

LDN and CFS and Fibromyalgia

Kent Holtorf, MD

CFS definition

1. Clinically evaluated, unexplained, persistent, or relapsing chronic fatigue that is of new or definite onset (has not been lifelong): is not the result of ongoing exertion; is not substantially alleviated by rest; and results in substantial reduction in previous levels of occupational, educational, social, or personal activities.

(CDC Criteria)

CFS definition

2. Concurrent occurrence of four or more of the following symptoms, all of which must have persisted or recurred during six or more consecutive months of illness and must not have predated the fatigue:

(CDC Criteria)

CFS definition

- A. Self-reported impairment in short term memory or concentration severe enough to cause substantial reduction in previous levels of occupational, educational, social, or personal activities.
- B. Sore throat
- C. Tender cervical or axillary lymph nodes
- D. Muscle pain
- E. Multi-joint pain without joint swelling or redness
- F. Headaches of a new type, pattern, or severity
- G. Unrefreshing sleep
- H. Postexertional malaise lasting more than twenty-four hours

Fibromyalgia definition 1990 ACR

A history of widespread pain. The patient must be experiencing pain or achiness, steady or intermittent, for at least 3 months. At times, the pain must have been present:

- On both sides of the body
- Both above and below the waist
- Midbody-for example, in the neck, midchest, midback, or headache.
- Pain on at least eleven of the eighteen tender points

Definition myalgic encephalomyelitis

- Postexertional fatigue
- Neurological impairment—cognitive dysfunction, Pain or sleep disturbance
- Immune/gastrointestinal impairment-sore throat, tender lymph nodes, poor immunity, abdominal dysfunction, or food sensitivities
- Energy metabolism/transport impairments-orthostatic, palpitations, air hunger, low body temp, sweating episodes, temperature intolerance

Definition CFS/FM/ME

Problems with definition?

- These are research definitions and exclude the majority of people that suffer from these syndromes
- Doesn't address underlying cause
- Promotes treatments limited to simple symptomatic therapies
- Disincentive to determine underlying abnormalities

CFS/FM/ME

CFS, CFIDS, FMS, MCS, ME, and GWS are overlapping syndromes and have same underlying pathophysiology.

CFS/FM/ME

- Many unanswered questions
- Vicious cycle pathophysiology
- Poorly treated in the “standard medical care” given in the US.

However, they are very
treatable conditions!

Specificity

- If the CDC criteria is met, the diagnosis of CFS carries a high specificity and is associated with numerous documented physiologic abnormalities

BMC Health Services Research 2003

Annals of Internal Medicine 1994

Specificity

- For instance, it has been shown that in patients diagnosed with both lupus and fibromyalgia, it is much more likely that the person has FM and that lupus is a misdiagnosis (although they can have both), the underlying pathophysiology is usually more consistent with FM and appropriate treatment is for FM and not lupus.
- *“Fibromyalgia is not merely a diagnosis of exclusion”*

Blumenthal, Cleveland Clinic Journal of Medicine 2002

How to quickly diagnose

Unexplained fatigue that significantly interferes with functioning and is associated with any two of the following:

1. Brain fog
2. Unrestful sleep
3. Diffuse achiness
4. Bowel dysfunction
5. Unexplained neuropathy
6. Recurrent and/or persistent infections or flu-like feelings
7. Post exertional malaise

Dysfunctions

- Immune dysfunction
- Disordered sleep
- Hormonal deficiencies (not picked up on standard blood tests)
- Nutritional deficiencies
- Infections
- Mitochondrial dysfunction
- Coagulation defect
- Gastrointestinal dysfunction

Associated Conditions

- Chronic Sinusitis
- Multiple Chemical Sensitivity (MCS)
- Sensitivity to medications
- Low body temperature
- Allergies
- Sensitivity to temperature or barometric changes
- Intolerance to alcohol
- Hypoglycemia
- Dizziness/vertigo
- Low blood pressure
- Low grade fevers
- Heart palpitations
- Frequent infections
- Irritable Bowel Syndrome
- Vulvadynia
- Headaches (migraine and tension)
- Depression

Associated conditions

- Autoimmune diseases (lupus, RA)
- Restless Leg Syndrome
- Weight Gain
- Increased thirst
- Low body temp
- Insulin resistance
- Yeast overgrowth
- Carpal tunnel syndrome
- Painful or irregular menstrual periods
- Sleep disturbances
- Brain fog
- Shortness of breath
- Confusion with numbers, names, words etc.
- Mood swings
- Numbness or tingling

Impact of CFS/FM

- An epidemiological study conducted in Australia published in the *Medical Journal of Australia* investigated the impact of CFS on patients' lives and found that 43% of patients that met the criteria for CFS were disabled to a degree that they were unable to attend school or work

Medical Journal of Australia, 1990

Prognosis with Standard Medical Treatment

- A 5 year study entitled, *Illness and Disability in Danish CFS Patients at Diagnosis and 5-year follow-up* concluded, “CFS patients exhibit severe, long-term functional impairment.
- *Substantial improvement is uncommon, less than 6%*

J. Psycho Res, 2004

Prognosis with Standard Medical Treatment

- An American study in which 64% of patients reported a certain degree of improvement.
- Only 2% experienced a complete recovery, with 40% remaining unable to work.

