Encephalomyelitis - PubMed (nih.gov)

In: Clinical Therapeutics. 2016 Jun;38(6):1263-1271.e9.
doi: 10.1016/j.clinthera.2016.04.038. Epub 2016 24. Mai 2016

„Abstract

Purpose: The pathogenesis of chronic fatigue syndrome or myalgic encephalomyelitis (CFS/ME) is complex and remains poorly understood. Evidence regarding the use of drug therapies in CFS/ME is currently limited and conflicting. The aim of this systematic review was to examine the existing evidence on the efficacy of drug therapies and determine whether any can be recommended for patients with CFS/ME.

Methods: MEDLINE, EMBASE, and PubMed databases were searched from the start of their records to March 2016 to identify relevant studies. Randomized controlled trials focusing solely on drug therapy to alleviate and/or eliminate chronic fatigue symptoms were included in the review. Any trials that considered graded exercise therapy, cognitive behavior therapy, adaptive pacing, or any other nonpharmaceutical treatment plans were excluded. The inclusion criteria were examined to ensure that study participants met specific CFS/ME diagnostic criteria. Study size, intervention, and end point outcome domains were summarized.

Findings: A total of 1039 studies were identified with the search terms; 26 studies met all the criteria and were considered suitable for review. Three different diagnostic criteria were identified: the Holmes criteria, International Consensus Criteria, and the Fukuda criteria. Primary outcomes were identified as fatigue, pain, mood, neurocognitive dysfunction and sleep quality, symptom severity, functional status, and well-being or overall health status. Twenty pharmaceutical classes were trialed. Ten medications were shown to be slightly to moderately effective in their respective study groups ($P < 0.05$).

Implications: **These findings indicate that no universal pharmaceutical treatment can be recommended**. The unknown etiology of CFS/ME, and complications arising from its heterogeneous nature, contributes to the lack of clear evidence for pharmaceutical interventions. However, patients report using a large number and variety of medications. This finding highlights the need for trials with clearly defined CFS/ME cohorts. Trials based on more specific criteria such as the International Consensus Criteria are recommended to identify specific subgroups of patients in whom treatments may be beneficial."

<u>Anmerkungen:</u> Dies ist ein Nachweis, dass keine wirksame rein medikamentöse Therapie (im Gegenzug zur Therapie mit Mikronährstoffen) existiert, so dass keine Alternative zur durchgeführten Protokoll-Infusions-Therapie existiert.

Veröffentlichung 27:

Possible role of oxidative stress and immunological activation in mouse model of chronic fatigue syndrome and its attenuation by olive extract - PubMed (nih.gov)

In: Journal of Neuroimmunology 2010 Sep 14;226(1-2):3-7.
doi: 10.1016/j.jneuroim.2010.05.021. Epub 2010 May 26.

„Abstract

Various putative theories involved in the development of chronic fatigue syndrome revolve around the role of stress, infection and oxidative stress. **Scientific evidence highlighting the protective role of nutritional supplements in chronic fatigue syndrome is lacking.** Based on these assumptions, the present study was designed to evaluate the effect of olive extract in a mouse model of immunologically-induced fatigue, wherein purified lipopolysaccharide (LPS) and Brucella abortus (BA) antigen were used as immunogens. The assessment of chronic fatigue syndrome was based on immobility period during chronic water-immersion stress test for 10 min daily. The stress-induced hyperalgesia was measured by tail withdrawal latency. Mice challenged with LPS or BA for 19 days showed significant increase in the immobility time, hyperalgesia and oxidative stress on the 19th day. Serum tumor necrosis factor-alpha (TNF-α) levels were also markedly increased with LPS or BA challenge. Concurrent treatment with olive extract resulted in a significant decrease in the immobility time as well as hyperalgesia. There was significant attenuation of oxidative stress as well as serum TNF-α levels. The results of the present study strongly indicate the role of oxidative stress and immunological activation in the pathophysiology of chronic fatigue syndrome and highlight the valuable role of olive extract in combating chronic fatigue syndrome.“

Veröffentlichung 28:

News and views in myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS): The role of co-morbidity and novel treatments - PubMed (nih.gov)

In: Medical Hypotheses. 2020 Jan;134:109444. doi: 10.1016/j.mehy.2019.109444. Epub 2019 Oct 22.

