International Journal of Neurology Research

Online Submissions: http://www.ghrnet.org/index./ijnr/
doi:10.17554/j.issn.2313-5611.2015.01.13

The 4I Hypothesis: A Neuro-Immunological Explanation for Characteristic Symptoms of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome

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Received: February 4, 2015 Revised: March 22, 2015
Accepted: March 28, 2015
Published online: May 13, 2015

ABSTRACT

Characteristic symptoms of Myalgic Encephalomyelitis (ME) are (muscle) weakness, muscle pain, cognitive deficits, neurological abnormalities, but above all post-exertional malaise: a long-lasting increase of symptoms after a minor exertion. In contrast, Chronic Fatigue Syndrome (CFS) is primarily defined by “chronic fatigue”. Since “chronic fatigue” is not mandatory for the diagnosis ME, and post-exertional malaise and cognitive deficits are not obligatory for the diagnosis CFS, the case criteria for ME and CFS define two distinct, partly overlapping nosological entities. ME and CFS are considered to be enigmatic diseases, qualified by some authors as “medically unexplained syndromes” of “functional syndromes”. However, specific abnormalities consistently observed over the years and their direct and indirect sequels can plausibly explain characteristic symptoms, e.g. “exhaustion” and pain. Abnormalities established repetitively incorporate immunological aberrations (inflammation, immune activation, immunosuppression, and immune dysfunction), persistent and/or reactivating infections, gastrointestinal dysbiosis, oxidative and nitrosative stress, mitochondrial dysfunction, a (prolonged) deviant response to exertion and orthostatic stress, circulatory deficits, and neurological abnormalities. This article depicts the 4I hypothesis, an explanatory model for ME (CFS) with a central role for four types of immunological abnormalities: inflammation, (Th2-dominated) immune activation, immunosuppression, and immune dysfunction. The potential direct sequels of these abnormalities, e.g. increased oxidative and nitrosative stress, (reactivating or chronic) infections, and their possible indirect consequences, e.g. mitochondrial dysfunction, hypothalamic-pituitary-adrenal axis (HPA) axis hypofunction, and cardiovascular dysregulation, can plausibly explain various distinctive symptoms of ME/CFS, e.g. “exhaustion”, (muscle) weakness, pain, cognitive deficits, a flu-like feeling, and post-exertional “malaise”.

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Key words: Myalgic Encephalomyelitis; Chronic fatigue syndrome; Immunology; Neurology; Oxidative stress; Nitrosative stress; Pathophysiology; Hypothesis; Post-exertional malaise


CORE TIPS

ME and CFS are two distinct, partially overlapping diagnostic entities.

More consistent findings in ME and/or CFS relate to four types of immunological abnormalities: inflammation (I1), (Th2-dominated) immune activation (I2), immunosuppression (I3), and immune dysfunction (I4). The potential sequels of these abnormalities encompass oxidative/nitrosative stress and infections. The possible indirect consequences of the immunological aberrations and increased oxidative/nitrosative stress include neurological...
abnormalities, mitochondrial dysfunction and cardiovascular disturbances.

The direct and indirect sequelae of the immunological abnormalities can plausibly explain distinctive symptoms of ME/CFS, e.g. cognitive deficits, and post-exertional “malaise”: a prolonged aggravation of characteristic symptoms, e.g. cognitive impairments and pain, after a minor exertion.

