REVIEW

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

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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.

Introduction

There is sufficient evidence that Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) is an organic disorder, characterized by aberrations in inflammatory and oxidative and nitrosative stress (IO&NS) pathways and a decreased anti-oxidant status (Maes, 2009; Maes *et al* 2007a; 2007b; 2007c; Lorusso *et al* 2009; Aspler *et al* 2008; Kerr *et al* 2008a; 2008b; Buchwald *et al* 1997; Nijs en De Meirleir, 2005; Gow *et al* 2009; Pietrangelo *et al* 2009). The most commonly used diagnostic ME/CFS criteria of the Centre for Disease Control and Prevention (CDC) (Fukuda *et al* 1994) require: a) a profound chronic fatigue lasting at least six months; and b) the presence of at least four of the following symptoms, substantial impairment in short – term memory or concentration; sore throat; tender cervical and axillary lymph nodes; muscle pain; multi – joint pain without selling or redness; headache of new type; unrefreshing sleep; and post exertion malaise lasting more than 24 hours. In the following paragraph the most important IO&NS pathways that take part in the pathophysiology of ME/CFS (Maes 2009) are summarized.

Pathophysiological pathways in ME/CFS

A) Inflammation

A key phenomenon underpinning the inflammatory response in ME/CFS is an increased production of inflammatory mediators, such as nuclear factor kappa B (NFκB), cyclo-oxygenase-2 (COX-2) and inducible NO synthase (iNOS) (Maes *et al* 2007b; 2007c; Maes, 2009). This upregulation of key inflammatory mediators may explain specific symptoms experienced by the patients, such as aches and pain, muscular tension, fatigue, irritability, sadness, and a feverish feeling and malaise (Maes, 2009; Maes *et al* 2006b; 2007b; 2007c; 2007d; 2008). ME/CFS is also accompanied by increased serum concentrations of pro-inflammatory cytokines, such as tumour necrosis factor alpha (TNFα) and interleukin-6 (IL-6) (Maes *et al* 2010b).

B) Increased O&NS

There is convincing evidence that the production of radical oxidative species (ROS), which include hydrogen peroxide, superoxide anion, hydroxyl radical and nitric oxide, is increased in ME/CFS. The presence of increased ROS and consequent O&NS is shown by increased isoprostane; thiobarbituric acid reactive substances (TBARS); protein carbonyl and peroxide levels (Vecchiet *et al* 2003; Kennedy *et al* 2005; Jammes *et al* 2005; Smirnova and Pall, 2003; Maes *et al* 2010a). Increased ROS and, thus, O&NS may cause damage to membrane lipids (lipid peroxidation), functional proteins and DNA. Damage by O&NS to membrane fatty acids in ME/CFS is shown by increased IgM-mediated immune responses against membrane fatty acids, e.g. oleic, palmitic and myristic acid; by-products of lipid peroxidation, e.g. malondialdehyde and azelaic acid; and functional lipid structures, e.g. phosphatidylinositol (Pi) (Maes *et al* 2006b; 2007e). Damage by O&NS to protein structures has been shown by increased IgM-mediated immune responses against N-oxide derivates, e.g. nitro-tyrosine, nitro-phenylalanine, nitro-arginine, nitro-tryptophan, and nitro-cysteinyl (Maes *et al* 2006b). This indicates that O&NS has disrupted otherwise inactive lipid and protein autoepitopes into antigens, which serve as triggers to impair or bypass immunological tolerance, leading to IgM autoantibody production against these neoepitopes.

Increased urinary levels of 8-hydroxy-2'-deoxyguanosine (8-OHdG) show that oxidative damage to DNA may occur in subgroups of ME/CFS patients. 8-OHdG is one of the mutagenic lesions to DNA as a result from hydroxylation of guanine. These DNA lesions are excised through the base excision repair pathway, which restores the oxidative damage to DNA and eliminates 8-OHdG (Wu *et al* 2004; Bohr, 2002). Inflammatory reactions inhibit the 8-OHdG base excision repair pathways and, thus, potentiate DNA damage (Jaiswal *et al* 2001). ROS not only attack nuclear, but also mitochondrial DNA, causing mitochondrial DNA lesions. One of the primary factors in degenerative disorders are accumulations of mutagenic lesions in mitochondrial DNA. These lesions cause defects in the mitochondrial respiratory chain and increased ROS leakage, which in turn induce more mitochondrial DNA mutations (Tanaka *et al* 1996). Several studies in ME/CFS have demonstrated mitochondrial damage (Zhang *et al* 1995; Hokama *et al* 2009) and dysfunctions (Vernon *et al* 2006; Behan *et al* 1991; Kaushik *et al* 2005; Gow *et al* 2009; Myhill *et al* 2009; Byrne and Trounce, 1987; Pieczenik and Neustadt, 2007); structural changes, e.g. a significantly lower number of mitochondria rich type 1 muscle fibers in ME/CFS patients with abnormal lactate responses to exercise (Lane *et al* 1998).

The presence of O&NS and the consequent damage may also explain specific symptoms experienced by patients with ME/CFS, such as aches and pain, muscular tension, fatigue, a flu-like malaise, sadness, and post-exertional malaise (Maes *et al* 2006b; 2007b; 2007c; 2008; Jammes *et al* 2005; Maes, 2009).

The abovementioned findings are corroborated by gene signature studies. Gow *et al* (2009) found differentially expressed genes in ME/CFS indicating immune modulation, oxidative stress and apoptosis. Aspler *et al* (2008) examined microarray profiles of peripheral blood and established altered expression of genes indicating inflammation, immune activation and B cell dysfunction. Studies in peripheral blood of patients with ME/CFS showed an increased gene expression for hematological and immune disease, cell death, cancer, infection and inflammatory pathways, such as the NFκB pathways (Kerr *et al* 2008). Others have demonstrated that patients with ME/CFS have a gene signature suggesting T cell activation, neuronal and mitochon-

drial dysfunctioning and viral infections (Kaushik *et al* 2005). Interestingly, after exercise, patients with ME/CFS exhibit an enhanced expression for sensory, adrenergic, and immune genes (Light *et al* 2009). This may explain why exercise and the combined treatment with cognitive behavioural therapy (CBT) and graded exercise therapy (GET) may deteriorate the condition of the patients and aggravate symptoms, like muscle pain, fatigue and neurocognitive symptoms (Twisk and Maes, 2009; Maes and Twisk, 2009).

C) Decreased anti-oxidants

There is also evidence that ME/CFS is accompanied by a significantly decreased levels of essential antioxidants, such as dehydroepiandrosterone-sulphate (DHEA-S), zinc and coenzyme-Q10 (CoQ10) (Maes *et al* 2005a; 2006a; 2009). Depletion of those antioxidants results into an impaired antioxidative protection which, in turn, may enhance induction of the O&NS pathways and, consequently, damage to membrane fatty acids, functional proteins and DNA (Maes, 2009). Moreover, since antioxidants like CoQ10 have anti-inflammatory effects, e.g. by reducing the production of pro-inflammatory cytokines, like TNFα (Schmelzer *et al* 2007a), their reduced levels could play a role in the induction of the inflammatory pathways in ME/CFS. Decreases in antioxidants cause specific symptom profiles, e.g. the low CoQ10 syndrome in ME/CFS causes fatigue and neurocognitive symptoms (Maes *et al* 2009).

