Aetiological model of Chronic Fatigue Syndrome: proposed pathophysiological process underlying ME/CFS and implications for treatment.

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Abstract

M.E. / CFS is a debilitating systemic disorder about which little is conclusively understood. There is a great deal of evidence to support the theory that M.E. / CFS symptom complexes result from accelerated oxidative injury. This evidence is discussed. Necessary aims of treatment are suggested as repairing damage caused by oxidants and preventing recurrence. An integrative management plan for the condition is proposed, addressing relevant biological and psychosocial factors. The areas addressed by this individualised protocol include treatment of latent infections / management of heavy metal poisoning (*detoxification*), improving oxygenation, diet and supplementation, reconditioning of body and reconditioning of mind.

Introduction

Chronic Fatigue Syndrome (CFS) or (M.E.) Myalgic Encephalomyelitis is an often poorly-understood, debilitating neurological condition (as classified by the WHO in ICD10) affecting at least 0.4% of the population of the UK (Chief Medical Officer's Working Group Report on CFS/ME, 2002). It is a growing problem worldwide, with tremendous costs to the individual as well as enormous economic costs to society. A study released in 2003 by Sheffield Hallam University on behalf of Action for M.E., a U.K. charity, estimated the cost of M.E. to the U.K. economy at £3.46 billion per year. In 2004, the annual total value of lost productivity due to M.E. / CFS in the United States was estimated at $9.1 billion (Reynolds et al, 2004). This is not including medical and disability costs to the state.

The Canadian Expert Consensus Panel Clinical Case Definition of ME/CFS (Carruthers et al, 2003) is now widely accepted as the most appropriate diagnostic criteria for this condition, as they incorporate dysautonomia, cardiac and immune symptoms as a key feature of the condition, when other diagnostic criteria focus only on the fatigue experienced, thereby broadening the diagnostic group to include those suffering from *chronic fatigue* or other conditions. Individuals meeting these criteria may be diagnosed with Fibromyalgia Syndrome (FMS), Chronic Fatigue Syndrome (CFS), Myalgic Encephalomyelitis (ME) or Post Viral Fatigue Syndrome (PVFS). Patients with these conditions may suffer to differing extents with differing symptoms, but it is proposed that the underlying pathological process is similar for each and therefore a similar treatment approach / protocol, tailored to the individual will be effective. The different names seem to reflect the most significant symptoms present at the time of diagnosis and/or the field of expertise of the diagnosing physician. ME/CFS is a useful term to encompass all the above diagnoses, covering those individuals who meet the Canadian criteria.

There is significant evidence to suggest that individuals with ME/CFS Complex have lower-than-normal levels of oxygen (O_2), both within the circulatory system (Alvarez et al, 1996) and intracellularly (Lund et al, 1986). Studies have also shown that oxygen therapies and other forms of treatment, which aim to increase intracellular oxygen levels, have a positive effect on ME/CFS patients (Scholey et al, 1998; Ali, 1999; Yildiz et al, 2004).

Since oxygen is the most important nutrient for the body (humans can survive weeks without food, days without water, but only minutes without oxygen), and is necessary for nearly all metabolic processes, it is perhaps unsurprising that a basic lack of it can produce such a debilitating, systemic disease.

It is proposed that the underlying cause of all presentations of ME/CFS is accelerated oxidative injury to biological structures throughout the body. It is suggested that many factors combine to cause cells immense oxidative stress. This greatly decreases oxygen delivery *to* cells and impairs oxygen metabolism *within* the cells. This causes severe oxygen deprivation at an intracellular level. When this impairment of vital metabolic processes occurs systemically, it is believed to cause the symptom complexes seen in ME/CFS. A feedback loop then exists; conditions are created which further impair O_2 delivery and metabolism and increasing the oxidative injury. This perpetuates the condition, worsening symptoms and preventing return to health.

It is concluded that if the oxidative damage can be reversed and further damage prevented, the condition of ME/CFS should be controllable; a state should be attainable in which the affected individual's own body system is able to heal and maintain itself to prevent all signs and symptoms of this condition.