Bombardier, C.H. and Buchwald, D. (1995)
'Outcome and prognosis of patients with
chronic fatigue and chronic fatigue
syndrome,' *Archives of Internal Medicine*,
155, p.2105-10

Prognosis with Standard Medical Treatment

- Joyce et al published a review entitled *The Prognosis of Chronic Fatigue and Chronic Fatigue Syndrome: A Systematic Review*.
- *This review of 26 studies found that adults who met the CDC criteria of CFS had a poor prognosis with less than 10% recovering and the majority do not improve over time with standard medical care.*

Joyce J, et al. *The prognosis of chronic fatigue and chronic fatigue syndrome: a systematic review.* Q J Med 1997;90(3):223-33

Prognosis with Standard Medical Treatment

- Prospective study of 146 FM patients compared standard medical care to standard medical care plus cognitive behavioral therapy (CBT).
- Standard medical care for CFS/FM includes muscle relaxants, antidepressants, NSAIDs, passive stretching and graded exercise
- Study found only 12% of individuals improved with standard care.

J Rheumatol. 2002

CFS/FM/ME

Why are these conditions so poorly treated?

1. Only simple symptomatic treatments approved for FM (pregabalin, duloxetine, milnacipran)
2. Many doctors don't believe it is a real condition-If they cannot treat it, it must not be real.
3. Standard laboratory tests are usually normal (Can pick out CFS/FM on blood test about 80% of time and likely severity)
4. Health insurers can avoid paying for treatment and testing if they can make believe these syndromes are not real or physical.
5. 75 percent of those affected are female.
6. These conditions cannot be treated with the average eight minute office visit.

Doctor's Knowledge

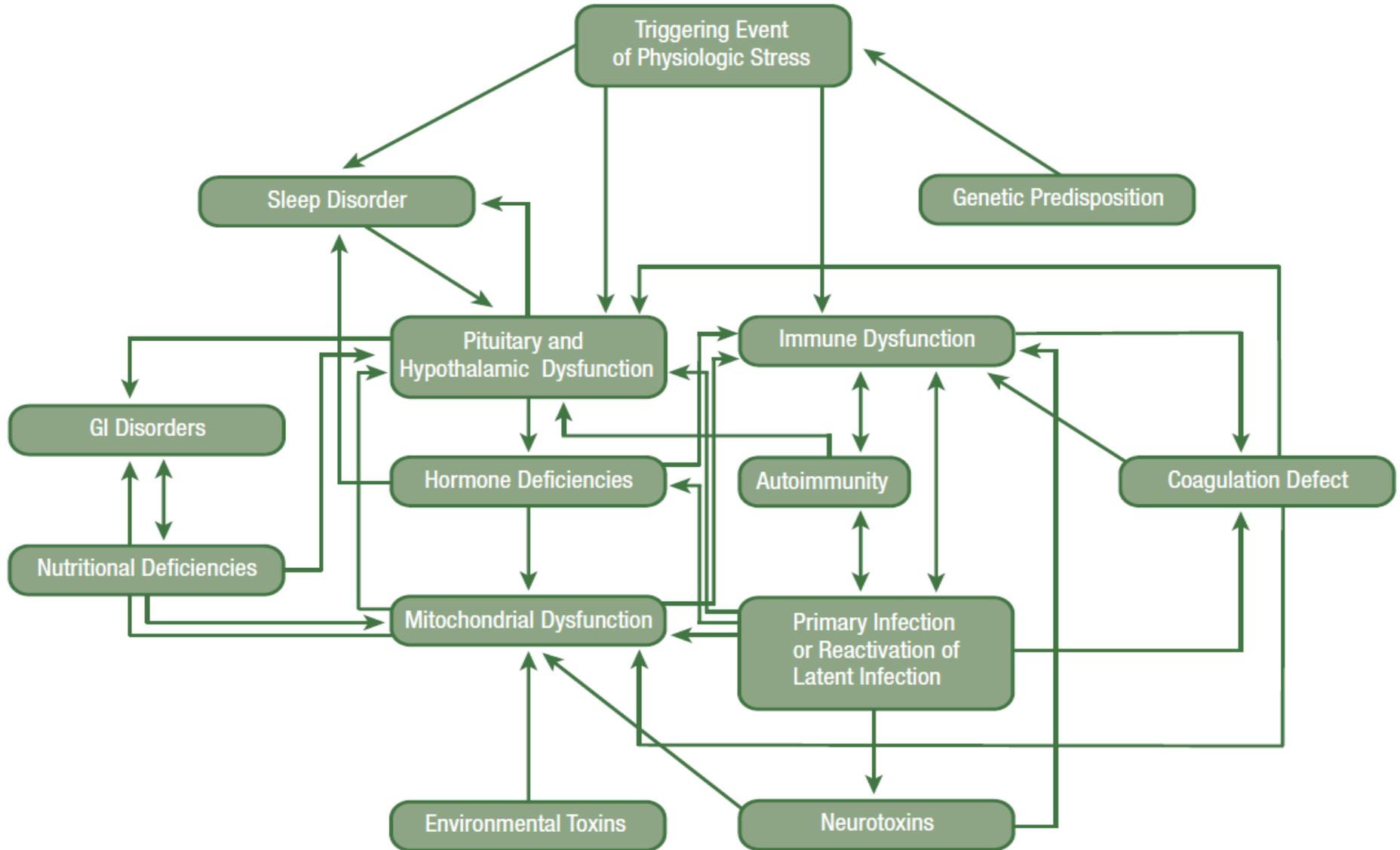
- A survey published in the April 2005 journal *Family Practice* entitled *Chronic Fatigue Syndrome: A Survey of GP's Attitudes and Knowledge* found that approximately half of primary care physicians did not even have rudimentary knowledge of CFS/FM and were not confident in their ability to even make the diagnosis.

Family Practice 2005

Pathophysiology of CFS/FM

- CFS/FM represent a mix of many different processes with a common endpoint
- Measurable hypothalamic, pituitary, immune and coagulation dysfunction.
- Each problem may trigger other problems

Cycle of Dysfunction



CFS/FM

Chronic Fatigue Syndrome and
Fibromyalgia are very treatable
Conditions!