D) Increased gut permeability (leaky gut)

Another potential cause of persistent inflammation in ME/CFS is increased gut permeability or a leaky gut (Maes *et al* 2007a; 2007d; 2008; Maes and Leunis, 2008). Indeed, increased IgM and IgA responses to the lipopolysaccharide (LPS) of different enterobacteria have been established in ME/CFS (Maes *et al* 2007a; 2007d). This implicates that normally non-invasive enterobacteria migrate from the gut into the blood and that the LPS from these bacteria generates an IgA and IgM-mediated immune response (Maes *et al* 2007a; 2007d; 2008). The leaky gut most likely originates from weakening of the tight junctions of the epithelial barrier by inflammatory processes, e.g. increased production of NFκB and IL-6 (Maes *et al* 2007a; 2007d). Once LPS enters the bloodstream, a cascade of inflammatory mechanisms is triggered, which results into extended NFκB production; increased levels of COX-2, iNOS, and pro-inflammatory cytokines; O&NS induced damage; and consequently symptoms of IO&NS. In this respect, we found that increased IgA responses to LPS are significantly correlated to a flu-like malaise and irritable bowel syndrome. Treatment of leaky gut by means of antioxidants, like zinc, N-acetyl-cysteine (NAC) and glutamine, normalized the increased bacterial translocation, which was accompanied by a gradual remission of the ME/CFS symptoms (Maes *et al* 2007a; 2007d; 2008; Maes and Leunis, 2008).

E) Lowered ω3 PUFA status

Other predisposing or maintaining factors are abnormal polyunsaturated fatty acids (PUFA) profiles, i.e. in ω3 versus ω6 PUFAS, and their relationship to monounsaturated or saturated fatty acids (Maes *et al* 2005b). In this regard, it is reported that ME/CFS is characterized by a) significantly lower eicosapentaenoic acid (EPA)/arachidonic acid (AA) and ω3/ω6 PUFA ratios partly caused by increased levels of ω6 PUFAs, i.e. linoleic acid and AA; and b) increased levels of monounsaturated fatty acids (MUFAs), i.e. oleic acid; and increased levels of saturated fatty acids, e.g. myristic, palmitic and stearic acid (Maes *et al* 2005b). Since ω3 PUFAs have anti-inflammatory effects, whereas ω6 PUFAs are proinflammatory (Maes *et al* 1999; Maes and Smith, 1998), the lowered ω3 and/or increased ω6 levels in ME/CFS predispose towards a pro-inflammatory state (Maes *et al* 2000).

F) Precipitating or perpetuating factors, i.e. psychological stress and infections

Finally, factors that may trigger or maintain the abovementioned IO&NS pathophysiology should be considered (Maes, 2009). A first factor that can trigger or maintain ME/CFS is psychological stress (Lim *et al* 2003). Other authors propose that ME/CFS may be due to persistent viral infections (Dowsett *et al* 1990; Denavur and Kerr, 2006; Vernon *et al* 2006; Chia and Chia, 1999; Kerr, 2005). Using different methods (PCR, ELISA techniques), the presence of various pathogens, like Epstein-Barr virus (EBV) (Lerner *et al* 2004), Cytomegalovirus (CMV) (Beqaj *et al* 2008), Herpes VI virus (Patnaik *et al* 1995; Nicolson *et al* 2003), and Parvovirus B19 (Seishima *et al* 2008; Kerr, 2005) were established in large subgroups. Very recently, the presence of a new infectious human gammaretrovirus, xenotropic murine leukemia virus-related virus (XMRV) was established in 67% of the patients (Lombardi *et al* 2009). Others have suggested that bacterial infections, such as Chlamydia pneumoniae or Mycoplasma pneumoniae, may be a causative factor in ME/CFS (Nijs *et al* 2002; Nicolson *et al* 2003).

Cardio-vascular disorder and ME/CFS

A study reported that among ME/CFS patients the causes of death cluster in three general domains: heart failure, suicide, and cancer (Jason *et al* 2006). Approximately 20% died from each of these three causes. The authors concluded that the ages at death for these three conditions were considerable lower in subjects with ME/CFS. The mean age of ME/CFS patients dying from heart failure, 58.7 years, was significantly lower than the age of those dying from heart failure in the general US population, 83.1 years (Jason *et al* 2006). These findings indicate that in ME/CFS there is premature risk of death associated with heart failure.

Other studies have showed that there is an increased incidence of cardiac and autonomic problems in patients with ME/CFS (Miwa and Fujita, 2009; Lerner *et al* 1997; Naschitz *et al* 2008; Peckerman *et al* 2003c; Hurwitz *et al* 2009; Stewart *et al* 1999; Newton *et al* 2009). Patients with ME/CFS display a significantly greater AIx@75 (the augmentation index normalized for a heart rate of 75 beats/min), which is a measure of arterial stiffness: an important cardiovascular risk factor (Spence *et al* 2008). Almost all patients with ME/CFS show intermittent tachycardia accompanied by T-wave abnormalities as measured by 24-hour Holter monitoring, such as labile T-wave abnormalities and repetitive T-wave flattening (Lerner *et al* 1997). Patients with ME/CFS exhibit frequent repetitively flat to inverted T waves alternating with normal T waves; with higher work load gross left ventricular dysfunction occur (Lerner *et al* 1993). Left ventricular dysfunction was found in those patients as indicated on MUGA (radioscopic multiple gated acquistion) studies (Dworkin *et al* 1994). The authors observed abnormal wall motion at rest and stress, dilatation of the left ventricle, and segmental wall motion abnormalities (Dworkin *et al* 1993). Also Peckerman *et al* (2003a) found that many patients with ME/CFS experience ejection fraction decreases, suggesting left ventricular dysfunction (Peckerman *et al* 2003a). Patients with ME/CFS have a lower cardiac output, striking decreases in circulating blood volume, and constricted blood vessels, while efforts to restore normal volume are met with limited success (Peckerman *et al* 2003b; Streeten *et al* 2000). Lerner *et al* (1997) concluded that the fatigue in ME/CFS patients could partly be explained by subtle cardiac dysfunctions following common work loads.

Other authors established orthostatic intolerance in ME/CFS patients, such as neurally-mediated syncopes with or without tachycardia (Schondorf and Freeman, 1999; Schondorf *et al* 1999). Adolescents with ME/CFS show a higher baseline peripheral resistance index, and a lower stroke index and end-diastolic volume index values. During 20 degrees head-up tilt testing, patients with ME/CFS prove to have greater increases in heart rate, diastolic blood pressure, mean blood pressure and total peripheral resistance index (Wyller *et al* 2007; 2008). Overall, these findings indicate abnormal cardiovascular responses to mild orthostatic stressors. This study also implicates that some patients with ME/CFS suffer from autonomic symptoms, which eventually may compromise the heart function. Importantly, a gene expression study of peripheral blood mononuclear cells of patients with ME/CFS suggests an association between oxidative stress and the immune system causing an impaired sympatho-vagal balance reflected in an abnormal heart rate variability (Broderick *et al* 2006).

