Paradigm Change

M.E. and Depression

Very frequently, Myalgic Encephalomyelitis (M.E.) and depression are confused for one another.

Medical practitioners, family members, co-workers and friends often misattribute the fatigue and cognitive difficulties of M.E. as being due to psychological rather than physical causes. In addition, some research studies that are nominally about M.E. or CFS include subjects who have uncomplicated depression, due to insufficiently rigorous case definitions used to screen study participants.

Studies have reported that 30% to 70% of “Chronic Fatigue Syndrome” patients also suffer from depression, in addition to the physical and cognitive components of their illness. One line of research suggests that the depression may be a physical consequence of the inflammatory state of the illness itself. In addition, some patients may experience reactive depression, as a result of the difficulties that the disease causes in their lives.

Regardless of whether individuals are suffering from depression, making a proper M.E. diagnosis is important. M.E. patients often respond negatively to interventions that are commonly used for depression, and they have the potential of being helped by interventions that appropriately address their M.E.

One major difference between M.E. and depression is the presence of “post-exertional malaise” or “post-exertional neuroimmune exhaustion.” People with uncomplicated depression frequently feel better after exercise, to the point where this is often recommended by doctors and psychologists as a therapeutic intervention. On the other hand, M.E. patients can be made much worse for extended periods of time after exercise, and thus need to engage in it very carefully.

This dynamic can extend to decisions to pursue activity other than exercise as well. People with uncomplicated depression are often encouraged to be as active as possible, with the assumption that (provided that positive interactions take place during activities) this will make them feel better. On the other hand, people with M.E. who push themselves to do things often feel worse afterwards no matter how much they enjoy themselves during the process, and thus may need to choose the activities in which they participate judiciously.

While both M.E. patients and people with uncomplicated depression often have sleep problems, the specific manifestations can be different. Depressed people often have

problems with insomnia or with oversleeping. M.E. patients often complain of unrefreshing sleep (associated with “agitated exhaustion”) that can respond better to drugs such as Klonopin (regardless of whether anxiety is present) than to conventional sleeping pills.

Antidepressants of all types often have a very negative effect on M.E. patients, prompting the inflammation that is one of the primary problems in the disease. These negative reactions tend to be markedly different than the side effects that are listed on the package inserts for the drugs or than the feelings of hypomania that people with latent bipolar conditions can get from taking them.

M.E. and depression both can present with mental slowing and lack of concentration, but M.E. patients often have more specific focal cognitive deficits (such as the inability to repeat a seven-digit phone number or count backwards in increments of 7 from 100) as well. Another difference is in physical symptoms: while people with uncomplicated depression generally have just a few non-emotional symptoms (such as fatigue and inability to concentrate), M.E. sufferers usually report a wide variety (sometimes dozens) of very specific physical complaints. Symptoms such orthostatic intolerance, loss of thermostatic ability, environmental sensitivities and air hunger tend to be particularly indicative that M.E. rather than plain depression is present.

Measurement of underlying physical abnormalities associated with M.E. is the most conclusive way to differentiate M.E. from depression. Some of the tests that have been published in the medical literature and that are used by doctors specializing in the disease include laboratory measurement of immunological markers (such as Natural Killer Cell activation and regulatory T cell counts); EEG spectral coherence analysis; and exercise challenge testing.

While people with uncomplicated depression may respond negatively to emotional setbacks, those with M.E. frequently decline as a result of a wide variety of different types of stress. This can include mental stress (such as reading a book or engaging in a thought-stimulating conversation), environmental stress (such as exposure to chemicals or watching a loud movie), physical exertion, or emotional stress. These declines can occur even when patients feel good while they are engaging in the activities, and in some cases can be triggered by even very small amounts of stimuli.

A high percentage of M.E. patients report alcohol intolerance, meaning that they are not able to drink at all or are disproportionately affected by even small amounts. Many have problems tolerating a wide variety of drugs as well. Thus, substance abuse may be less common in M.E. patients who are depressed than in other depressed people.

Some research suggests that the depressions that M.E. patients experience tend to be focused less on feelings of self-reproach than on the difficulties of living with the illness.

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M.E. causes physical pain and discomfort, career restrictions or loss, challenges in having and caring for children, financial problems, loss of self-sufficiency, relationship issues and (in many cases) feelings that others do not believe that they are “really sick.” Getting M.E. in the prime of life and knowing that few people recover from the severe form of the illness can be very discouraging.

A high percentage of severely ill M.E. patients seriously consider or actually commit suicide.