When the multiple dysfunctions present are treated, significant improvement is seen, almost without exception.

Studies

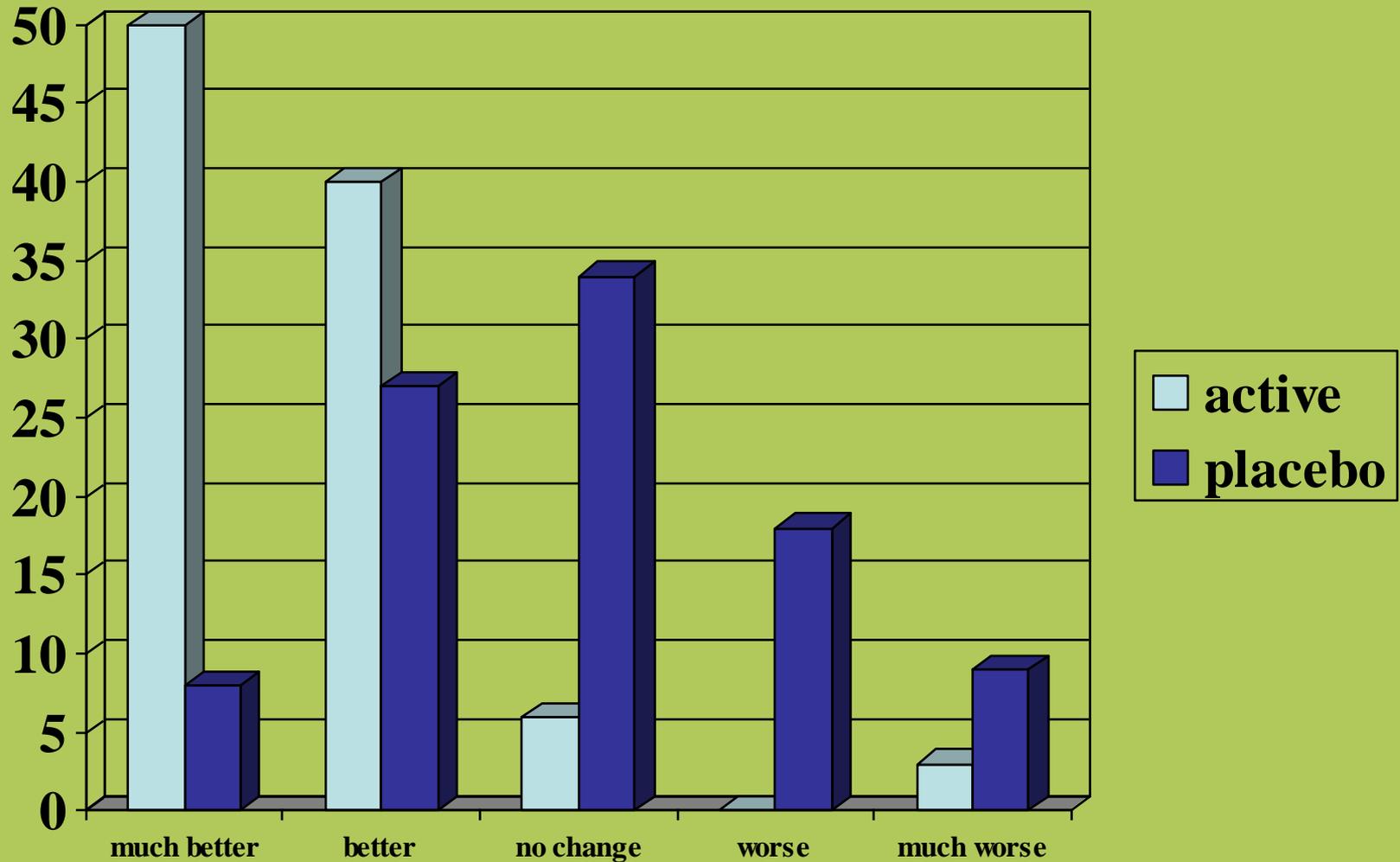
(Randomized double-blind, placebo control trial)

When the multiple dysfunctions are treated, including nutritional deficiencies, disorder sleep, hormonal deficiencies, infections and mitochondrial dysfunction, 57% of patients with CFS/FM will have complete resolution of symptoms and 39% will have incomplete but significant resolution of symptoms.

Summary: 96% will have significant improvement or total resolution of symptoms

Teitelbaum J, Bird B Greenfield R, et al. Effective Treatment of Chronic Fatigue Syndrome and Fibromyalgia-A Randomized, Double-Blind, Placebo-Controlled, Intent-To-Treat Study. J Chronic Fatigue Syndrome 2001;8(2):3-28