„Abstract

Though affecting many thousands of patients, myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) should be considered an orphan disease, since the cause remains elusive and no treatment is available that can provide complete cure. There is reasonable insight into the pathogenesis of signs and symptoms, and treatments specifically directed to immunological, inflammatory and metabolic processes offer relief to an increasing number of patients. Particular attention is given to the importance of co-morbidity requiring appropriate therapy. Promising results are obtained by treatment with Metformin, or possibly Momordica charantia extract, which will correct insulin resistance, with Meldonium improving the transportation of glucose into the mitochondria, with sodium dichloroacetate activating pyruvate dehydrogenase, and **with nutraceutical support reducing oxidative and inflammatory impairment**.“

Veröffentlichung 29:

Mercury-induced autoimmunity: Drifting from micro to macro concerns on autoimmune disorders - PubMed (nih.gov)

In: Journal of Clinical Immunology. 2020 Apr;213:108352.
doi: 10.1016/j.clim.2020.108352. Epub 2020 Feb 4.

„Abstract

Mercury (Hg) is widely recognized as a neurotoxic metal, besides it can also act as a proinflammatory agent and immunostimulant, depending on individual exposure and susceptibility. Mercury exposure may arise from internal body pathways, such as via dental amalgams, preservatives in drugs and vaccines, and seafood consumption, or even from external pathways, i.e., occupational exposure, environmental pollution, and handling of metallic items and cosmetics containing Hg. In susceptible individuals, chronic low Hg exposure may trigger local and systemic inflammation, even exacerbating the already existing autoimmune response in patients with autoimmunity. Mercury exposure can trigger dysfunction of the autoimmune responses and aggravate immunotoxic effects associated with elevated serum autoantibodies titers. The purpose of the present review is to provide a critical overview of the many issues associated with Hg exposure and autoimmunity. In addition, the paper focuses on individual susceptibility and other health effects of Hg.“

Anmerkungen: Zusammenhang zwischen Quecksilber und Autoimmunität. Deshalb müssen diese Parameter laborchemisch bestimmt werden!

Veröffentlichung 30:

Evidence supporting a link between dental amalgams and chronic illness, fatigue, depression, anxiety, and suicide - PubMed (nih.gov)

In: Neuroendocrinology Letters. 2014;35(7):537-52.

Abstract

The purpose of this review is to examine the evidence for a relationship between mercury (Hg) exposure from dental amalgams and certain idiopathic chronic illnesses--chronic fatigue syndrome (CFS), fibromyalgia (FM), depression, anxiety, and suicide. Dental amalgam is a commonly used dental restorative material that contains approximately 50% elemental mercury (Hg0) by weight and releases Hg0 vapor. Studies have shown that chronic Hg exposure from various sources including dental amalgams is associated with numerous health complaints, including fatigue, anxiety, and depression--and these are among the main symptoms that are associated with CFS and FM. In addition, several studies have shown that the removal of amalgams is associated with improvement in these symptoms. Although the issue of amalgam safety is still under debate, the preponderance of evidence suggests that Hg exposure from dental amalgams may cause or contribute to many chronic conditions. **Thus, consideration of Hg toxicity may be central to the effective clinical investigation of many chronic illnesses, particularly those involving fatigue and depression**.“

Veröffentlichung 31:

The frequency of mercury intolerance in patients with chronic fatigue syndrome and healthy controls - PubMed (nih.gov)

In: Contact Dermatitis. 1999 Jul;41(1):60-1. doi: 10.1111/j.1600-0536.1999.tb06225.x.

Kein Abstract verfügbar, Zusammenhang zwischen Quecksilber und CFS offensichtlich aber schon 1999 diskutiert!