Many M.E. patients express frustrations with regard to their experiences with mental health care practitioners. Insofar as psychiatrists, psychologists and other counselors focus on helping sufferers cope with the many challenges of having M.E. or on prescribing appropriate medications, they have the potential of being very helpful for some patients. Unfortunately, many people working in the mental health field are poorly informed about the specifics of M.E., and a bad experience with one practitioner can discourage patients from ever again pursuing services that might be of value to them. More education of mental health professionals about M.E. thus is needed.

-Lisa Petrison, Ph.D.

Paradigm Change

M.E. AND DEPRESSION

MEDICAL LITERATURE

Inflammation:

Christley Y, Duffy T, Everall IP, Martin CR. The neuropsychiatric and neuropsychological features of chronic fatigue syndrome: revisiting the enigma. Curr Psychiatry Rep. 2013 Apr;15(4):353. PMID: 23440559

The possibility that the overlap between CFS and major depression might be explained in terms of shared oxidative and nitrosative (IO&NS) pathways is reviewed.

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Maes M, Mihaylova I, Kubera M, Leunis JC, Twisk FN, Geffard M. IgM-mediated autoimmune responses directed against anchorage epitopes are greater in Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) than in major depression. Metab Brain Dis. 2012 Dec;27(4):415-23. PMID: 22614823

The aim of this study was to examine IgM-mediated autoimmune responses to different self-epitopes in ME/CFS versus depression. We examined serum IgM antibodies to three anchorage molecules (palmitic and myristic acid and S-farnesyl-L-cysteine); acetylcholine; and conjugated NO-modified adducts in 26 patients with major depression; 16 patients with ME/CFS, 15 with chronic fatigue; and 17 normal controls.

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Maes M, Kubera M, Leunis JC, Berk M. Increased IgA and IgM responses against gut commensals in chronic depression: further evidence for increased bacterial translocation or leaky gut. J Affect Disord. 2012 Dec 1;141(1):55-62. PMID: 22410503

The results of this study indicate that increased bacterial translocation with immune responses to the LPS of commensal bacteria may play a role in the pathophysiology of depression, particularly chronic depression.

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Anderson G, Maes M, Berk M. Biological underpinnings of the commonalities in depression, somatization, and Chronic Fatigue Syndrome. Med Hypotheses. 2012 Jun;78(6):752-6. PMID: 22445460

The data suggest co-ordinated and interacting biological pathways driving the occurrence of physio-somatic symptoms across depression and somatization.

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Maes M, Mihaylova I, Kubera M, Leunis JC, Twisk FN, Geffard M. IgM-mediated autoimmune responses directed against anchorage epitopes are greater in Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) than in major depression. Metab Brain Dis. 2012 Dec;27(4):415-23. PMID: 22614823

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Maes M, Twisk FN, Ringel K. Inflammatory and cell-mediated immune biomarkers in myalgic encephalomyelitis/chronic fatigue syndrome and depression: inflammatory markers are higher in myalgic encephalomyelitis/chronic fatigue syndrome than in depression. Psychother Psychosom. 2012;81(5):286-95. PMID: 22832503

Plasma proinflammatory cytokines were significantly higher in ME/CFS than in depression and higher in both patient groups than in controls. Serum neopterin did not differ significantly between depression and ME/CFS but was higher in both patient groups than in controls. The significant positive correlations between neopterin and either IL-1 or TNF-α were significantly greater in depression than in ME/CFS.

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Maes M, Mihaylova I, Kubera M, Ringel K. Activation of cell-mediated immunity in depression: Association with inflammation, melancholia, clinical staging and the fatigue and somatic symptom cluster of depression. Prog Neuropsychopharmacol Biol Psychiatry. 2012 Jan 10;36(1):169-75. PMID: 21945535

Depression and melancholia are accompanied by cell-mediated immunity activation, suggesting that neopterin plays a role in their pathophysiology, e.g. through activation of oxidative and nitrosative stress and apoptosis pathways. The intertwined CMI and inflammatory responses are potentially associated with the onset of depression and with the melancholic and CF symptoms of depression.

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Maes M, Ringel K, Kubera M, Berk M, Rybakowski J. Increased autoimmune activity against 5-HT: a key component of depression that is associated with inflammation and activation of cell-mediated immunity, and with severity and staging of depression. J Affect Disord. 2012 Feb;136(3):386-92. PMID: 22166399

The incidence of anti-5-HT antibody activity was significantly higher in depressed patients, and in particular in those with melancholia, than in controls. Patients with positive 5-HT antibodies showed increased serum neopterin and lysozyme, and plasma TNFα and IL-1; higher scores on the HDRS and FF scales, and more somatic symptoms, including malaise and neurocognitive dysfunctions. There was a significant association between autoimmune activity to 5-HT and the number of previous depressive episodes.