In the following paragraphs we will review how the abovementioned pathways in ME/CFS may contribute to the increased cardiovascular risk and the increased risk of death associated with heart failure in patients with ME/CFS.

IO&NS pathways in ME/CFS as possible causes for cardiovascular disorder

A) Inflammation in ME/CFS and cardiovascular disorder

In this first paragraph we will review the evidence that inflammatory reactions in ME/CFS provide a mechanism explaining the increased incidence of cardiovascular problems in ME/CFS. Atherosclerosis is now considered to be a disease characterized by dynamic interactions between inflammatory reactions and endothelial dysfunction (Mahmoudi *et al* 2007). Low-grade inflammation or microinflammation play a key role in the initial phases from lesion formation to rupture of atherosclerotic plaques (Paramo *et al* 2005). Systemic inflammatory markers, like C-reactive protein (CRP), pro-inflammatory cytokines, and intracellular inflammation, e.g. increased NFκB, are likely to be involved in this process. Numerous studies show a higher vascular risk in patients with increased plasma concentrations of pro-inflammatory cytokines, such as TNFα and IL-6 and acute-phase proteins, e.g. CRP and fibrinogen (Mahmoudi *et al* 2007). Large population-based studies have shown that inflammatory markers are independent predictors of cardiovascular disorder (Corrado and Novo, 2005). Clinical trials with anti-inflammatory agents, e.g. statins, demonstrate that the risk reduction is more pronounced in patients with inflammatory signs (Mahmoudi *et al* 2007).

The abovementioned inflammatory markers, such as TNFα and CRP, are directly implicated in the pathophysiological processes that are important in vascular and cardiac dysfunctions. Firstly, it has been shown that TNFα partly mediates the cardiac aberrations caused by disruptions of macrovascular and microvascular circulation following sepsis, endotoxemia, hemorrhagic shock, and myocardial ischemia (Meng and Harken, 2002). Cardiac stress has been shown to induce the production of TNFα in cardiac myocytes and macrophages (Sarzi-Puttini *et al* 2005). A direct etiological link between TNFα and cardiovascular disorder is suggested by findings that TNFα is correlated to the severity of heart failure and that this cytokine is a predictive marker for an increased mortality risk in heart failure patients (Anker *et al* 1997b; Muller-Ehmsen and Schwinger, 2004). The latter authors proved that patients with heart failure show increased TNFα levels sufficient enough to depress cardiac contractility. TNFα may also play a role in triggering and perpetuating atherosclerosis (Sack, 2002). Mechanisms involved in TNFα-induced cardiac pathology are: increased ROS production, which results in endothelial dysfunctions (see further); increased vascular permeability; depressed myocardial contractility; and a prothrombotic state (Zhang *et al* 2009; Vadlamani and Iyengar, 2004). Secondly, CRP upregulates IL-8 in

human aortic endothelial cells via NFκB, attenuates endothelial progenitor cell survival, differentiation, and function, and induces matrix metalloproteinase-1 expression, which is implicated in plaque instability and promotes atherothrombosis (Venugopal *et al* 2005).

Inflammatory mediators, such as NFκB, have cardiovascular effects. There is evidence that NFκB plays a pivotal role in the cardiac cell and is involved in cardiac disorders, e.g. ischemia-reperfusion injury, ischemic precondition, hypertrophy, atherosclerosis and cardiac arrest (Gutierrez *et al* 2007; Hall *et al* 2006; Valen *et al* 2001). NFκB - as a redox-sensitive transcription factor - is a key regulator of cardiac gene expression in physiological and pathological states (Jones *et al* 2003). The proteins produced mediate inflammation, O&NS, smooth muscle cell proliferation, and angiogenesis. Activated NFκB is found in atherosclerotic lesions, atherosclerosis, myocarditis, ischemia/reperfusion, congestive heart failure, cardiomyopathy, heat shock, burn trauma, and in hypertrophy of isolated cardiomyocytes (Jones *et al* 2003; Xanthoulea *et al* 2005). The abovementioned cardiac effects of NFκB may be explained by the assertion that this transcription factor induces proinflammatory cytokines from cardiomyocytes, resulting in damage to vessel walls and an impaired vascular cell function; exhibits pro-apoptotic effects; and mediates cell death after ischemia/reperfusion injury (Gutierrez *et al* 2008; Hall *et al* 2006; De Martin *et al* 2000; Jones *et al* 2005).

Although many studies were performed to clarify the role of COX-2 in cardiovascular disorders, atherosclerosis and atherothrombosis, its exact role has remained controversial (Streicher and Wang, 2008). Conflicting data show that COX-2 has either cardioprotective or detrimental effects. COX-2 may have plaque-destabilizing effects depending on the prostaglandin synthase coupled with it, e.g. PGE synthase versus lipocalin-type PGD synthase (Cuccurullo *et al* 2007). Other data show that COX-2 is a risk factor for cardiovascular disorder and subclinical atherosclerosis and that is contributes to lesion formation (Paramo *et al* 2005).

B) O&NS in ME/CFS and cardiovascular disorder

An increased production of ROS, as can be observed in ME/CFS, causes a deleterious process with subsequent damage to cell structures, including fatty acids, proteins and DNA. The latter processes are strongly implicated in the initiation and progression of cardiovascular disorders. Characteristic to the early phases of cardiovascular disorder is the production of ROS by different cells, like endothelial and vascular smooth muscle cells and monocytes/macrophages (Fearon and Faux, 2009). In addition to direct effects, ROS also exerts indirect effects through the generation of other more potent radicals, e.g. peroxynitrite (ONOO-*). Deleterious effects of increased ROS formation on the vasculature include: oxidative damage, e.g. tissue injury, protein oxidation and DNA lesions; and induction of proinflammatory responses. Moreover: inactivation of nitric oxide (NO), a potent signalling molecule and vasodilator, causing endothelial dysfunction; aberrant signal transduction affecting gene transcription, which results in deviant enzymes and proteins; myocyte hypertrophy; apoptosis; and interstitial fibrosis by activating matrix metalloproteinases (Xu and Touyz, 2006; Tsutsui, 2006; Li and Shah, 2004). It should also be noted that ROS modulates the expression of many angiogenic genes and that during ishemia and reperfusion, ROS may potentiate the repair process which triggers the angiogenic responses in vascular tissues (Maulik, 2002). On the other hand, in postishemic myocardium, ROS are formed in an accelerated rate by cardiac myocytes, endothelial cells and infiltrating neutrophils. This may cause necrosis, which contributes to myocardial infarction (Lefer and Granger, 2000).