**INTRODUCTION**

Although ME and CFS are often used interchangeably, the case criteria for ME[1,3] and CFS[13] define two distinct, partially overlapping diagnostic entities[9]. The diagnosis ME requires specific neurological/neurocognitive and immunological symptoms and energy production and/or transport impairment, but the distinctive feature of ME is post-exertional malaise or “neuro-immune exhaustion”: a pathological inability to produce sufficient energy on demand resulting into symptom exacerbation, e.g. flu-like symptoms and pain, after minor exertion[11]. The distinctive feature of CFS[2] on the other hand is (unexplained) chronic fatigue, which should be accompanied by at least four out of a eight symptoms, e.g. sore throat, unrefreshing sleep, and headaches. While post-exertional malaise is not obligatory for CFS[3], “fatigue” is not mandatory for the diagnosis ME[1]. The distinction between patients with post-exertional malaise and without post-exertional malaise seems to be reflected by specific immunological differences[4-5]. Although ME and CFS criteria select partially overlapping, partially disjoint patient groups, the majority of the research into ME/CFS in the last decades has been conducted in patients selected by CFS criteria[5-6]. However, since many optional symptoms of CFS are mandatory for the diagnosis ME, the CFS criteria also apply to a substantial ME patient subgroup reporting “fatigue” (Figure 1). In conclusion, while ME is a neuro-immunological disease in nature[7], the CFS criteria[8] select a heterogeneous patient population of people with self-reported “chronic fatigue”.

**SYMPTOMS**

Notwithstanding the debate about the distinction between ME and CFS[8,9] and definitional criteria of ME and CFS[10], including obligatory symptoms, many patients with ME/CFS experience a plethora of symptoms[11], which differ inter-individually and seem to fluctuate in number and severity within an individual over time as a consequence of daily activity[12]. Symptoms experienced by substantial patient subgroups are: post-exertional malaise, “fatigue”/lack of energy, muscle weakness, (muscle/joint) pain, cognitive impairment (“brain fog”), a flu-like feeling, sleep dysfunction (“unrefreshing sleep”), hypersensitivity to food, light, sound and odours (“central sensitisation”), stress intolerance, orthostatic intolerance and depression[9] (Table 1). Various characteristic symptoms can be assessed objectively using well-accepted methods[13], e.g. neurocognitive tests, while other symptoms due to their nature, e.g. (muscle) pain, cannot be assessed objectively.

**ABNORMALITIES**

Partly due to the heterogeneity[14] of the CFS[3] patient population and the variety of methods employed and samples investigated, research into ME/CFS has yielded contradictory results. However, various typical aberrations (Table 2) have been observed repetitively in the ME/CFS patient population or subgroups thereof[15-17]. Several abnormalities are confirmed by differential gene expression[18-21].

**Onset**

Contrary to gradual onset ME/CFS, sudden-onset ME/CFS is often preceded by a (viral) infection/“flu-like” illness[22,23]. The onset is

![Figure 1 ME and CFS case definitions.](image_url)

**Table 1** Characteristic symptoms present in many patients with ME/CFS.

<table>
<thead>
<tr>
<th>Symptom</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post-exertional malaise</td>
<td>[9,11]</td>
</tr>
<tr>
<td>Muscle weakness/fatigability</td>
<td>[13,14]</td>
</tr>
<tr>
<td>Widespread muscle and/or joint pain</td>
<td>[15,16]</td>
</tr>
<tr>
<td>Orthostatic intolerance</td>
<td>[17,18]</td>
</tr>
<tr>
<td>Depression</td>
<td>[19,20]</td>
</tr>
<tr>
<td>Headaches</td>
<td>[21,22]</td>
</tr>
<tr>
<td>Hyperalgesia and hypersensitivity to light, sound etc.</td>
<td>[21,23]</td>
</tr>
<tr>
<td>Neurocognitive impairment</td>
<td>[19,24]</td>
</tr>
<tr>
<td>Sleep disturbances</td>
<td>[19,25]</td>
</tr>
<tr>
<td>Stress intolerance</td>
<td>[20,26]</td>
</tr>
<tr>
<td>Abdominal pain and discomfort</td>
<td>[20,27]</td>
</tr>
<tr>
<td>Post-exertional malaise</td>
<td>[30,31]</td>
</tr>
</tbody>
</table>

*1 A clear distinction should be made between the perception of “fatigue”, a feeling, and (muscle) fatigueability: a (prolonged) decline of muscle power after repeated muscle contractions, which can be assessed objectively using dynamometers.