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Felger JC, Cole SW, Pace TW, Hu F, Woolwine BJ, Doho GH, Raison CL, Miller AH. Molecular signatures of peripheral blood mononuclear cells during chronic interferon-α treatment: relationship with depression and fatigue. Psychol Med. 2012 Aug;42(8):1591-603. PMID: 22152193

Depression and fatigue during chronic IFN-α administration were associated with alterations in the expression (OAS2) and transcriptional control (CREB/ATF) of genes linked to behavioral disorders including CFS and major depression, further supporting an immune contribution to these diseases.

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Maes M, Mihaylova I, Kubera M, Leunis JC, Geffard M. IgM-mediated autoimmune responses directed against multiple neoepitopes in depression: new pathways that underpin the inflammatory and neuroprogressive pathophysiology. J Affect Disord. 2011 Dec;135(1-3):414-8. PMID: 21930301

Depression is characterized by IgM-related autoimmune responses directed against a) neoepitopes that are normally not detected by the immune system but that due to damage by O&NS have become immunogenic; and b) anchorage epitopes, i.e. palmitic and myristic acids, and S-farnesyl-L-cysteine. These autoimmune responses play a role in the inflammatory and O&NS pathophysiology of depression and may mediate the cellular dysfunctions that contribute to neuroprogression, e.g. aberrations in signal transduction, cellular differentiation and apoptosis.

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Maes M, Kubera M, Obuchowiczwa E, Goehler L, Brzeszcz J. Depression's multiple comorbidities explained by (neuro)inflammatory and oxidative & nitrosative stress pathways. Neuro Endocrinol Lett. 2011;32(1):7-24. PMID: 21407167

There is now evidence that depression, as characterized by melancholic symptoms, anxiety, and fatigue and somatic (F&S) symptoms, is the clinical expression of peripheral cell-mediated activation, inflammation and induction of oxidative and nitrosative stress (IO&NS) pathways and of central microglial activation, decreased neurogenesis and increased apoptosis. This review gives an explanation for the multiple "co-morbidities" between depression and a large variety of a) brain disorders related to neurodegeneration, e.g. Alzheimer's, Parkinson's and Huntington's disease, multiple sclerosis and stroke; b) medical disorders, such as cardiovascular disorder, chronic fatigue syndrome, chronic obstructive pulmonary disease, rheumatoid arthritis, psoriasis, systemic lupus erythematosus, inflammatory bowel disease, irritable bowel syndrome, leaky gut, diabetes type 1 and 2, obesity and the metabolic syndrome, and HIV infection; and c) conditions, such as hemodialysis, interferon-α-based immunotherapy, the postnatal period and psychosocial stressors.

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Maes M, Mihaylova I, Kubera M, Uytterhoeven M, Vrydags N, Bosmans E. Lower whole blood glutathione peroxidase (GPX) activity in depression, but not in myalgic encephalomyelitis / chronic fatigue syndrome: another pathway that may be associated with coronary artery disease and neuroprogression in depression. Neuro Endocrinol Lett. 2011;32(2):133-40. PMID: 21552194

The authors found that whole blood glutathione peroxidase (GPX) activity was significantly lower in depressed patients than in normal controls and that there were no significant differences between ME/CFS and controls. In depression and ME/CFS, there were significant and inverse relationships between GPX activity and ratings on a scale measuring ME/CFS and fibromyalgia symptoms.

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Gardner A, Boles RG. Beyond the serotonin hypothesis: mitochondria, inflammation and neurodegeneration in major depression and affective spectrum disorders. Prog Neuropsychopharmacol Biol Psychiatry. 2011 Apr 29;35(3):730-43. PMID: 20691744

The authors present data suggesting that migraine, irritable bowel syndrome, CFS, fibromyalgia and generalized anxiety disorder are linked by mitochondrial dysfunction and inflammation, and argue that monoamines, energy metabolism and inflammatory pathways are inter-related in many complex ways.

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Maes M, Mihaylova I, Kubera M, Ringel K. Activation of cell-mediated immunity in depression: Association with inflammation, melancholia, clinical staging and the fatigue and somatic symptom cluster of depression. Prog Neuropsychopharmacol Biol Psychiatry. 2011 Sep 16. PMID: 21945535

Depression and melancholia are accompanied by cell-mediated immunity (CMI) activation, suggesting that neopterin plays a role in their pathophysiology, e.g. through activation of oxidative and nitrosative stress and apoptosis pathways. The intertwined CMI and inflammatory responses are potentially associated with the onset of depression and with the melancholic and chronic fatigue symptoms of depression.