Another important mechanism whereby ROS can induce cardiovascular disorder is lipid peroxidation. Accumulation of LDL-derived lipids in the arterial wall is one of the pathways causing atherosclerosis (Adibhatla and Hatcher, 2008). However, in contrast to major depression, only a trend towards increased oxidized LDL antibodies was found in ME/CFS (Maes *et al* 2010b). We think that other pathways involving increased lipid peroxidation may be more important in ME/CFS, like extended oxidative damage to phospholipids, as established by higher IgM-mediated responses against phosphatidylinositol (Pi) (Maes *et al* 2006b). Oxidized phospholipids (oxPL) are known to be modulators of inflammation in atherosclerotic processes (Leitinger, 2003). Moreover, oxPLs induce various signal transduction pathways in cardiomyocytes, endothelial cells and fibroblasts, thereby regulating pro- and anti-atherogenic genes. These genes differ from those induced by LPS or TNFα (Leitinger, 2003; Berliner *et al* 2009). As such, oxPLs may propagate chronic inflammation and play a role in all stages of atherosclerosis. In addition, Pi pathways have been shown to modulate many heart functions and dysfunctions. The Pi turnover pathway, including phosphoinositide-3 kinase, which generates phosphatidylinositides, are expressed in cardiomyocytes and endothelial cells and partly modulates cell survival / apoptosis, hypertrophy, contractility and metabolism. This may explain why disorders in the Pi turnover pathway are involved in cardiovascular disorders (Oudit *et al* 2004). This pathway also regulates intracellular Ca2+ signalling. By altering Ca2+ homeostasis, it can cause arrhythmogenesis (Woodcock *et al* 2009). Changes in Pi affinity may in some cases cause the long QT syndrome and thus sudden death (Park *et al* 2005).

The increased urinary levels of 8-OHdG in ME/CFS expands the number of possible IO&NS-related factors creating an environment which promotes cardiovascular disorders. Increased amounts of 8-OHdG and oxidatively modified DNA are detected in atherosclerotic

plaques (Wu *et al* 2004). The levels of 8-OHdG in DNA isolated from lymphocytes are significantly higher in atherosclerotic patients than in controls (Gackowski *et al* 2001). Increased oxidative stress is responsible for the accumulation of mutagenic DNA damage in coronary artery disease (Botto *et al* 2005). In humans and in animal models of oxidative stress, increased ROS activity in mitochondria, and accumulation of mutagenic DNA lesions in the mitochondria, resulting into respiratory chain dysfunction, are associated with atherosclerosis or cardiomyopathy (Madamanchi and Runge, 2007). Moreover, chronic mitochondrial ROS causes increased LDL oxidation and other pro-atherogenic factors in endothelial cells (Madamanchi and Runge, 2007).

C) Decreased antioxidant defenses in ME/CFS and cardiovascular disorder

C1) The lower CoQ10 syndrome in ME/CFS and cardiovascular disorder

Another factor that may participate in an increased risk for cardiovascular mortality in ME/CFS relates to CoQ10. CoQ10 is an essential element of the mitochondrial respiratory chain (Butler *et al* 2003), a strong antioxidant, which extends resistance to mitochondrial damage by O&NS (Chaturvedi and Beal, 2008), and an anti-inflammatory agent (Schmelzer *et al* 2007a; 2007b; 2008). Thus, the lower CoQ10 syndrome in many patients with ME/CFS (Maes *et al* 2009) may impair defenses against O&NS and inflammatory reactions and, consequently, predispose towards increased activity of the IO&NS pathways, including increased CRP and TNFα levels and oxidative damage to membrane fatty acids, functional proteins and DNA (Maes *et al* 2009). It has been established that CoQ10 is a protective factor for coronary artery disease (CAD) (Yalcin *et al* 2004), and that CoQ10 increases the resistance to lipid peroxidation and has a direct anti-atherogenic effect (Yalcin *et al* 2004; Chapidze *et al* 2005). A low CoQ10 syndrome may cause cardiac disorders, such as chronic heart failure (CHF), while low CoQ10 is an independent risk factor to mortality in CHF (Molyneux *et al* 2008). It has been shown that CoQ10 supplementation is of therapeutic value in congestive HF (Singh *et al* 2007). CoQ10 has been proven to improve heart function since it enhances systolic function, left ventricular ejection fraction and myocardium contractility (Sander *et al* 2006; Belardinelli *et al* 2005) and endothelium-dependent relaxation and endothelium-bound extracellular superoxide dismutase (Tiano *et al* 2007).

It is also well established that statins significantly reduce plasma CoQ10 and induce symptoms in compliance with characteristic ME/CFS complaints, such as myalgia, fatigue, neurocognitive symptoms and neuropathy (Langsjoen *et al* 2005; Passi *et al* 2003; Mabuchi *et al* 2005; Chu *et al* 2006; Berthold *et al* 2006). In HepG2 cells, simvastatin decreases mitochondrial CoQ10 and at higher doses increases cell death and damage to DNA caused by O&NS (Tavintharan *et al* 2007). In rats, administration of simvastatin decreases CoQ10 levels in the heart and skeletal muscles (Kucharska *et al* 2007). Thus, treatment with statins could seriously affect plasma levels of CoQ10 in patients with ME/CFS, which in many cases are already low. For that reason, Littarru and Tiano (2007) state that treatment with statins in patients with depleted CoQ10 may seriously reduce plasma and tissue levels of CoQ10, thereby impairing myocardial bioenergetics. All in all, ME/CFS patients are a population at risk for treatment with statins. Supplementation with CoQ10 reverses the statin-induced depletion of plasma CoQ10 levels due to statin administration (Mabuchi *et al* 2007; Keith *et al* 2008) and statin-induced symptoms, like fatigue, myalgia, memory disorders and neuropathies as well (Langsjoen *et al* 2005). For that reason, ME/CFS is a relative contraindication for treatment with statins without CoQ10 supplementation (Maes *et al* 2009).

C2) Zinc deficiency in ME/CFS and cardiovascular disorder

In this paragraph we will focus on the role of zinc deficiency, which has been established in many ME/CFS patients (Maes *et al* 2006a). Patients with CAD not only have significantly higher serum CRP concentrations, but also lower serum zinc levels, suggesting that zinc depletion is a consequence of inflammation (Ghayour-Mobarhan *et al* 2008). There is evidence that zinc deficiency is a contributory factor to atherosclerosis, CAD and CHF. a) Deficiencies in minerals and micronutrient homeostasis, including zinc, are an integral component of the pathophysiological phenomena that contributes to the systemic and progressive nature of CHF (Alsafwah *et al* 2007). b) A decreased intake of dietary zinc and lowered zinc levels are associated with increased risk for cardiovascular diseases (Shen *et al* 2008). c) Zinc depletion has been suggested as an environmental risk factor promoting atherosclerosis (Giacconi *et al* 2008; Beattie *et al* 2008).