**Table 2** Abnormalities in ME/CFS patients or major patient subgroups.

<table>
<thead>
<tr>
<th>Abnormality</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immunological aberrations - inflammation, - (TH2-dominated) immune activation, - immunosuppression and - immune dysfunction; which seem consistent with an infectious state;</td>
<td>[42-45]</td>
</tr>
<tr>
<td>Infections (reactivating and/or persistent)</td>
<td>[45-48]</td>
</tr>
<tr>
<td>Intestinal dysbiosis, inflammation and hyperpermeability; possibly associated with systemic inflammation;</td>
<td>[49-52]</td>
</tr>
<tr>
<td>Enhanced oxidative and nitrosative stress;</td>
<td>[53-55]</td>
</tr>
<tr>
<td>Mitochondrial dysfunction and damage to mitochondria;</td>
<td>[56-59]</td>
</tr>
<tr>
<td>Hypovolaemia and/or low cardiac output and reduced blood and oxygen supply to muscles and brain; notably in an upright position and during exercise;</td>
<td>[60-64]</td>
</tr>
<tr>
<td>Reduced (maximum) oxygen uptake and anaerobic threshold;</td>
<td>[65-68]</td>
</tr>
<tr>
<td>Neurological abnormalities (including neuro-inflammation);</td>
<td>[69-72]</td>
</tr>
<tr>
<td>HPA axis dysfunction, including hypocortisolism and blunted HPA axis responses to response to adrenocorticotropic hormone (ACTH);</td>
<td>[73-76]</td>
</tr>
<tr>
<td>Channelopathy (ion channel dysfunction);</td>
<td>[77-79]</td>
</tr>
<tr>
<td>(Long-lasting) abnormal responses to exertion.</td>
<td>[80-82]</td>
</tr>
</tbody>
</table>
reflected by distinctive immunological aberrations[96,97] and other abnormalities[98,99]. Several pathogens have been reported to initiate ME/CFS, e.g. Epstein-Barr virus[100], parvovirus B19[101], and enterovirus[102]. For example, 10-15% of individuals do not recover from infectious mononucleosis and fulfill the criteria for CFS[103] after six months[104,105]. The severity of the acute infection seems to predict the clinical outcome, rather than demographic, psychological, or microbiological factors[102,106].

Infections

Although contradicted by some studies, applying various methods various studies have found (multiple) infections or related antigens in patient subgroups (Table 3).

### Table 3 Pathogens/pathogen-related antigens observed in ME/CFS patient subgroups

<table>
<thead>
<tr>
<th>Pathogen/pathogen-associated antigens</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Viruses</strong></td>
<td></td>
</tr>
<tr>
<td>Epstein-Barr Virus (EBV, HHV4)</td>
<td>[104-106]</td>
</tr>
<tr>
<td>Cytomegalovirus (CMV, HHV5)</td>
<td>[47,107,108]</td>
</tr>
<tr>
<td>Human Herpesvirus 6 (HHV6A and B)</td>
<td>[109,110]</td>
</tr>
<tr>
<td>Human Herpesvirus 7 (HHV7)</td>
<td>[106,111,132]</td>
</tr>
<tr>
<td>Enteroviruses</td>
<td>[113-115]</td>
</tr>
<tr>
<td>Parvovirus B19</td>
<td>[116-118]</td>
</tr>
<tr>
<td>Bornavirus</td>
<td>[119-122]</td>
</tr>
<tr>
<td><strong>Bacteria</strong></td>
<td></td>
</tr>
<tr>
<td>Coxiella burnetii</td>
<td>[122-124]</td>
</tr>
<tr>
<td>Chlamydia pneumonia</td>
<td>[46,47,108]</td>
</tr>
<tr>
<td>Borrelia burgdorferi</td>
<td>[47,108-110]</td>
</tr>
<tr>
<td>Enterobacteria</td>
<td>[50,53]</td>
</tr>
<tr>
<td><strong>Other</strong></td>
<td></td>
</tr>
<tr>
<td>Mycoplasma</td>
<td>[127-129]</td>
</tr>
</tbody>
</table>

**Intestinal dysbiosis and hyperpermeability**

Some studies have observed intestinal dysbiosis[107,108], intestinal inflammation and immune activation[109,110] and intestinal hyperpermeability, conceivably resulting in translocation of enterobacteria to the blood stream, thereby inducing systemic inflammation[111]. Inflammation and immune activation observed in ME/CFS have been associated with these gastro-intestinal abnormalities[112,113]. Bacteriotherapy (transcolonoscopic infusion of non-pathogenic enteric bacteria) showed long-term positive effects[114] and antibiotic depletion / increased antioxidant activity, e.g. vitamin A[115], B[116], C[117], D[118], glutathione[119], super oxide dismutase[120] and zinc[121] have been observed repetitively.