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Maes M. An intriguing and hitherto unexplained co-occurrence: Depression and chronic fatigue syndrome are manifestations of shared inflammatory, oxidative and nitrosative (IO&NS) pathways. Prog Neuropsychopharmacol Biol Psychiatry. 2010 Jul 4. PMID: 20609377

Depression and ME/CFS show major clinical differences, which allow to discriminate them with a 100% accuracy. Numerous studies have shown that depression and ME/CFS are characterized by shared aberrations in inflammatory, oxidative and nitrosative (IO&NS) pathways, like systemic inflammation and its long-term sequels, including O&NS-induced damage to fatty acids, proteins and DNA; dysfunctional mitochondria; lowered antioxidant levels, like zinc and coenzyme Q10; autoimmune responses to neoepitopes formed by O&NS; lowered omega-3 polyunsaturated fatty acid levels; and increased translocation of gram-negative bacteria. Some IO&NS-related pathways are more specific to depression, whereas other pathways, are specific to ME/CFS.

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Maes M, Twisk FN. Chronic fatigue syndrome: Harvey and Wessely's (bio)psychosocial model versus a bio(psychosocial) model based on inflammatory and oxidative and nitrosative stress pathways. BMC Med. 2010 Jun 15;8:35. PMID: 20550693

The authors 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) for CFS, and compare this model with a biological model, in which inflammatory, immune, oxidative and nitrosative (IO&NS) pathways are key elements.

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Maes M, Twisk FN.Treatment of myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS), a multisystem disease, should target the pathophysiological aberrations (inflammatory and oxidative and nitrosative stress pathways), not the psychosocial "barriers" for a new equilibrium. Patient Educ Couns. 2010 Mar 17. PMID: 20303231

Inflammatory and oxidative and nitrosative (IO&NS) pathways underpin the pathophysiology of ME/CFS.

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Maes M, Mihaylova I, Kubera M, Uytterhoeven M, Vrydags N, Bosmans E. Increased plasma peroxides and serum oxidized low density lipoprotein antibodies in major depression: markers that further explain the higher incidence of neurodegeneration and coronary artery disease. J Affect Disord. 2010 Sep;125(1-3):287-94. PMID: 20083310

Major depression is accompanied by increased oxidative stress and lipid peroxidation of the type also found to be present in coronary artery disease and in CFS.

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Maes M, Mihaylova I, Kubera M, Uytterhoeven M, Vrydags N, Bosmans E. Increased 8-hydroxy-deoxyguanosine, a marker of oxidative damage to DNA, in major depression and myalgic encephalomyelitis / chronic fatigue syndrome. Neuro Endocrinol Lett. 2009;30(6):715-22. PMID: 20035260

ME/CFS and depression patients display DNA damage as a result of oxidative stress.

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Maes M. Inflammatory and oxidative and nitrosative stress pathways underpinning chronic fatigue, somatization and psychosomatic symptoms. Curr Opin Psychiatry. 2009 Jan;22(1):75-83. PMID: 19127706

'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.

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Maes M. "Functional" or "psychosomatic" symptoms, e.g. a flu-like malaise, aches and pain and fatigue, are major features of major and in particular of melancholic depression. Neuro Endocrinol Lett. 2009;30(5):564-73. PMID: 20035251

There is a strong co-morbidity between CFS and major depression, and many people with major depression have symptoms such as subjective feeling of infection, fatigue and aches and pain. The authors suggest that this is because a common physiological etiology (related to oxidative stress and inflammation) is involved in both diseases.

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Maes M, Mihaylova I, Kubera M, Uytterhoeven M, Vrydags N, Bosmans E. Lower plasma Coenzyme Q10 in depression: a marker for treatment resistance and chronic fatigue in depression and a risk factor to cardiovascular disorder in that illness. Neuro Endocrinol Lett. 2009;30(4):462-9. PMID: 20010493

The authors suggest that low Coenzyme Q10 can be a factor in both CFS and depression, and that this can contribute to cardiovascular problems in both diseases. Since statins lower CoQ10, they should be used with caution.