Different mechanisms may explain these negative effects of zinc deficiency. A first possible explanation why zinc deficiency is a risk for atherosclerosis is the protective role of zinc against upregulation of inflammatory cytokines and activation of O&NS pathways through regulation of O&NS sensitive transcription factors (Connell *et al* 1997). For example, in zinc deficient endothelial cells, the induced O&NS pathways, and the increased production of IL-6 and NFκB may be partially blocked by zinc administration (Hennig *et al* 1999). Second, zinc deficiency may potentiate disruption of endothelial cell integrity by lipids and inflammatory mediators by inducing pathways that cause apoptosis and up-regulate caspase genes (Meerarani *et al* 2000). Third, zinc may is also anti-atherogenic because, as a consequence of its ability to inhibit IO&NS pathways, it is critical for maintenance of vascular endothelial cell integrity during inflammation. Fourth, zinc is essential for the epigenome; via metallothioneins homeosta-

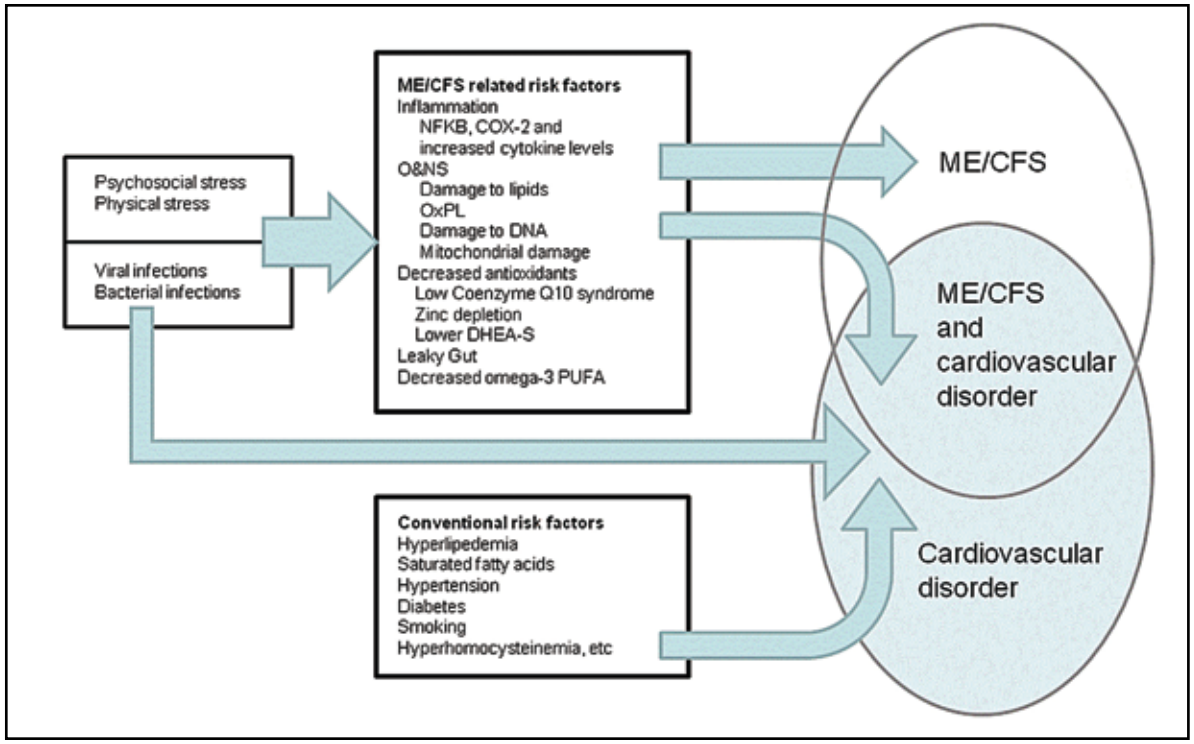

Figure 1. Risk factors for cardiovascular disorder: 1) related to inflammatory and oxidative and nitrosative (IO&NS) pathways of myalgic encephalomyelitis (ME) / chronic fatigue syndrome (CFS); and 2) the conventional risk factors.
NFKB: nuclear factor κB; COX-2: cyclooxygenase-2; oxPL: oxidized phospholipids; DHEA-S: dehydroepiandrosterone-sulphate; PUFA: poly unsaturated fatty acids

sis, zinc-gene interactions modulate the production of cytokines, such as IL-6 and TNFα (Mocchegiani *et al* 2008). Cytokine genes are highly polymorphic and some of the gene polymorphisms related to inflammation are predictive for atherosclerosis (Vasto *et al* 2006). Consequently, it may be hypothesized that zinc deficiency may play a crucial role in atherosclerosis in patients who are genetically predisposed to enhanced responses in IO&NS pathways.

Zinc deficiency not only causes NFκB-related upregulation of IO&NS pathways, but also interferes with peroxisome proliferator activate receptors (PPAR) transactivation activity (Shen *et al* 2008). Zinc deficiency downregulates PPARα expression in cultured endothelial cells, which is important since PPAR can inhibit NFκB signaling (Shen *et al* 2008). Data obtained in LDL-R-deficient mice show that zinc deficiency is accompanied by a pro-inflammatory environment and that zinc is required for the anti-inflammatory and protective functions of PPAR (Shen *et al* 2008). In mice, it has been shown that zinc deficiency is not only accompanied by increased cholesterol and triacylglycerides in the VLDL and HDL fractions and increased NFκB, but also by reductions in the DNA binding activity of PPARs in liver extracts and increased mRNA expression levels of PPARγ in thoracic aortae, indicating decreased PPAR signaling (Reiterer *et al* 2005). Taken together, these observations suggest that zinc is a critical factor in protective PPAR signaling during atherosclerosis.

Another mechanism whereby zinc has anti-atherogenic properties is the reduction in iron-catalyzed free radical reactions (Jenner *et al* 2007). In New Zealand White rabbits administration of zinc decreases the development of atherosclerosis, most likely by depleting iron levels in lesions, resulting into inhibition of the above reactions (Ren *et al* 2006). Finally, zinc deficiency increases erythrocyte fragility and alters erythrocyte membrane fluidity (McClain *et al* 1995).

C3) Low DHEA-S in ME/CFS and cardiovascular disorder

There is evidence that DHEA and DHEA-S protect against atherosclerosis and CAD (Porsova-Dutoit *et al* 2000). Serum DHEA-S is significantly associated with a the risk of carotid artery atherosclerosis in women (Bernini *et al* 1999). In diabetic postmenopausal women serum DHEA-S is associated with atherosclerosis, independently from age, body stature, diabetic status, and other atherosclerotic risk factors (Kanazawa *et al* 2008). Plasma DHEA-S is decreased in patients with CHF in proportion to their clinical status and O&NS (Moriyama *et al* 2000). In male CHF patients, DHEA-S depletion is an independent marker of poor prognosis and relates to a higher mortality rate (Jankowska *et al* 2006). Serum DHEA-S is negatively correlated to carotid atherosclerosis as determined by ultrasonographically evaluated intima-media thickness and plaque score (Fukui *et al* 2005). DHEA and DHEA-S shortages not only are risk factors for developing cardiovascular diseases, but

have also beneficial effects on CAD, atherosclerosis and plaque progression (Williams *et al* 2002).