**Mitochondrial dysfunction and damage**

Some studies have found structural mitochondrial damage, e.g. branching and fusion of mitochondrial cristae/mitochondrial degeneration[122], substantially higher rates of deletion of common 4977 bp of mitochondrial DNA[123] and unusual patterns of mitochondrial DNA deletions in skeletal muscle[124], while other studies implicate mitochondrial dysfunction[125,126]. Future research should provide clarity on hypometabolism[127] and low oxygen uptake[128] and extraction[129] in ME/CFS is due to mitochondrial dysfunction and/or mitochondrial damage, circulatory deficits (see next paragraph) or other causes.

**Low blood volume, cardiac output and/or blood and oxygen supply**

Several studies have established markedly reduced blood volume[130,131] and impaired cardiac function, indicated by decreased cardiac index/output and stroke volume[132,133,134], when compared to healthy sedentary controls. Post-exertional malaise, flu-like symptoms and cognitive deficits seem to differentiate those with severe CFS from those with less severe CFS and to predict lower cardiac output[135]. In addition, some studies indicate low cardiac mass[136,137]. So, low cardiac output in ME/CFS could be due to reduced cardiac mass (a ‘small heart’) [138] and/or hypovolemia[139]. Low cardiac output and/or blood/oxygen supply to muscles[140] and brain[141] and/or mitochondrial abnormalities could explain the low exercise capacity/oxygen uptake[142] and elevated (ventricular) lactate levels[143].

**Orthostatic abnormalities**

Orthostatic intolerance, (delayed) orthostatic hypotension and/or tachycardia (POTS), in patient subgroups has been implicated by various studies[144,145]. Orthostatic stress seems to induce cognitive deficits[146,147] and reduced angle-related mental task-activated cerebral blood flow velocity[148]. According to some authors[149,150], POTS marks a distinct group of patients with distinct phenotypical features. Some studies have also observed abnormalities in (parasympathetic and sympathetic) heart rate variability at rest and on standing[151].

**Neurological abnormalities**

Over time various researchers have observed various neurological aberrations in ME/CFS patient subgroups[152,153], e.g. diminished grey[154,155] and white matter[156,157], reduced blood flow and hyperfusion[158,159], glucose hypometabolism in specific regions of the cerebrum and the brain stem[160], an increased number of defects on SPECT cans, predominantly in the frontal and temporal lobes[161], intracranial abnormalities on MRI and SPECT scans[162], neuro-inflammation in various brain areas[163], cerebrospinal fluid anomalies suggesting inflammation and immune activation[164,165], and elevated ventricular lactate levels[166].

**HPA axis dysfunction**

HPA axis hypofunction in ME/CFS[167,168] can potentially manifest itself in (a) low basal levels and diurnal production levels (total production, variation during the day) of stress hormones, especially cortisol (hypocortisolism)[169,170], (b) hyporesponsiveness of the HPA axis: blunted responses of the pituitary and the adrenal glands to provocation, e.g. reduced cortisol response to ACTH[171], (c) diminished HPA axis responses to stress and exercise[172,173] and (d) enhanced sensitivity of the HPA axis to negative feedback to
cortisol[183,184] and increased sensitivity of the cellular immune system to the immunosuppressive effects of cortisol[140,144].