Journal of Chronic Fatigue Syndrome 2001



Outcomes

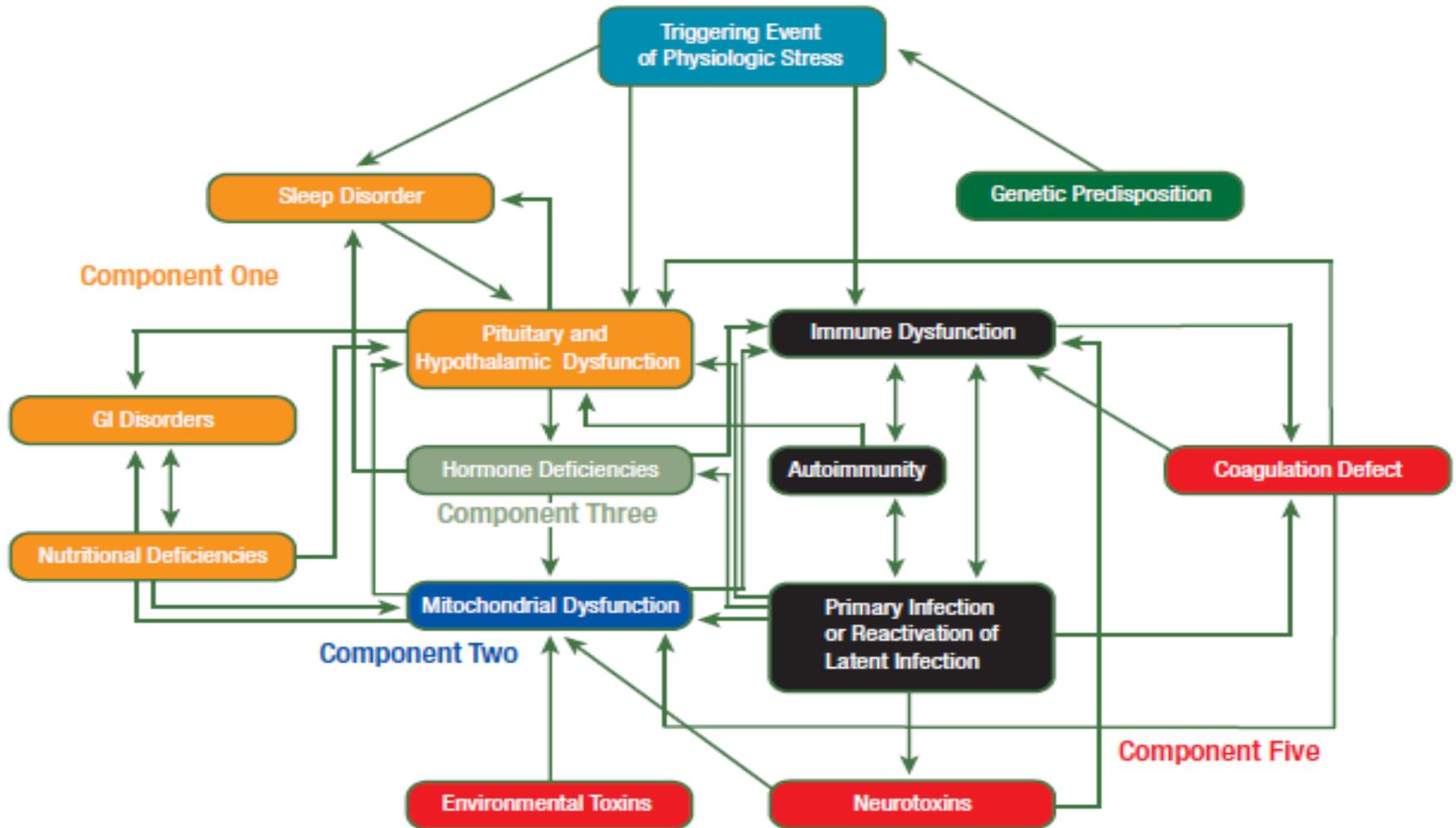
Published in JCFS

- 500 consecutive patients on computerized outcome assessment demonstrated that a multi-system treatment protocol that addresses the known physiologic abnormalities in CFS and fibromyalgia resulted in:
 - 94 percent of patients having overall improvement by the 4th visit
 - 75 percent noting significant overall improvement
 - 62 percent reported substantial overall improvement.
 - The average energy level and sense of well-being for patients doubled by the fourth visit.
- The effectiveness of this multi-system treatment was further confirmed through the analysis of the cumulative findings of over 40 independent physicians and over 5,000 patients.
- Prior to treatment at the Holtorf Medical Group, the patients had seen an average of 7.2 different physicians for the treatment of CFS and/or FM without significant improvement.

Six Component Approach

- Component One Stabilize the Patient
- Component Two Mitochondrial Enhancement
- Component Three Balance the Hormones
- **Component Four** **Treat the Infectious/Immune Components**
- Component Five Addressing Unique Etiologies
- Component Six Maintenance

Integrated Approach to the Cycle of Dysfunction



Component Six: Your maintenance plan

Component 4

Treat the immune dysfunction and
Infectious component

- TH1 to TH2 imbalance leads to vicious cycle of chronic infections
 - Becomes “chicken and the egg”
- Thus, immune modulatory treatment is a key to the ability to successful treatment of chronic infections and overall successful treatment of CFS/FM

Viral

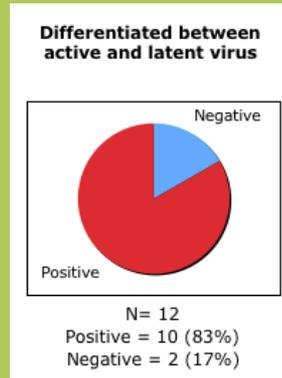
- Many possible
- EBV, HHV-6, CMV, enterovirus
- Did symptoms start with Mono and never fully recovered?
- Recurrent viral syndrome

HHV-6 and CFS

- 70% of CFS/FM patients positive for HHV-6 using primary cell cultures and confirmation assays of monoclonal antibodies and PCR

Annals of Internal Medicine 1992

HHV-6 and CFS/FM



83% of the studies demonstrate a large portion of CFS/FM patients have an active HHV-6 infection.