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Maes M, Mihaylova I, Kubera M, Leunis JC. An IgM-mediated immune response directed against nitro-bovine serum albumin (nitro-BSA) in chronic fatigue syndrome (CFS) and major depression: evidence that nitrosative stress is another factor underpinning the comorbidity between major depression and CFS. Neuro Endocrinol Lett. 2008 Jun;29(3):313-9. PMID: 18580855

Both CFS and major depression are accompanied by a) an increased gut permeability which has allowed an exaggerated passage of BSA through a compromised epithelial barrier; b) increased nitrosative stress which has induced damage to BSA; and c) an IgM-mediated immune response which is directed against the nitro-BSA neoepitopes. Nitrosative stress seems to be one of the factors underpinning the comorbidity and clinical overlap between CFS and depression.

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Maes M, Mihaylova I, Kubera M, Bosmans E. Not in the mind but in the cell: increased production of cyclo-oxygenase-2 and inducible NO synthase in chronic fatigue syndrome. Neuro Endocrinol Lett. 2007 Aug;28(4):463-9. PMID: 17693978

The authors examine the production of COX-2 and iNOS by peripheral blood lymphocytes (PBMC) and the relationships between those inflammatory markers and the severity of illness in CFS patients. The production of COX-2 and iNOS by PBMCs was significantly related to aches and pain, muscular tension, fatigue, concentration difficulties, failing memory, sadness and a subjective experience of infection.

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Maes M, Mihaylova I, Leunis JC. Increased serum IgM antibodies directed against phosphatidyl inositol (Pi) in chronic fatigue syndrome (CFS) and major depression: evidence that an IgM-mediated immune response against Pi is one factor underpinning the comorbidity between both CFS and depression. Neuro Endocrinol Lett. 2007 Dec;28(6):861-7. PMID: 18063934

The prevalence and mean value for the serum IgM levels directed against phosphatidyl inositol were significantly greater in patients with major depression and CFS than in normal controls and patients with partial CFS.

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Maes M, Mihaylova I, Bosmans E. Not in the mind of neurasthenic lazybones but in the cell nucleus: patients with chronic fatigue syndrome have increased production of nuclear factor kappa beta. Neuro Endocrinol Lett. 2007 Aug;28(4):456-62. PMID: 17693979

CFS symptoms such as fatigue, muscular tension, depression and feeling of infection reflect an inflammatory response and increased oxidative stress, attributed to increased production of NF-kappa-beta.

Comparisons to Depression:

Duffy FH, McAnulty GB, McCreary MC, Cuchural GJ, Komaroff AL. EEG spectral coherence data distinguish chronic fatigue syndrome patients from healthy controls and depressed patients--a case control study. BMC Neurol. 2011 Jul 1;11:82. PMID: 21722376

EEG spectral coherence analysis identified unmedicated patients with CFS and healthy control subjects without misclassifying depressed patients as CFS, providing evidence that CFS patients demonstrate brain physiology that is not observed in healthy normals or patients with major depression. Studies of new CFS patients and comparison groups are required to determine the possible clinical utility of this test. The results concur with

other studies finding neurological abnormalities in CFS, and implicate temporal lobe involvement in CFS pathophysiology.

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Griffith JP, Zarrouf FA. A Systematic Review of Chronic Fatigue Syndrome: Don't Assume It's Depression. Prim Care Companion J Clin Psychiatry. 2008;10(2):120-8. PMID: 18458765

CFS is underdiagnosed in more than 80% of the people who have it; at the same time, it is often misdiagnosed as depression. Genetic, immunologic, infectious, metabolic, and neurologic etiologies were suggested to explain CFS. A biopsychosocial model was suggested for evaluating, managing, and differentiating CFS from depression.

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Juruena MF, Cleare AJ. Overlap between atypical depression, seasonal affective disorder and chronic fatigue syndrome. Rev Bras Psiquiatr. 2007 May;29 Suppl 1:S19-26. PMID: 17546343

A literature review analysis suggests that CFS, seasonal affective disorder and depression overlap biologically, showing hypofunction of central corticotropin releasing factor neuronal systems.

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Hawk C, Jason LA, Torres-Harding S. Differential diagnosis of chronic fatigue syndrome and major depressive disorder. Int J Behav Med. 2006;13(3):244-51. PMID: 17078775

The best differentiators of CFS and major depression were postexertional malaise, unrefreshing sleep and impaired memory-concentration.

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Li YJ, Gao XG, Wang DX, Lin T, Bai XL, Yang FZ. Cognitive function and psychological characteristics of patients with chronic fatigue syndrome. Zhonghua Yi Xue Za Zhi. 2005 Nov 2;85(41):2926-9. PMID: 16324367

The CFS patients in China have an obvious impairment of remembrance and show different psychological abnormalities that are different from those of the patients with primary psychological diseases.