Genetic Predisposition

There is believed to be a genetic predisposition to development of ME/CFS, which manifests as cells more easily damaged by oxidative stress. This may be quantifiable as an "inferior anti-oxidant system" (i.e. reduced levels / mutations of enzymes such as superoxide dismutase, catalase or glutathione peroxidase), another specific inborn error of metabolism (relevant enzyme mutation) or alterations in cell mitochondria (Behan et al, 1991).

It is considered that this genetic predisposition is the first in a series of events that eventually culminate in the potentially debilitating ME/CFS complex.

Pre-Disease State

Throughout life, human beings are subject to high numbers of endogenous and exogenous oxidants (free radicals). A free radical is a cluster of atoms (or a single atom), one of which contains an unpaired electron in its outermost shell. This is an extremely unstable configuration, so free radicals react easily with other molecules to achieve greater stability: an outermost shell containing a full complement of electrons.

The term *reactive oxygen species* (ROS) is also used to describe free radicals and other molecules that are themselves easily converted to free radicals or are powerful oxidising agents. Sequential reduction of molecular oxygen (i.e. sequential addition of electrons) leads to formation of the following ROS: superoxide anion, hydrogen peroxide and then hydroxyl radical (OH·) (most reactive).

ROS are formed via several different mechanisms; endogenously and exogenously. These can be categorised into three groups of oxidants: metabolic (unavoidable by-products of cellular respiration), microbial (toxins and waste products generated by microbes and via the destruction of microbes by immune system cells) and man-made (such as those formed through exposure to ionising radiation, pesticides, cigarette smoke, synthetic hormones, antibiotics and other medications) (Ali, 1998).

By reacting to gain a stable configuration, free radicals convert their target species into a radical. So a chain reaction begins that will propagate until two radicals react with each other and each contributes its unpaired electron to form a covalent bond. This chain reaction can result in damage to innate / biological molecules. The resultant damage is termed oxidative stress.

In order to prevent oxidative injury, the body utilises its anti-oxidant system. Antioxidants have been defined as *"any substance which delays or inhibits oxidative damage to a target molecule."* (Gutteridge and Halliwell, 1994).

The exact activity of an antioxidant depends on the ROS involved, the area of the body affected and the exact molecular target of attack. Oxidative stress (injury) occurs when there is either a decrease in anti-oxidant defences or an overwhelming increase in generation of ROS (or both).

Cellular components especially vulnerable to oxidative injury are lipids (via peroxidation e.g. in cell membranes), proteins (e.g. enzymes, cell receptors) and DNA. Free radicals can cause fragmentation of DNA within cell nuclei. Among the most important damaging actions of free radicals, is that done to fatty acid side chains of lipids in mitochondrial membranes (directly exposed to the superoxide anions produced during cellular respiration).

In those genetically more susceptible to oxidative injury, the following may be a consequence of rising free radical levels:

- Structures of cellular components become altered and dysfunctional (due to radical chain reactions).
- Mutations occur, producing dysfunctional enzymes.
- Numbers of oxygen molecules within the cell are exhausted by damaging oxidation reactions, leading to decreased levels of O_2 available for cellular metabolism.

The human cell is believed to be able to withstand certain levels of uncontrolled oxidation. In health it is estimated that an intracellular partial pressure of oxygen as low as 1-3 mm Hg is sufficient to support cellular metabolism (Coher, 1984). This indicates a substantial reserve under physiological conditions, since the average partial pressure value is estimated at 23 mm Hg (by direct measurement in lower animals) (Coher, 1984). However, it is not known whether such conditions can support active cellular metabolism in a state of accelerated oxidative injury.

It is suggested that, with certain levels of uncontrolled oxidation, cells within the human body are able to function adequately due to the large reserve of oxygen and other cellular resources. However, this is considered to be a pre-morbid state of ME/CFS. If the high levels of oxidants are not addressed at this point, a trigger event may precipitate ME/CFS Complex.

Trigger Events

With such high rates of oxidation, it takes only a small amount of extra stress (a "trigger event") in terms of radical generation or O_2 demand, for cellular respiration and other metabolic processes (and consequently cellular function) to become impaired. When this occurs systemically, the body begins to exhibit the signs and symptoms attributed to ME/CFS; a state of accelerated oxidative molecular injury (Ali, 1993).