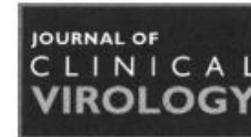
Assays that differentiated between active and latent virus: 83% positive

Author	Year	CFS +	Controls +	Method used	Result	Size of study
Nicolson	2003	31%	9%	PCR on serum or plasma	Positive	200 CFS, 100 controls
Koelle	2002	0%	0%	PCR on serum or plasma	Negative	22 CFS, 22 controls (twins)
Ablashi	2000	54%	8%	IgM Early Antigen antibodies	Positive	35 CFS, 25 controls
Ablashi	2000	+++	+	Lymphocyte response	Positive	10 CFS, 6 controls
Ablashi	2000	57%	16%	IgM Early Antigen antibodies	Positive	35 CFS, 25 controls
Reeves	2000	0%	0%	Viral isolation	Negative	26 CFS, 52 controls
Zorzenon	1996	73%	0%	CPE/IFA Positive	Positive	52 CFS, 51 controls
Wagner	1996	39%	-	Primary culture/isolation	Positive	107 CFS
Patnaik	1995	77%	12%	IgM Early Antigen antibodies	Positive	119 CFS, 165 controls
Secchiero	1995	3%	0%	PCR on serum or plasma	Positive*	39 patients, 37 controls
Buchwald	1992	70%	20%	Primary cell culture	Positive	113 CFS, 40 controls
Josephs	1991	43%	0%	Short term culture	Positive	7 CFS, 2 controls

HHV-6 and CFS/FM



Journal of Clinical Virology 37 Suppl. 1 (2006) S33–S38



www.elsevier.com/locate/jcv

Use of valganciclovir in patients with elevated antibody titers against Human Herpesvirus-6 (HHV-6) and Epstein–Barr Virus (EBV) who were experiencing central nervous system dysfunction including long-standing fatigue

Andreas M. Kogelnik^a, Kristin Loomis^b, Mette Hoegh-Petersen^c,
Fernando Rosso^{a,c}, Courtney Hischier^b, Jose G. Montoya^{a,c,*}

^aStanford University School of Medicine, Stanford, CA, USA

^bHHV-6 Foundation, Santa Barbara, CA, USA

^cPalo Alto Medical Foundation Research Institute, Palo Alto, CA, USA

Abstract

Background: Twelve patients with long-standing symptoms of central nervous system (CNS) dysfunction were found to have elevated antibody titres to human herpesvirus-6 (HHV-6) and Epstein–Barr virus (EBV). All patients had four or more of the following neurocognitive symptoms: impaired cognitive functioning, slowed processing speed, sleep disturbance, short-term memory deficit, fatigue and symptoms consistent with depression.

Objectives: We sought to determine whether elevated antibodies to EBV and HHV-6 indicated chronic viral activation in patients with CNS dysfunction and if their symptoms could be improved by suppressing viral activity with oral valganciclovir.

Study design: Patients with high IgG antibody titers against HHV-6 and EBV who were suffering from central nervous system dysfunction and debilitating fatigue for more than one year (median 3 years, range 1–8 years) were treated with 6 months of valganciclovir in an open label study.

Results: Nine out of 12 (75%) patients experienced near resolution of their symptoms, allowing them all to return to the workforce or full time activities. In the nine patients with a symptomatic response to treatment, EBV VCA IgG titers dropped from 1:2560 to 1:640 ($p=0.008$) and HHV-6 IgG titers dropped from a median value of 1:1280 to 1:320 ($p=0.271$). Clinically significant hematological toxicity or serious adverse events were not observed among the 12 patients.

Conclusion: These preliminary clinical and laboratory observations merit additional studies to establish whether this clinical response is mediated by an antiviral effect of the drug, indirectly via immunomodulation or by placebo effect.

© 2006 Elsevier B.V. All rights reserved.

HHV-6 and CFS/FM

 Open Access Full Text Article

ORIGINAL RESEARCH

Subset-directed antiviral treatment of 142 herpesvirus patients with chronic fatigue syndrome

This article was published in the following Dove Press journal:
Virus Adaptation and Treatment
24 May 2010
[Number of times this article has been viewed](#)

A Martin Lerner¹
Safedin Beqaj²
James T Fitzgerald³
Ken Gill⁴
Carol Gill⁴
James Edington⁴

¹Department of Medicine, William Beaumont Hospital, Royal Oak;

²Wayne State University School of Medicine, Detroit; ³Department of Medical Education, University of Michigan Medical School, Ann Arbor, Michigan; ⁴The Dr A Martin Lerner Chronic Fatigue Syndrome Foundation, Beverly Hills, Michigan, USA

Purpose: We hypothesized that chronic fatigue syndrome (CFS) may be caused by single or multiple Epstein–Barr virus (EBV), cytomegalovirus (HCMV), or human herpesvirus 6 (HHV6) infection. To determine if CFS life-altering fatigue and associated findings including muscle aches, tachycardia at rest, chest aches, left ventricular dysfunction, syncope, and elevated herpesvirus serum antibody titers are reversed by long-term subset-directed valacyclovir and/or valganciclovir.

Patients and methods: Data were collected at physician visits every 4–6 weeks from 142 CFS patients at one clinic from 2001 to 2007. To be included in this study, patients had to be followed for at least six months. The data captured included over 7000 patient visits and over 35,000 fields of information. Severity of fatigue was monitored by a validated Energy Index Point Score® (EIPS®). Baseline and follow-up serum antibody titers to EBV, HCMV, and HHV6, as well as coinfections with *Borrelia burgdorferi*, *Anaplasma phagocytophila*, *Babesia microti*, and antistreptolysin O, 24-hour ECG Holter monitors, 2D echocardiograms, cardiac dynamic studies, symptoms, and toxicity were captured and monitored. International criteria for CFS plus a specifically designed CFS diagnostic panel were used.