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Pazderka-Robinson H, Morrison JW, Flor-Henry P. Electrodermal dissociation of chronic fatigue and depression: evidence for distinct physiological mechanisms. Int J Psychophysiol. 2004 Aug;53(3):171-82. PMID: 15246671

Despite overtly similar cognitive and symptom profiles, depression and CFS patients can be differentiated with psychophysiological measures.

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Van Hoof E, Cluydts R, De Meirleir K. Atypical depression as a secondary symptom in chronic fatigue syndrome. Med Hypotheses. 2003 Jul;61(1):52-5. PMID: 12781640

The authors cite anecdotal evidence that atypical depression is common in CFS, and suggest that atypical depression may be a symptom of physiological illness rather than an affective disorder.

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Daly E, Komaroff AL, Bloomingdale K, Wilson S, Albert MS. Neuropsychological function in patients with chronic fatigue syndrome, multiple sclerosis, and depression. Appl Neuropsychol. 2001;8(1):12-22. PMID: 11388119

CFS patients differed from controls primarily in the area of memory. The findings support the view that the cognitive deficits found in CFS cannot be attributed solely to the presence of depressive symptomatology in the patients.

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Morehouse RL, Flanigan M, MacDonald DD, Braha D, Shapiro C. Depression and short REM latency in subjects with chronic fatigue syndrome. Psychosom Med. 1998 May-Jun;60(3):347-51. PMID: 9625223

Short REM latency is associated with depression in the CFS population.

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DeLuca J, Johnson SK, Ellis SP, Natelson BH. Cognitive functioning is impaired in patients with chronic fatigue syndrome devoid of psychiatric disease. J Neurol Neurosurg Psychiatry. 1997 Feb;62(2):151-5. PMID: 9048715

Patients with chronic fatigue syndrome without psychiatric comorbidity were impaired relative to controls and patients with chronic fatigue syndrome with concurrent psychiatric disease on tests of memory, attention, and information processing.

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Itoh Y, Hamada H, Imai T, Seki T, Igarashi T, Yuge K, Fukunaga Y, Yamamoto M. Antinuclear antibodies in children with chronic nonspecific complaints. Autoimmunity. 1997;25(4):243-50. PMID: 9344332

The authors looked at Japanese children complaining of chronic nonspecific symptoms such as headache, fatigue, abdominal pain, and low grade fever are commonly seen in daily pediatric outpatient clinics, many of whom had been diagnosed with “school refusal.” 52% of these were positive for anti-nuclear antibodies, compared to only 6% of healthy children ($p<0.0001$). They propose that chronically complaining children should be evaluated with immunological approaches before being diagnosed with psychogenic illness.

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DeLuca J, Johnson SK, Ellis SP, Natelson BH. Sudden vs gradual onset of chronic fatigue syndrome differentiates individuals on cognitive and psychiatric measures. J Psychiatr Res. 1997 Jan-Feb;31(1):83-90. PMID: 9201650

Researchers compared CFS patients with sudden vs. gradual onset. The rate of concurrent psychiatric disease was significantly greater in the CFS-gradual group relative to the CFS-sudden group. While both CFS groups showed a significant reduction in information processing ability relative to controls, impairment in memory was more severe in the CFS-sudden group.

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Johnson SK, DeLuca J, Natelson BH. Depression in fatiguing illness: comparing patients with chronic fatigue syndrome, multiple sclerosis and depression. J Affect Disord. 1996 Jun 20;39(1):21-30. PMID: 8835650

CFS patients exhibited a significantly lower percentage of self-reproach symptoms and a higher percentage of physical symptoms than depressed patients.

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Komaroff AL, Fagioli LR, Doolittle TH, Gandek B, Gleit MA, Guerriero RT, PURPOSE: Health status in patients with chronic fatigue syndrome and in general population and disease comparison groups. Am J Med. 1996 Sep;101(3):281-90. PMID: 8873490

Patients with CFS had marked impairment, in comparison with the general population and disease comparison groups. The degree and pattern of impairment was different from that seen in patients with depression.

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Schwartz RB, Komaroff AL, Garada BM, Gleit M, Doolittle TH, Bates DW, Vasile RG, Holman BL. SPECT imaging of the brain: comparison of findings in patients with chronic fatigue syndrome, AIDS dementia complex, and major unipolar depression. AJR Am J Roentgenol. 1994 Apr;162(4):943-51. PMID: 8141022

Researchers used 99mTc-hexamethylpropyleneamine oxime to examine patients with CFS, AIDS, depression and controls. The midcerebral uptake index was found to be significantly lower in the patients with CFS and with AIDS than in patients with major depression or healthy control subjects. Also, a significant negative correlation was found between the number of defects and midcerebral uptake index in patients with CFS or AIDS, but not in depressed patients or control subjects.These findings are consistent with the hypothesis that chronic fatigue syndrome may be due to a chronic viral encephalitis.