The trigger event causes either:

- Increased energy (ATP production) demand,
- Reduction in O_2 levels,
- Further increase in free radical numbers,
- A combination of the above factors.

Examples of trigger events involving increased energy demand are physical trauma such as musculo-skeletal injury and surgery, or excessive emotional stress such as bereavement. Examples of trigger events involving generation of increased radicals include bacterial or viral infection. One theory regarding trigger events is that an infectious agent, such as a virus (CMV / EBV / HHV6) (Cheney, 1999), bacteria, or vaccine (e.g. Hepatitis B) stimulates T-cell proliferation, producing large numbers of cytokines, which consequently increase blood viscosity, thereby resulting in a temporary but potentially significant decrease in oxygenation of tissues (Berg et al, 1999). This is an example of a "combined effect" trigger event, since the above pathway causes reduced availability of O_2, plus the infectious agent is likely to increase free radical generation through production of toxins and waste products.

A second trigger event theory starts with the observation that infections which precede and may therefore precipitate ME/CFS act to induce production of inflammatory cytokines (as above) that induce, in turn, inducible nitric oxide synthase (iNOS). This enzyme then synthesizes excessive amounts of nitric oxide, which reacts with superoxide to produce the potent oxidant peroxynitrite. Excessive peroxynitrite levels in an anti-oxidant-deficient system cause accelerated oxidative injury, thereby initiating symptomatic ME/CFS Complex. Once produced, peroxynitrite also acts via biochemical mechanisms to increase the levels of both nitric oxide and superoxide, which react to produce more peroxynitrite. In this way, once peroxynitrite levels are elevated, they may act to continue the elevation, thus producing a self-sustaining vicious cycle (Pall, 2001).

Nitric oxide (NO) is known to stimulate the nociceptors that initiate pain perception; high nitric oxide levels may therefore be associated with the body-wide pain observed in ME/CFS (Pall, 2000). NO has a central role in learning and memory and excessive production may also provide a partial explanation for the cognitive dysfunction in ME/CFS (Pall, 2000). Other symptoms potentially explained by NO excess include immune dysfunction, fatigue and post-exertional malaise (Pall, 2000).

Not only infections but also instances of severe physical or psychological trauma may produce a similar NO vicious cycle effect via activation of the Hypothalamic-Pituitary-Adrenal (HPA) Axis and consequent cytokine production (Pall, 2000). Pesticide and organic solvent exposure has also been reported to cause accelerated oxidative injury via the cytokine pathway described above (Pall and Satterlee, 2001), and in some individuals this may be the trigger event precipitating ME/CFS (Behan and Haniffah, 1994; Behan, 1996).

The consequence is the same for each type of trigger event; an individual moves from the pre-morbid state into symptomatic ME/CFS. This occurs because cells are unable to function normally in the anaerobic, structurally-deforming conditions of accelerated oxidative injury; they are forced to exist in a more 'primitive' state, able to sustain very limited function via anaerobic fermentation rather than aerobic respiration (Ali, 1998).

Symptom Complex Explanations

As described above, there is significant evidence to suggest that accelerated oxidative injury to biological structures, with consequent defects in aerobic metabolism may be a major causative factor in ME/CFS (Behan et al, 1999; Fulle et al, 2000; Richards et al, 2000 A; Vecchiet et al, 2003;)

Extensive evidence also exists supporting the proposal that the ME/CFS symptom complex is associated with decreased levels of oxygen. In ME/CFS individuals, studies have demonstrated hypoperfusion and poor O_2 delivery (Ichise et al, 1992; Costa et al, 1995; Alvarez et al, 1996; Van Ness et al, 2000;), abnormal erythrocyte function (Simpson, 1989) and reduced plasma volume and red blood cell mass compared with healthy controls (Streeten and Bell, 1998; Farquar et al, 2002).