Results and conclusions: The Group A herpesvirus CFS patients (no coinfections) returned to a near-normal to normal life ($P = 0.0001$). The long-term EIPS value increased (primary endpoint, $P < 0.0001$) with subset-directed long-term valacyclovir and/or valganciclovir therapy. Secondary endpoints (cardiac, immunologic, and neurocognitive abnormalities) improved or disappeared. Group B CFS patients (herpesvirus plus coinfections) continued to have CFS.

Keywords: valacyclovir, valganciclovir, treatment, chronic fatigue syndrome, CFS, Energy Index Point Score®, EIPS®

Mycoplasma and CFS/FM

- 68% of CFS/FM patients were positive for Mycoplasma by PCR

Journal Immunology and Medical Microbiology, 2002

- 63% of patients had active Mycoplasma vs. 9% controls with 50% having *M. fermentans* vs. 0% of controls

Biomed. Therapy 1998

Mycoplasma and CFS/FM

- 565 CFS/FM patients vs. 71 controls. 53% were positive for Mycoplasma vs. 10% of normals by PCR. 53% positive for *M. Fermentans* vs. 3% normals

International Journal Medicine Biology Environment 2000

- 59% of CFS/FM patients had multiple Mycoplasma species with 48% having *M. fermentans*, 31% having *M. hominis* and 20% having *M. pentrans*

Eur J Clin Microbiol Infect Dis 1999

Infections and CFS/FM

- 52% of CFS/FM patients were positive for Mycoplasma, 31% positive for HHV-6 and 7.5% positive for CP vs. 6%,9% and 1% of normals respectively

Acta Pathologica, Microbiologica et Immunologica Scandinavica 2003

Lyme

- CDC estimates that the yearly reported cases are 10 fold what was previously thought (300,000 new cases/year up from 30,000), which is more prevalent than breast cancer and HIV combined
- Standard testing IFA with reflex to WB misses 40-90% of cases.
- Exploding likely secondary to multiple modes of transmission, including tics, mosquitoes, fleas, sexually transmitted

Lyme disease

- Patients with chronic Lyme are severely ill with a multisystem illness, with dysregulation and possibly damage to nearly every organ system
- Antibiotics alone unlikely to successfully treat
- RESULT- more and more patients are seeking CAM physicians to treat their CFIDS-like illness
- The longer one is ill with Lyme, the more difficult to treat

Lyme disease

- When to expect Lyme
 - The more severe the CFS/FM
 - The more neurologic/autonomic symptoms/brain fog
 - The more “strange” symptoms the more likely Lyme disease

Markers of Immune Dysfunction

- Low NK cell function <30
- low CD 57
- Elevated C4a
- VEGF
- ECP
- ACE above 30
- Immune activation of coagulation (D-dimer, soluble fibrin monomer, prothrombin fragment 1+2, thrombin antithrombin complex, PAI-1)
- Abnormal immunoglobulins
- IGG subclass

NK Cell

Low NK cell activity is an objective marker for severe disabling CFS

Ojo-Amaize EA, Conley EJ, Peter JB. Decreased natural killer cell activity is associated with severity of chronic fatigue immune dysfunction syndrome. Clin Infect Dis. 1994 Jan;18 Suppl 1:S157-9.

A decrease in the CD57 is a marker for chronic Lyme disease and significant neurologic disease.

Clin Infect Dis 1994

Stricker RB, Winger EE. Decreased CD57 lymphocyte subset in patients with chronic Lyme disease. Immunol Lett. 2001 Feb 1;76(1):43-8.

C4(a)/C3(a)

CLINICAL IMMUNOLOGY

doi: 10.1111/j.1365-3083.2008.02191.x

Complement Split Products C3a and C4a in Chronic Lyme Disease

R. B. Stricker*,†, V. R. Savely*,†, N. C. Motanya† & P. C. Giclas‡

*International Lyme and Associated Diseases Society, Bethesda, MD, USA; †Union Square Medical Associates, San Francisco, CA, USA; and ‡Allergy and Immunology Division, Department of Pediatrics, National Jewish Medical and Research Center, Denver, CO, USA

Received 6 June 2008; Accepted in revised form 14 October 2008

Correspondence to: R. B. Stricker, MD, Union Square Medical Associates, 450 Sutter Street, Suite 1504, San Francisco, CA 94108, USA. E-mail: rstricker@usmamed.com

Abstract

Complement split products C3a and C4a are reportedly elevated in patients with acute Lyme disease. We have now examined these immunologic markers in patients with chronic Lyme disease compared to appropriate disease controls. The study population consisted of 29 healthy controls, 445 patients with chronic Lyme disease, 11 patients with systemic lupus erythematosus (SLE) and six patients with AIDS. The Lyme disease patients were divided according to predominant musculoskeletal symptoms (324 patients) or predominant neurologic symptoms (121 patients). C3a and C4a levels were measured by radioimmunoassay. All patients with chronic Lyme disease and AIDS had normal C3a levels compared to controls, whereas patients with SLE had significantly increased levels of this marker. Patients with predominant musculoskeletal symptoms of Lyme disease and AIDS patients had significantly increased levels of C4a compared to either controls, patients with predominant neurologic symptoms of Lyme disease or SLE patients. Response to antibiotic therapy in chronic Lyme disease was associated with a significant decrease in the C4a level, whereas lack of response was associated with a significant increase in this marker. In contrast, AIDS patients had persistently increased C4a levels despite antiretroviral therapy. Lyme patients with positive single-photon emission computed tomographic (SPECT) scans had significantly lower C4a levels compared to Lyme patients with normal SPECT scan results. Patients with predominant musculoskeletal symptoms of Lyme disease have normal C3a and increased C4a levels. This pattern differs from the increase in both markers seen in acute Lyme disease, and C4a changes correlate with the response to therapy in chronic Lyme disease. **C4a appears to be a valuable immunologic marker in patients with persistent symptoms of Lyme disease.**