Since DHEA is metabolized to androgens or estrogens, it is difficult to determine whether the abovementioned effects of DHEA are accomplished by DHEA itself or by these derivative hormones. However, Williams *et al* (2002) provided evidence that at least some effects of DHEA are independent of either androgens or estrogens, since they are mediated by a DHEA-specific receptor involving ERK1 signaling pathways (Williams *et al* 2002). In hypercholesterolemic New Zealand white rabbit with aortic intimal injury, DHEA administration significantly reduced plaque size (> 50%) and fatty infiltration of the heart and liver, suggesting that DHEA-S may inhibit the development of atherosclerosis (Gordon *et al* 1988).

The antiatherogenic actions and the protective role of DHEA-S against cardiovascular disorders may be ascribed to various mechanisms. A first mechanism revolves around the association between DHEA-S and LDL-cholesterol (LDL-C) or high DL-C (HDL-C). For example, in a large cohort of Japanese subjects, DHEA-S levels were positively correlated to HDL-C and negatively correlated to LDL-C and an atherogenic index (Okamoto, 1998). DHEA has been shown to increase HDL(2)-C and the HDL(2)-C/HDL(3)-C ratio, which seem to have atheroprotective effects (Bednarek-Tupikowska *et al* 2008).

A second mechanism relates to the antioxidative properties of DHEA and DHEA-S. DHEA inhibits LDL oxidation in vitro (Lopez-Marure *et al* 2007). The DHEA incorporated into LDL has been shown to increase the resistance of LDL to oxidation in a concentration-dependent manner (Khalil *et al* 2000). DHEA exerts its antioxidative effect on LDL by scavenging free radicals produced during O&NS in a very early state; by protecting endogenous vitamin E from disappearance from LDL being oxidized; by reducing the synthesis of conjugated dienes and TBARS; and by reducing the chemotactic activity of oxidized LDL towards monocytes (Khalil *et al* 1998). DHEA administration may also improve platelet superoxide dismutase activity, which protects cells against oxidative damage (Bednarek-Tupikowska *et al* 2000).

A third mechanism relates to the inhibition of processes involved in vascular inflammation and atherosclerotic cardiovascular disease by DHEA (Altman *et al* 2008). A rise in inflammatory markers, e.g. TNFα levels, is significantly related to a higher cortisol/DHEA (catabolic/anabolic) ratio, which in turn is related to the clinical severity of heart failure (Anker *et al* 1997a). In endothelial cells, administration of DHEA-S significantly inhibited TNFα-induced activation of NFκB and increased IκBα, the NFκB inhibitor (Altman *et al* 2008). DHEA inhibits the expression of inflammatory molecules shown to be important in atherosclerosis, e.g. TNFα or oxLDL-induced expression of adhesion molecules and ROS production; and mRNA expression of IL-8 (Gutierrez *et al* 2007; Lopez-Marure *et al* 2007). DHEA-S reduces the inflammatory reactions in vascular endothelial cells through regulation of the PPARα pathway, which inhibits transcription factors involved in endothelial cell inflammation (Altman *et al* 2008).

There are other possible mechanisms through which DHEA may prevent cardiovascular disease. For example, short-term treatment with DHEA increases platelet cGMP, which is accompanied by a decrease in PAI-1 and LDL cholesterol levels, suggesting DHEA exerts antiatherogenic effects (Martina *et al* 2006). DHEA may also elevate serum IGF-1 concentrations and decreasing homocysteine levels (Bednarek-Tupikowska *et al* 2008). Finally, DHEA counteracts the enhanced AGE receptor activation in the heart of diabetic rats and prevents impairment of cardiac myogenic factors, heart autonomic nervous system and neural crest derivatives and myogenic enhancer factor-2, which are early indicators of diabetic cardiomyopathy (Aragno *et al* 2006).

D) Increased gut permeability in ME/CFS and cardiovascular disorder

CHF is a multi-organ disease with increasing evidence for the involvement of leaky gut (Krack *et al* 2005). Leaky gut with consecutive local and systemic inflammation may worsen the clinical symptoms of CHF (Sandek *et al* 2008). As explained above, bacterial translocation triggers an inflammatory cascade. Increased levels of circulating pro-inflammatory cytokines act as cardiosuppressors, thereby driving disease progression and predicting increased mortality in CHF (Sandek *et al* 2008). In a clinical study, CHF patients showed an increased bowel wall thickness in the terminal ileum and colon and an increase of small intestinal permeability with more adherent bacteria in the mucosal bacterial biofilm (Sandek *et al* 2007). The latter may contribute to the origin of chronic inflammatory reactions (Sandek *et al* 2007). Charalambous *et al* (2007) proposed that this proinflammatory state in CHF may be sustained through a chronic release of enterically derived bacterial endotoxin. Increased levels of LPS and cytokines are found in patients with CHF during acute oedematous exacerbations, suggesting that endotoxins may trigger immune activation in patients with CHF during oedematous episodes (Niebauer *et al* 1999). In humans, bacterial decontamination of the gut with concomitant decrease in LPS has a positive outcome on heart disease (Charalambous *et al* 2007). Another study reported that not only induction of IO&NS pathways as a result of bacterial translocation is of importance, but also the direct cardiac effects of increased serum LPS levels. Cardiac cells, such as the human aortic valve interstitial cells express functional Toll-Like receptors (TLR), e.g. TLR2 and TLR4, which, as a consequence of stimulation by LPS, induce proinflammatory mediators, thereby promoting aortic valve inflammation and stenosis (Meng *et al* 2008). LPS may induce changes in cardiomyocytes with signs of late-stage apoptosis, i.e.

condensed nucleus and cytoplasm (Lapsha and Gurin, 2007). LPS has a direct effect on the cardiac pacemaker current I(f) which may contribute to the reduction in heart rate variability in CHF heart failure (Zorn-Pauly *et al* 2007). Bacterial toxins damage the outer membrane of mitochondria, and down-regulate mitochondrial SOD and glutathione peroxidase activity resulting into increased O&NS and an impaired defence against ROS (Zang *et al* 2007). Endotoxins also increase myocardial cytokine production with an accelerated synthesis of NFκB (Zang *et al* 2007). Interestingly, differential cardiac effects of various types of bacterial LPS have been registered. LPS from Pseudomonas aeruginosa, but not E.Coli, is able to induce interstitial edema, congestion, intramyocardial bleeding, myocardial necrosis, infiltration of inflammatory cells, and formation of fibrin thrombi in the heart (Matsushita *et al* 2007). In addition, the induction of TNFα observed in rats treated with LPS from Pseudomonas aeruginosa is higher that the TNFα synthesis in rats inoculated with LPS from E.Coli (Matsushita et al.,. 2007). This is relevant to the pathophysiology of ME/CFS, since we established highly significant inflammatory responses to LPS of Pseudomonas aeruginosa in many ME/CFS patients.