It is proposed that, as a result of the above state, excess reactive oxidative species, progressive anoxia and accumulation of organic acids create cellular ecologic conditions that closely resemble a primordial state (Ali, 1998). The enforced anaerobic conditions in cells body-wide causes a respiratory-to-fermentative (RTF) shift in terms of ATP production. Inefficient and subsequently dysfunctional cells then produce the symptom complexes of ME/CFS (Ali, 1998).

The Krebs (Citric acid / Tricarboxylic acid) Cycle is the final common pathway for oxygen-driven breakdown of sugars, fats and proteins to produce usable energy for the body. If the enzymatic pathways of Krebs Cycle are impaired (e.g. secondary to the oxidative damage previously described), the cycle is effectively blocked. This causes a build up of metabolites, which are then excreted. It has been demonstrated that individuals with ME/CFS excrete increased levels of Krebs Cycle metabolites (organic acids) (Ali, 2003). This accumulation predictably results in intracellular acidosis, which further impedes oxygen metabolism (see below).

Ali (1998) describes how the oxidative regression to a primordial ecology of cells (ORPEC), as described above, results in rapid multiplication in blood and tissues of pleomorphic anaerobic organisms with yeast-like morphological features. These are designated primordial life forms (PLFs), due to lack of precise nucleotide sequence and taxonomic data. PLFs are readily observed with high-resolution phase-contrast and dark field microscopy in freshly prepared and unstained smears of peripheral blood. Strong homology (up to 40 percent) among yeast and mammalian DNA sequences has been reported (Altschul et al, 1990; Botstein et al, 1997). Such homology indicates that the genetic codes for PLF growth may already exist in human cells and that organisms observed may not indicate an infection from an outside source. Organic acids such as tartaric acid and carboxycitric acid and other toxins produced by the growing number of PLFs worsen

acidic conditions and generate oxidative cycles that feed upon each other, causing further damage to antioxidant systems and oxygen metabolism within the body.

If it is agreed that ME/CFS Complex is due to abnormal oxygen metabolism at a cellular level, causing significantly reduced levels of ATP production and other disrupted intracellular processes, the diverse, variable and often debilitating ME/CFS complex symptoms can perhaps be better understood.

Novel Coagulopathy

There is strong evidence for a novel coagulopathy in ME/CFS individuals. This is caused by a host of oxidative phenomena, leading to structural damage to erythrocytes, polymorphonuclear cells, and abnormal micro-clot and micro-plaque formation (Ali, 1993B; Ali, 1997). The micro-clotting process can be reversed using antioxidants such as vitamins E or C (Ali, 1990), demonstrating the oxidative nature of such changes. This hypercoaguable state has also been documented in ME/CFS patients using markers such as fibrinogen, thrombin-anti-thrombin complexes and soluble fibrin monomer (Harrison et al, 2004). The phenomenon, which effectively increases blood viscosity, decreases delivery of nutrients (including oxygen) to tissues, thus further decreasing tissue oxygenation.

Lymphopathy

A state of *oxidative lymphopathy* in ME/CFS is also proposed, similar to the oxidative coagulopathy described above (Ali M, 1999). It is suggested that oxidative denaturation of proteins, lipids and sugars occurs within the circulating and stagnant lymph, as has been demonstrated in the blood of ME/CFS individuals. Myofascial trigger points (the tender points included in the American College of Rheumatology 1990 Criteria for the Classification of Fibromyalgia) are believed to develop as a result of accumulation of oxidised and stagnant lymph components within muscles, tendons and ligaments (Ali, 1999).

Autonomic Dysfunction

Signs and symptoms reflecting autonomic dysfunction occur frequently in patients with ME/CFS (Gibson et al, 1993; Bou-Holaigah et al, 1995; De Lorenzo et al, 1997; Freeman & Komaroff, 1997; De Becker et al, 1998; Stewart et al, 1999). These include delayed gastric emptying, urinary frequency, neurally mediated hypotension and other forms of orthostatic intolerance. Oxidative stress has been linked to development of autonomic dysfunction (Demir et al, 2005).