ACE

Serum Angiotensin-Converting Enzyme as a Marker for the Chronic Fatigue-Immune Dysfunction Syndrome: A Comparison to Serum Angiotensin-Converting Enzyme in Sarcoidosis

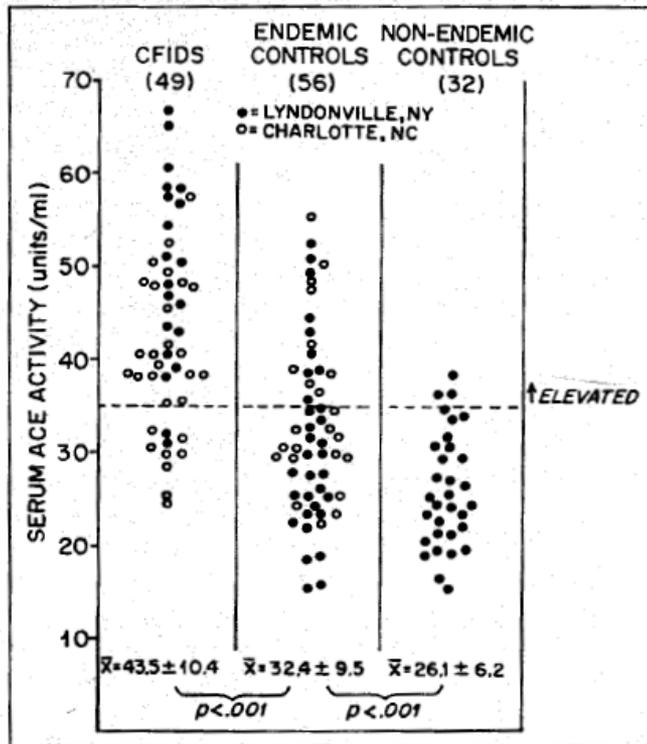


Figure 1. Serum ACE levels in CFIDS patients, endemic controls, and nonendemic controls. CFIDS patients from Lyndonville, New York, and Charlotte, North Carolina, are combined as are the two groups of endemic controls.

Serum ACE levels were elevated in 80% of patients with CFIDS and 30% of endemic control subjects as compared with 9.4% of nonendemic California control subjects

ECP/VEGF

American Journal of Pathology, Vol. 163, No. 4, October 2003
Copyright © American Society for Investigative Pathology

Infectious Angiogenesis: *Bartonella bacilliformis* Infection Results in Endothelial Production of Angiopoietin-2 and Epidermal Production of Vascular Endothelial Growth Factor

Franческа Cerimele,* Lawrence F. Brown,[†] Francisco Bravo,[‡] Garret M. Ihler,[§] Philomene Kouadio,[¶] and Jack L. Arltser*

From the Emory Skin Disease Research Core Center,* Department of Dermatology, Emory University School of Medicine, Boston, Massachusetts; the Department of Pathology,[†] Beth Israel Deaconess Hospital, Boston, Massachusetts; the Department of Medical Biochemistry,[‡] College of Medicine, Texas A&M University System Health Science Center, College Station, Texas; and the Departments of Pathology,[§] Universidad Nacional Capesano Heredia, Heredia, Costa Rica

Pathological angiogenesis, the development of a microvasculature by neoplastic processes, is a critical component of the development of tumors. The role of oncogenes in the induction of angiogenesis has been extensively studied in benign and malignant tumors. However, the role of infection in inducing angiogenesis is not well understood. Verruga peruana is a clinical syndrome caused by the bacterium *Bartonella bacilliformis*, and is characterized by the development of hemangioma-like lesions, in which bacteria colonize endothelial cells. To gain insight into how this bacteria induces angiogenesis *in vitro*, we performed *in situ* hybridization of clinical specimens of verruga peruana for the angiogenesis factors vascular endothelial growth factor (VEGF), its receptors VEGFR1 and VEGFR2, and angiopoietin-2. High-level expression of angiopoietin-2 and VEGF receptors was observed in the endothelium of verruga peruana. Surprisingly, the major source of VEGF production in verruga peruana is the overlying epidermis. Infection of cultured endothelium with *B. bacilliformis* also resulted in induction of angiopoietin-2 *in vitro*. These findings imply a collaboration between infected endothelium and overlying epidermis to induce angiogenesis. (Am J Pathol 2003; 163:1321-1327)

inflammatory processes. Oncogenes have been shown to induce the expression of angiogenic factors including vascular endothelial growth factor (VEGF).²⁻⁴ Infections can also induce angiogenesis, and both viral and bacterial infections have been known to result in increased angiogenesis *in vivo*. The viral infections most commonly associated with increased angiogenesis *in vivo* include papovaviruses (SV40, human papillomavirus, polyoma), and herpesvirus (Epstein-Barr virus, human herpesvirus 8).⁵⁻⁹ These viral infections result in neoplasia and increased angiogenesis in part through viral-specific oncogenes, including SV40 large T antigen, polyoma middle T antigen, papillomavirus E6 and E7 genes, latent membrane protein 1 (LMP-1), and HHV8/KSHV-specific G proteins. The mechanisms through which bacterial infections cause angiogenesis is not well understood.¹⁰