E) PUFAs, MUFAs and saturated fatty acids in ME/CFS and cardiovascular disorder

This review does not aim to review the current status of fatty acids as risk factors for cardiovascular disorder in detail. There are many reviews available, some of which are cited in this review. Nevertheless, we will point out some highlights with regard to the role that the lowered ω3, versus increased ω6, MUFAs and saturated fatty acids may play in an increased risk for cardiovascular disease in ME/CFS.

E1) Decreased ω3 in ME/CFS and cardiovascular disorder

Recently, it was reported that the red blood cell membrane ω3 PUFA profiles of eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA) provide a better prediction of risks of heart disease than the Framingham risk factors, based on age, smoking behavior, gender, total and HDL-cholesterol, diabetes and hypertension history (Yongsoon Park *et al* 2009). The authors found that a higher ω3 index (the sum of EPA and DHA in the red blood cells) predicts a decreased risk of myocardial infarction, while the ω3 fatty acid index was significantly lower in heart attack patients than in healthy controls. Harris *et al* (2007) demonstrated that DHA was consistently decreased in patients with CHD. The number of plaques in the common carotid artery was inversely correlated with ω3 levels, whereas there was a positive correlation with ω6 fatty acids. In Alaska, natives had less atherosclerosis, higher ω3 and lower ω6 levels in their adipose tissues than non-natives (McLaughlin *et al* 2005).

There are numerous epidemiological and therapeutical trials showing the protective effects of ω3 PUFAs, such as EPA, DHA and α-linolenic acid (LNA), against atherosclerosis and cardiac mortality. Intake of fish oil (rich in ω3 PUFAs) reduces atherosclerosis progression in individuals with CAD (Erkkila *et al* 2004). In Japan, measures of atherosclerosis, such as pulse wave velocity of the aorta, intima-media thickness of the carotid artery, and atherosclerotic plaques, were significantly lower in a fishing village than in a farming village (Yamada *et al* 2000). Americans who consume approximately 2 fatty fish servings per week have a significantly lower risk of myocardial infarctions, heart attacks, CHD, and CVD (Daviglus *et al* 1997). Higher consumption of DHA and EPA, i.e. equalling approximately 5 fatty fish servings per week, reduces the risk for CHD and cardiovascular disease by 40% (Dolecek, 1992). In a meta-analysis study, including over 220.000 subjects, higher fish consumption, 5 or more servings per week, has been shown to be associated with a reduced CHD mortality (He *et al* 2004).

These protective effects of ω3 fatty acids may be ascribed to different mechanisms. 1) ω3 PUFAs have lipid lowering effects, e.g. triglyceride levels. 2) ω3 PUFAs have beneficial effects on blood pressure and coronary artery restenosis after angioplasty, exercise capacity in patients with coronary atherosclerosis, and possibly heart rate variability, particularly in patients with recent myocardial infarction. 3) ω3 have antithrombotic and anti-arrhythmic effects resulting from a decreased blood viscosity. 4) ω3 PUFAs may reduce inflammation and endothelial activation. The intake of ω3 is inversely correlated with inflammatory markers, such as IL-6, matrix metalloproteinase-3, CRP and soluble intercellular adhesion molecule-1 (He, 2009; Balk *et al* 2004; Thijssen and Mensink, 2005; Yongsoon Park *et al* 2009).

The effects of ω3 cannot be discussed without considering the effects of ω6 PUFAs. In mice, a lower ω6/ω3 PUFA ratio in the diet did significantly decrease the values of inflammatory markers and macrophage cholesterol accumulation. This was associated with less aortic lesion formation (Wang *et al* 2009). In another study, the risk for CHD was negatively related to ω3 and positively to ω6 PUFA profiles (Rhee *et al* 2008).

E2) Increased saturated fatty acids and MUFAs in ME/CFS and cardiovascular disorder

It is well established that saturated fatty acids increase the risk of atherosclerosis and CAD, in humans as well as in animals (Wolfe *et al* 1994; Hu *et al* 1997). The incidence of cardiac death and heart failure in subjects with a Mediterranean diet, in which saturated fats are replaced by MUFAs or PUFAS, is significantly reduced (de Lorgeril *et al* 1999). In 939 incident cases of major CHD events, the intake of longer-chain (12:0-18:0) saturated fatty acids was significantly associated with an increase in CHD risk (Hu *et al* 1999). The authors

established that the polyunsaturated/saturated fatty acid ratio was strongly and inversely associated with CHD risk. Among 12,763 middle-aged men, significant positive correlations were established between 25-year death rates from coronary heart disease and average intake of the saturated fatty acids, lauric, myristic, palmitic, and stearic acid (Kromhout *et al* 1995). The abovementioned effects of saturated fatty acids are also partly related to their ability to increase insulin resistance, which contributes to vascular dysfunctions (Maron *et al* 1991).

The relation between MUFAs and the prevalence of cardiovascular disorders is more complex. Firstly, there is evidence that MUFAs have protective effects against atherosclerosis in humans (Salas *et al* 1999). The American Heart Association and the US Food and Drug Administration have advocated to replace saturated fat intake by MUFA intake, as in the Mediteranean diet. The positive effects of MUFAs are partly related to their ability to improve cholesterol profiles, including total and LDL cholesterol (Abbey *et al* 1994). However, in experimental animals it has been shown that a diet rich in MUFAs is not more atheroprotective in comparison with saturated fatty acid intake (Brown *et al* 2007).

F) Psychological stress and infections, i.e. trigger or maintaining factors for ME/CFS, and cardio-vascular disorder

Chronic bacterial infections, e.g. Chlamydia pneumoniae (Chia and Chia, 1999; Nicolson *et al* 2003) and Mycoplasma species (Choppa *et al* 1998; Vojdani *et al* 1998; Nijs *et al* 2002); viral infections, e.g. EBV (Lerner *et al* 2004; Hickie *et al* 2006; Straus *et al* 1985), CMV (Beqaj *et al* 2008; Hilgers and Frank, 1996; Lerner *et al* 2002); Herpes-6 virus (Patnaik *et al* 1995; Nicolson *et al* 2003; Ablashi *et al* 2000; Chapenko *et al* 2006), Parvovirus B19 (Seishima *et al* 2008; Jacobson *et al* 1997; Kerr *et al* 1996; 2003) and enterovirus (Yousef *et al* 1988; Clemens *et al* 1995; Gow and Behan, 1991) and psychological (Lim *et al* 2003) and physiological (Harvey *et al* 2008) stressors are factors that are associated with the initiation or maintenance of ME/CFS.

Chronic bacterial, viral infections, and psychosocial stress have been established as important risk factors for CHD and atherosclerosis. Studies show synergistic effects of viral and bacterial infections with the conventional risk factors in the development for CAD, e.g. hyperlipidemia, hypertension, diabetes, smoking and hyperhomocysteinemia.