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Bakheit AM, Behan PO, Dinan TG, Gray CE, O'Keane V. Possible upregulation of hypothalamic 5-hydroxytryptamine receptors in patients with postviral fatigue syndrome. BMJ. 1992 Apr 18;304(6833):1010-2. PMID: 1586780

The results suggest upregulation of hypothalamic 5-hydroxytryptamine receptors in patients with postviral fatigue syndrome but not in those with primary depression.

Psychiatric Co-morbidity

Kempke S, Van Den Eede F, Schotte C, Claes S, Van Wambeke P, Van Houdenhove B, Luyten P. Prevalence of DSM-IV Personality Disorders in Patients with Chronic Fatigue Syndrome: A Controlled Study. Int J Behav Med. 2013 Jun;20(2):219-28. PMID: 23065435

Although a sample of CFS patients was characterized by depressive and obsessive-compulsive personality features, this study provides no evidence for the assumption that these patients generally show a higher prevalence of axis II personality disorders.

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Bould H, Collin SM, Lewis G, Rimes K, Crawley E. Depression in paediatric chronic fatigue syndrome. Arch Dis Child. 2013 Jun;98(6):425-8. PMID: 23619200

Depression is commonly comorbid with CFS/ME, much more common than in the general population, and is associated with markers of disease severity.

ter Wolbeek M, van Doornen LJ, Kavelaars A, Tersteeg-Kamperman MD, Heijnen CJ. Fatigue, depressive symptoms, and anxiety from adolescence up to young adulthood: a longitudinal study. Brain Behav Immun. 2011 Aug;25(6):1249-55. PMID: 21549830

In young women who were non-fatigued during adolescence and who experienced a notable increase in fatigue, fatigue development was preceded by emotional problems and CFS-related complaints during adolescence. Higher interferon (IFN)-γ, higher IFN-γ/interleukin (IL)-4 ratio, lower tumor necrosis factor-α and lower IL-10 at baseline were related to fatigue severity at follow up. The rise in total number of CFS-related symptoms at follow up was predicted by anxiety and decreased physical activity during adolescence.

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Dansie EJ, Furberg H, Afari N, Buchwald D, Edwards K, Goldberg J, Schur E, Sullivan PF. Conditions comorbid with chronic fatigue in a population-based sample. Psychosomatics. 2012 Jan-Feb;53(1):44-50. PMID: 22221720

These results support findings in clinically based samples that CFS-like illness is frequently cormorbid with chronic widespread pain, irritable bowel syndrome, and/or major depressive disorder. We found no evidence that CFS-like illnesses with comorbidities are clinically distinct from those without comorbidities.

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Brown M, Kaplan C, Jason L. Factor Analysis of the Beck Depression Inventory-ii With Patients With Chronic Fatigue Syndrome. J Health Psychol. 2011 Nov 21. PMID: 22104663

This study examined the properties of the Beck Depression Inventory-II (BDI-II) in a sample of 111 patients with chronic fatigue syndrome (CFS). Exploratory factor analysis

identified two factors. The mean score for the Somatic-Affective factor was significantly higher than the Cognitive factor.

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Sepede G, Racciatti D, Gorgoretti V, Nacci M, Pizzigallo E, Onofrj M, Di Giannantonio M, Niolu C, Salerno RM, Gambi F. Psychophysical distress and alexithymic traits in chronic fatigue syndrome with and without comorbid depression. Int J Immunopathol Pharmacol. 2011 Oct-Dec;24(4):1017-25. PMID: 22230407

Patients with chronic fatigue syndrome (CFS) often report a comorbid depressive disorder. Depressed patients in this study had a higher fatigue severity.

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Pinquart M, Shen Y. Depressive symptoms in children and adolescents with chronic physical illness: an updated meta-analysis. J Pediatr Psychol. 2011 May;36(4):375-84. PMID: 21088072

Children and adolescents with chronic illness have, on average, higher levels of depressive symptoms than their healthy peers. Differences are strongest for chronic fatigue syndrome, fibromyalgia, cleft lip and palate, migraine/tension head ache, and epilepsy.