Autonomic nervous system changes (autonomic dysfunction) in ME/CFS may develop due to "channelopathy". Abnormal ion channel functions as the mechanism of neurological disorders (including epilepsies and migraine) now constitute a new group of diseases termed channelopathies (Chaudhuri and Behan, 1999). Accelerated oxidative injury may alter the configuration of plasma-membrane receptors and neurotransmitters. These alterations may lead to abnormalities in the normal receptor and ligand-gated ion channel function, causing perturbations of cell transport mechanisms and the action of neurotransmitters. Evidence of a cell membrane transport defect (Watson et al, 1997) and alterations in neurotransmitter activity (Spence et al, 2000) has already been demonstrated in individuals with ME/CFS.

It is proposed that Neuropeptide-Y (NPY) is amongst the neurotransmitters affected. NPY co-exists with norepinephrine in the sympathetic nervous system. Released by sympathetic activity, NPY is a major mediator of stress, responsible for prolonged vasoconstriction via Y_1 receptors (Zukowska et al, 1993). Studies have shown that NPY levels are significantly elevated in individuals with ME/CFS (Anderberg et al, 1999). It has also been demonstrated that, in female patients, during the luteal phase of the menstrual cycle (between ovulation and onset of menstruation) levels of the peptide were higher than during the rest of the cycle. This correlates with a worsening of symptoms observed in female ME/CFS patients during this phase of their cycle (Anderberg et al, 1998). NPY is also believed to have considerable immunoregulatory effect on natural killer (NK) cell activity (Nair et al, 1993). Dysfunction of this may explain some of the immune system abnormalities observed in ME/CFS (Patarca et al, 2001).

Pain

Dysregulation of Substance P (via neurotransmitter oxidative injury as described above) is proposed as a contributing factor to the multi-organ pain commonly experienced in ME/CFS. Substance P (SP) is a short-chain polypeptide that functions particularly as a neurotransmitter in pain transmission. Higher levels of SP cause increased pain. Levels of SP in cerebro-spinal-fluid (CSF) in individuals with ME/CFS are three times higher than in healthy controls (Russel et al, 1994; Larson et al, 2000), and also higher than in Rheumatoid Arthritis patients (Vaerov et al, 1988). Oxygen deficit triggers the release of SP (Kim et al, 2001; Chen et al, 2001). Since it is proposed that individuals with ME/CFS have a *global* oxygen deficit, this, combined with the oxidative SP dysregulation described above, may go some way to explaining the non-specific, body-wide pain experienced in this condition.

SP levels tend to have an inverse relationship with norepinephrine (noradenaline), in part (or entirely) as a result of neuronal competition for nerve growth (Davis et al, 1994). This is consistent with findings of hyposecretion of norepinephrine in ME/CFS patients (Goldstein, 1996) and consequent high pain levels and adrenergic dysfunction.

Hormonal Dysregulation

Oxidative injury to cell membrane receptors, hormones and neurotransmitter substances within the hypothalamo-pituitary-adrenal (HPA) axis may cause dysregulation of several hormones. Biochemical evidence for hypothalamic dysfunction in ME/CFS complex is rapidly accumulating (Demitrack et al, 1991; Bou-Holaigah et al, 1995; De Becker et al, 1996; Suhadolnik et al, 1996) with the following hormonal deficits (and consequent symptom complexes) commonly observed in ME/CFS: dopamine (Moorkens et al, 2000), serotonin (Dinan et al, 1997) and human growth hormone (HGH) (Moorkens et al, 2000; Allain et al, 1997).

The mechanisms of oxidative injury described previously are thought to cause a state of chronic, global, cellular dehydration (Ali & Ali, 1997). This not only directly causes symptoms but in turn increases the degree of oxidative damage, anoxia and acidosis.

Acidosis

In ME/CFS, there is chronic and unremitting intracellular acidosis, caused by the build up of organic acids secondary to anaerobic metabolism. The body compensates for this acidosis by increasing renal bicarbonate resorption, and developing tissue alkalosis (Ali, 1999). Extracellular alkalosis decreases levels of 2,3-diphosphoglycerate (2,3 DPG). Since this substance lowers the affinity of haemoglobin for oxygen, the effect is inhibition of oxygen transport to tissues and organs, constriction of blood vessels, and reduction of overall circulating blood volume. This increases tissue hypoxia and a vicious cycle is created: hypoxia increases acidosis, causing greater blood alkalosis, which lowers 2,3 DPG even further, worsening hypoxia.