Verruga peruana are lesions associated with human infection with *B. bacilliformis*, an arthropod transmitted disease endemic to the highlands of Peru.¹¹ Infection with *B. bacilliformis* results in Oroya fever, a severe immunosuppressive infection characterized by high fever and anemia, which has a high mortality rate if untreated.¹² This disorder is also known as Carrion's disease, after a Peruvian medical student, Daniel Carrion, who infected himself with verruga peruana tissue to prove the etiology of the disease.¹³ The convalescent state is associated with the development of hemangioma-like lesions which have been termed verruga peruana. These lesions ultrastructurally demonstrate endothelial colonization with *Bartonella* organisms.¹⁴ The mechanisms of induction of hemangioma-like lesions by *Bartonella* infection are not well understood, but has been postulated to be due to elaboration of a proangiogenic factor from infected endothelium. We demonstrate that infection of endothelium by *Bartonella* results in induction of angiopoietin-2 *in vitro* and *in vivo*. We found evidence of active angiogenesis in these lesions with high level expression of VEGFR1 and

MedGenMed. 2007; 9(1): 38.
Published online 2007 February 27.

PMCID: PMC1925019

Copyright ©2007 Medscape

Are Various *Babesia* Species a Missed Cause for Hypereosinophilia? A Follow-up on the First Reported Case of Imatinib Mesylate for Idiopathic Hypereosinophilia

James L. Schaller, MD, MAR, Director, Glenn A. Burkland, DMD, Associate Clinical Professor, and PJ Langhoff, Medical author and science research assistant

James L. Schaller, Professional Medical Services of Naples, Naples and Tampa, Florida; Contributor Information.

Disclosure: James L. Schaller, MD, MAR, has disclosed that he has received unrestricted research grants from Forest, Cephalon, Wyeth, BioRay, Vitacost.com, QMEDRX, Zeneca, and AstraZeneca. He is a medical advisory board consultant with stock ownership in Nutraceutical Sciences Institute, and the inventor of a nutraceutical transdermal bioidentical antidepressant with a patent pending. Dr. Schaller has also disclosed that he is the author of books on babesiosis, artemisinin, and Suboxone and that all 3 topics are mentioned in this article.

Disclosure: Glenn A. Burkland, DMD, has disclosed no relevant financial relationships.

Disclosure: PJ Langhoff has disclosed no relevant financial relationships.

Abstract

Other Sections ▼

Introduction

In 2001 we reported the first case of use of imatinib mesylate (*Gleevec*) for treatment of idiopathic hypereosinophilia syndrome (HES). These findings have been replicated in some patients with HES. After 1 year of taking imatinib, the patient stopped this medication, and during the last 5 years the patient has not experienced a relapse. He has, however, recently been diagnosed with babesiosis. This new diagnosis might relate to his HES.

Methods

After 6 years we decided to follow up on this patient's treatment. We interviewed the patient, his son, his aunt, and 2 consulting physicians and also reviewed relevant laboratory results to determine whether his HES had returned and whether his residual morbidity had changed.

Results

The patient has had no relapse of HES and his eosinophil counts have remained low-normal. He was recently diagnosed with babesiosis, and was prescribed atovaquone and azithromycin with a significant decrease in morbidity. His eosinophil cationic protein levels have also fallen to low-normal since starting atovaquone and azithromycin.

Discussion

New *Babesia* species are emerging as human infections. Most do not have available antibody or polymerase chain reaction diagnostic testing at this time. Manual differential examinations are of variable utility due to low numbers of infected red blood cells, suboptimal technique, and limited experience. Therefore, a diagnosis might need to be empirical at times, and should be based on signs

MedGenMed

MedGenMed

MedGenMed

MedGenMed

Coagulation Defect

- Studies have found that 60-90% of CFS, FM and GWS patients have abnormal activation of the clotting system.

Blood Coagulation and Fibrinolysis, 1999

Blood Coagulation and Fibrinolysis, 2000

American Association of Clinical Chemistry, 2003

Immune modulation

- Increase TH1 and decrease TH2
- Boosting NK cell and lowering inflammatory cytokines
 - LDN
 - GG 0.3- 1 gram IM/IV 3 grms and up
 - Thymus/Thymic proteins
 - Ozone/UVBI
 - LDA (allergy elimination) *gluten
 - Regenapep
 - Antivirals
 - Antibiotics
 - Transfer factors
 - Mushroom extracts
 - Isoprinosine
 - High dose B12
 - GcMAF
 - Interferons
 - GM-CSF
 - Heparin

LDN and FM

- Pilot study (12 FM patients, placebo-controlled, single blind, crossover design)
- Daily self-reported symptoms: baseline (2 weeks), placebo (2 weeks), LDN (8 weeks)
- Primary outcome of self-reported overall FM symptom severity, secondary symptom severity and mechanical pain testing q 2 weeks
- LDN reduced FM symptoms of FM by 30%
- Elevated ESR predicted response

Younger J, Mackey S. Fibromyalgia Symptoms Are Reduced by Low-Dose Naltrexone: A

Pilot Study. *Pain Med.* 2009 ; 10(4): 663–672.

LDN and FM

- Thirty-two FM patients, randomized, double-blind, placebo-controlled, crossover study
- Daily self-reported symptoms: baseline (2 weeks), placebo 4 weeks or LDN 12 weeks and 4 week f/u
- Primary outcome of self-reported overall FM symptom severity, secondary symptom severity and mechanical pain testing q 2 weeks.
- LDN reduced FM symptoms of FM by 28.8% vs. 18% with placebo
- LDN also associated with improved satisfaction with life and improved mood
- 32% met criteria for response (defined as a significant reduction in pain plus a significant reduction in either fatigue or sleep)

Younger J, Noor N, McCue R, Mackey S. Low-Dose Naltrexone for the Treatment of Fibromyalgia. *Arthritis & Rheum* 2013;65(2):529-538.

Thank You

Questions?