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Nater UM, Jones JF, Lin JM, Maloney E, Reeves WC, Heim C. Personality features and personality disorders in chronic fatigue syndrome: a population-based study. Psychother Psychosom. 2010;79(5):312-8. PMID: 20664306

CFS patients were more neurotic (e.g. experience negative and unstable affect), less extraverted (e.g. activity, sociability and positive affect), less conscientious (e.g. diligence, goal orientation, fastidiousness and dependability) and less agreeable than control subjects. There was no difference on openness to experience (e.g. intellectual/aesthetic tendencies and interest in novelty)

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Van Houdenhove B, Kempke S, Luyten P. Psychiatric aspects of chronic fatigue syndrome and fibromyalgia. Curr Psychiatry Rep. 2010 Jun;12(3):208-14. PMID: 20425282

Chronic fatigue syndrome and/or fibromyalgia (CFS/FM) consists of highly overlapping, medically unexplained symptoms, including long-lasting fatigue, effort intolerance, cognitive dysfunction, and widespread pain and tenderness. CFS/FM often seems to be triggered by infections and physical trauma, but depression, sleep disturbances, and personality may also be involved. Moreover, dysregulation of the stress system, the immune system, and central pain mechanisms may determine the pathophysiology of the illness, leading to a loss of capacity to adapt to all kind of stressors.

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Nater UM, Lin JM, Maloney EM, Jones JF, Tian H, Boneva RS, Raison CL, Reeves WC, Heim C. Psychiatric comorbidity in persons with chronic fatigue syndrome identified from the Georgia population. Psychosom Med. 2009 Jun;71(5):557-65. PMID: 19414619

In a population of 113 CFS patients, 57% had at least one current psychiatric diagnosis and 89% had at least one lifetime psychiatric diagnosis. Only 10% reported having seen a mental healthcare specialist during the past 6 months.

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Jones JF, Lin JM, Maloney EM, Boneva RS, Nater UM, Unger ER, Reeves WC. An evaluation of exclusionary medical/psychiatric conditions in the definition of chronic fatigue syndrome. BMC Med. 2009 Oct 12;7:57. PMID: 19818157

The diagnosis of chronic fatigue syndrome (CFS) in research studies requires the exclusion of subjects with medical and psychiatric conditions that could confound the analysis and interpretation of results. This study compares illness parameters between individuals with CFS who have and those who do not have exclusionary conditions. Those with exclusionary conditions are equally impaired as those without exclusions.

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Walker K, Lindner H, Noonan M. The role of coping in the relationship between depression and illness severity in chronic fatigue syndrome. J Allied Health. 2009 Summer;38(2):91-9. PMID: 19623790

Analyses in a population of CFS sufferers in Australia revealed that almost 70% of the participants were moderately or severely depressed.

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Fuller-Thomson E, Nimigon J. Factors associated with depression among individuals with chronic fatigue syndrome: findings from a nationally representative survey. Fam Pract. 2008 Dec;25(6):414-22. PMID: 18836094

Thirty-six per cent of individuals with CFS were depressed. Among individuals with CFS, depression was associated with lower levels of mastery and self-esteem. The odds of depression among individuals with CFS were higher for females, younger respondents, those with lower incomes and food insecurity and those whose activities were limited by pain. Two in five depressed individuals had not consulted with any mental health professional in the preceding year. Twenty-two per cent of depressed respondents had seriously considered suicide in the past year. Individuals with CFS who were depressed were particularly heavy users of family physicians, with an average of 11.1 visits annually.

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Yoshiuchi K. Psychological symptoms in chronic fatigue syndrome. Nihon Rinsho. 2007 Jun;65(6):1023-7. PMID: 17561692

Psychological symptoms and psychiatric comorbidity in CFS patients is discussed.

Paradigm Change

M.E. AND DEPRESSION

MEDIA ARTICLES

March 1, 2011
The Huffington Post
Chronic Fatigue Syndrome and Psychotherapy
By John Falk

http://www.huffingtonpost.com/john-falk/chronic-fatigue-syndrome-_b_829651.html?ref=fb&src=sp

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January 3, 2011
The New York Times
Fido's No Doctor. Neither Is Whiskers.
By Hal Herzog

http://www.nytimes.com/2011/01/04/opinion/04herzog.html?scp=7&sq=%22chronic+fatigue+syndrome%22&st=nyt

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November 29, 2010
ABC News
Chronic Fatigue Syndrome Patients Grow Weary of Doubt
By Mikaela Conley

http://abcnews.go.com/Health/MindMoodResourceCenter/chronic-fatigue-syndrome-link-personality-disorders/story?id=12102316#.TtsSnM1DFD8