F1) Bacterial infections, ME/CFS and cardiovascular disorder

Chronic bacterial infections, for example Chlamydia pneumoniae infections, have been implicated as precipitating and perpetuating factors in the development and progression of atherosclerosis and the clinical complications of unstable angina, myocardial infarction, and stroke (Muhlestein, 2000). Numerous papers demonstrated an association between serological evidence of Chlamydia pneumoniae (and other bacterial pathogens) and chronic coronary heart disease, acute myocardial infarction and atherosclerotic disease (Stassen *et al* 2008). Chlamydia pneumoniae is a gram-negative bacterium that can remain dormant in the cells for years after the primary infection. Chlamydia pneumoniae has a biphasic developmental cycle switching between a proliferative and a nonreplicative state (Kern *et al* 2009). Different studies proved Chlamydia pneumoniae (and other pathogens) to be present in atherosclerotic lesions, suggesting that this bacterium plays a role in the development of atherosclerosis (Jha *et al* 2007). These bacteria persistently present in the arteries and atherosclerotic lesions are often resistant to antibiotic treatments (Kern *et al* 2009). Moreover, in CAD patients, there is evidence for ongoing Chlamydia pneumoniae infections, as can be deduced from positive nPCR findings and high Chlamydia pneumoniae specific antibody titers (Jha *et al* 2008).

Chlamydia pneumoniae is involved in the two main pathways that define cardiovascular disorders and atherosclerosis, i.e. angiogenesis and inflammation (Kern *et al* 2009; Mahmoudi *et al* 2007). Bacterial antigens promote T cell activation in atherosclerotic plaques, a phenomenon that participates in destabilization of intimal cap and an atherosclerotic inflammatory response (Leowattana, 2001; van der Meer *et al* 2008). These infectious agents may enhance structural and proinflammatory changes in the vascular wall, causing atherogenesis, e.g. cell lysis, stimulation of adhesion molecule expression, cytokine production by infected cells, and increased production of microbial heat shock protein 60 (Kol and Santini, 2004). The latter may induce antigenic mimicry and consequently induce an immunological attack on the vascular wall (Kol and Santini, 2004; Villegas *et al* 2008). Moreover, Chlamydial antigens, including LPS and HSP60, participate in atherosclerosis by induction of inflammatory mediators such as IL-18 (Mousa *et al* 2009). Chlamydia pneumoniae may facilitate foam cell formation via activation of both MyD88-dependent and MyD88-independent pathways, and by suppressing the expression of PPARα and PPARγ at mRNA and protein levels in macrophages (Mei *et al* 2009; Chen *et al* 2008).

Mycoplasma pneumoniae is present in the coronary artery segments of myocardial infarction patients (Ramires and Higuchi, 2002). This bacterium can be found in stable and subendothelial active accumulation of macrophages proving that it is related to the initial development of atherosclerotic lesions (Gois *et al* 2006). CAD patients with myocardial infarction exhibit an increased seropositivity to Chlamydia pneumoniae and Mycoplasma pneumoniae (Goyal *et al* 2007). The association of both abovementioned bacteria increases their virulence, inducing adventitial inflammation and rupture of plaques (Ramires and Higuchi, 2002). Only in patients with Chlamydia pneumonia seropositivity an association between Mycoplasma pneumonia antibodies and CAD was detected (Momiyama *et al* 2004).

This indicates that a coinfection of Mycoplasma and Chlamydia pneumoniae is an important risk factor for CAD. In mice, inoculation of Mycoplasma pneumoniae caused an aggravation of atherosclerosis induced by a cholesterol-enriched diet (Damy *et al* 2009). There is also evidence that Mycoplasma causes recurrent pericarditis and myocarditis (Farraj *et al* 1997; Paz and Potasman, 2002).

F2) Viral infections, ME/CFS and cardiovascular disorders

Not only persistent bacterial infections, but also chronic viral infections seem to play an important role as triggers of the pathophysiology of ME/CFS and vascular disease. In particular, viruses from the Herpes viridae family, e.g. CMV, EBV, Herpesvirus, are known to enhance atherogenesis (Rusiecka, 2004). CMV infection is associated with accelerated atherosclerosis following cardiac transplantation and an increased risk of restenosis after coronary angiography (Corrado and Novo, 2005). As discussed before, T-cell activation participates in atherosclerotic plaque inflammation. EBV DNA and EBV-specific cytotoxic T-cells can be detected in atherosclerotic plaques, suggesting that a T-cell responses against EBV may contribute to plaque inflammation (de Boer *et al* 2006). EBV and CMV are present in the arterial wall, while there is a significant association between CMV DNA and atherosclerosis progression (Horvath *et al* 2000).

Shi and Tokunaga (2002) found Herpes simplex virus type-1, EBV, and CMV DNA significantly more often in atherosclerotic lesions than in non-atherosclerotic tissues. Other authors found that increased IgG EBV and herpes simplex virus type 2 antibodies are associated with an increase of intima-media thickness or progression of atherosclerosis, suggesting that the number of infections an individual has contracted during his life contributes to the extent of atherosclerosis (Espinola-Klein *et al* 2002). In another study, Herpes simplex-1, CMV and EBV DNA were observed in plaques while the Herpes viral DNA was significantly related to arterial hypertension, suggesting that herpes viral infections may alter the vessel wall (Ibrahim *et al* 2005). Taken together, herpes viral infections seem to increase the risk and the severity of atherosclerotic lesions.

F3) Psychological stressors, ME/CFS and cardiovascular disorder

There is evidence supporting the view that psychosocial factors can cause cardiovascular disease events and that stress management might reduce future cardiac events in patients with cardiovascular disease (Figueredo, 2009). Psychological stressors may cause cardiovascular dysfunctions by alterations in different IO&NS pathways. These stressors a) induce the production of inflammatory mediators, such as NFκB (Munhoz *et al* 2006) and pro-inflammatory cytokines, like TNFα and IL-6 (Maes *et al* 1998); b) impair antioxidant defenses, such as the glutathione antioxidant pathway (Goncalves *et al* 2008); and c) induce ROS and consequent oxidative damage, including lipid peroxidation and DNA damage (Aleksandrovskii *et al* 1988; Pertsov *et al* 1995; Sivonova *et al* 2004; Irie *et al* 2001).

Conclusions

In conclusion, in this review we have shown that various IO&NS pathways that participate in the pathophysiology of ME/CFS have several deleterious effects on the cardiovascular system and may cause cardiovascular disease. The activated IO&NS pathways and its sequels could explain the young mortality rates due to cardiovascular disorders in ME/CFS. Each of the IO&NS pathways involved may promote cardiovascular diseases through different mechanisms involving chronic low grade inflammation with an increased production of NFκB, COX-2 and TNFα; increased ROS and oxidative damage to phosphatidylinositol; decreased levels of antioxidants, such as CoQ10, zinc and DHEA-S; decreased ω3 polyunsatutared fatty acids; bacterial translocation; and the presence of psychosocial stressors, bacterial and viral infections.

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