Seasonal Variation

Between 43% and 79% of ME/CFS patients report increased symptoms during winter (Terman et al, 1998). This may be due to a variety of reasons including the following:

- Lower levels of oxygen in the atmosphere, secondary to the loss of leaves from deciduous trees and decrease in herbaceous plants (Keeling and Shertz, 1992).
- Increasing vitamin D hypovitaminosis.

Low levels of vitamin D are a common finding in individuals with ME/CFS (Al-Allaf et al, 2003). This may be linked to winter exacerbations, as wintertime supplies of Vitamin D depend on the previous summer's exposure creating adequate stores in the liver, or on dietary sources (Webb et al, 1988). One study of 504 patients with ME/CFS found that 97.8% had a vitamin D deficiency (Hock, 1997). The cause of this is not currently understood, but may be due to enzymatic mutations (caused by oxidative injury) preventing production of active vitamin D (Calciferol) from precursors. Another possibility is pancreatic enzyme insufficiency (also driven by accelerated oxidative injury), causing malabsorption of fats and consequent malabsorption of dietary vitamin D (ergocalciferol); a fat-soluble "vitamin". Deficiency may also be linked to illness preventing ME/CFS individuals from being out in the sun as much as their healthy counterparts.

Aims of Treatment

Symptomatic treatment can be useful in any medical condition. However, addressing the underlying cause of a disease will have greater impact and a more sustained effect on patients' health. This entails reversing the underlying problem as well as preventing further occurrence. With any chronic disease, it is also important to address biological and psycho-social aspects of the condition that have resulted from the illness state.

Additional factors come into play when dealing with any chronic disease. ME/CFS is no exception to this and the following issues must be recognised when formulating a treatment plan for the condition, as they affect the overall well-being of the individual and can exacerbate symptom complexes, thereby inhibiting recovery.

- Deconditioning of muscles and joints, due to lack of use, fatigue and pain (Donald et al, 1996).
- Psychological distress; depression / anxiety etc due to physical pain, cognitive impairment, as well as the loss of health, independence, employment, relationships etc.
- Social effects; isolation secondary to poor physical health and psychological effects.
- Nutritional deficiency (e.g. B-vitamins); this can be exacerbated by digestive dysregulation and poor / inappropriate dietary intake.
- Sleep disturbance; this has previously been cited as the *cause* of ME/CFS. However, it is suggested that as in many chronic conditions (especially those in which pain is a significant feature) the sleep disturbance is a *consequence* or *symptom* of the condition, caused by the above factors.

Combining consideration of these factors with the previously discussed theory of aetiology, the proposed aims of treatment for ME/CFS are to normalise cellular metabolism, promote repair of cellular structures and elimination of toxins and prevent further oxidative damage. More simply, these aims can be stated as follows:

- Improve oxygen delivery to cells

- Improve oxygen metabolism
- Increase anti-oxidant defences
- Remove toxins and prevent further build up
- Counteract negative biological and psychosocial effects of chronic disease

It is imperative to carry out all the above in a controlled manner so that full health can be achieved, without causing a relapse in condition by placing demands which are too great on the individual's over-burdened, often hypersensitive body system.

Based on the above aims, using personal experience and research carried out by various investigators, the following Management Plan has been compiled. The plan covers six areas that need to be addressed to differing extents by individuals with ME / CFS. Each individual will require a tailor-made programme of treatment dependent on his or her personal needs and situation. Research is currently underway to establish effectiveness of this regime.

Holistic Recovery

Areas to be addressed:

- ❖ Detoxification and Lymphatic Decongestion
- ❖ Improving Oxygenation
- ❖ Nutrition - Diet and Appropriate Supplementation
- ❖ Physical Release & Reconditioning of Body
- ❖ Mental Release & Reconditioning of Mind
- ❖ Emotional Release

For more information, for a full reference list or to enquire about a consultation to explore your own Holistic Recovery Programme, please contact Dr C J Bowen:
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