Abnormal responses to exercise
Several studies have established (long-lasting) deviant responses to physical exertion in ME/CFS, when compared to sedentary controls, e.g. substantially lower values for oxygen uptake and workload at peak exercise and at the ventilatory or anaerobic threshold at a second exercise test 24 hours later[278,284]; a long-term increase of gene expression of metabolite-detecting receptors after sustained moderate exercise[291]; decreased prefrontal oxygenation during exercise and recovery[292]; (prolonged) severe oxidative stress[293] and (long-lasting) suppression of protective heat shock proteins[294] in response to exercise, especially when a history of high level physical activity and infection is present[295], cognitive deficits induced by exercise[296], and substantially higher increments of NO metabolites in relation to workload during exercise[297]. Post-exertional malaise in ME/CFS seems to be related to exercise-induced inflammation and immune activation[298,299].

PLAUSIBLE CAUSAL RELATIONSHIPS BETWEEN ABNORMALITIES

Figure 2, the 4I hypothesis: a key role for four types of immunological abnormalities
Four immunological abnormalities underpin the 4I hypothesis for ME/CFS (Figure 2): inflammation (I1), Th2-predominant immune activation (I2), immunosuppression (I3) and immune dysfunction (I4).

Potential immunological stimuli in ME/CFS
The immune system seems to face three potential stimuli in ME/CFS: pathogens and associated antigens, due to acute, chronic and/or reactivated infections (Figure 2, A, B1 and B2), gastro-intestinal inflammation and hyperpermeability of the intestines, possibly resulting into translocation of enterobacteria to the blood stream (Figure 2, D), and auto-epitopes, due to oxidative and nitrosative damage to proteins, lipids etc. (Figure 3, K).

A vicious cycle of oxidative and nitrosative stress induced by inflammation
Oxidative and nitrosative stress play an important intermediate role in the 4I hypothesis. Inflammation will generate oxidative and nitrosative stress[298,299] (Figure 3, E), while oxidative and nitrosative stress can induce or amplify inflammation[298,299] (Figure 3, F). NO and reactive oxygen species (ROS) exert multiple immune-modulating effects[292,293,294]. ROS and reactive nitrogen species (RNS), including NO, can suppress NK[216,217,218] and T[214,215] cell cytotoxicity, which could contribute to immunosuppression (Figure 3, G). High levels of NO, produced by cytotoxic activated macrophages[294] may also play an important role in the shift from a Th1 to Th2 response[217,218] (Figure 3, H). While NO seems to suppress both Th1- and Th2-cell-mediated immunity at the early proliferation stage, high levels of NO appear to inhibit the Th1-cell differentiation of mature T helper (Th) cells[219].

Through several feedback loops oxidative and nitrosative stress can induce a self-perpetuating cycle of elevated oxidative and nitrosative stress, inflammation, elevated N-methyl-D-aspartate (NMDA) receptor activity, and ATP depletion, which is mediated by O2-, NO and ONOO-[220] (Figure 3, I).
Mitochondrial dysfunction induced by oxidative and nitrosative stress
In addition to causing damage to lipids, proteins and DNA, inducing neo-epitopes, oxidative and nitrosative stress can have various other negative effects (Figure 5).

ROS and RNS, including ONOO-, exert multiple effects on mitochondria, including mitochondrial dysfunction, damage, and apoptosis[224–227] (Figure 5, N). NO and RNS inhibit the respiratory chain, leading to elevated O2 production, and, after reaction with NO, to increased ONOO- levels, further impeding mitochondrial respiration[228] (Figure 5, O).

Cardiovascular abnormalities due to oxidative and nitrosative stress
NO plays an important role in the cardiovascular system and increased levels of NO can have various adverse cardiovascular effects[229] (Figure 5, P). NO is a potent vasodilator[230,231] and seems essential in autoregulation of blood flow, both in large arteries and at the microcirculatory level, thereby determining the distribution of flow among the various vascular networks[222]. Therefore elevated basal NO levels in ME/CFS could explain decreased peripheral resistance and low blood pressure (hypotension)[102]. Although possibly mediated by other pathways, these phenomena are induced in healthy subjects by exercise[228]. Exercise-induced NO, added to elevated basal levels, might partially account for post-exertional hypotension and delayed recovery in ME/CFS[224]. Furthermore, elevated NO levels could also be involved in reduced myocardial contractility, disrupted autonomic modulation of myocardial function and abnormalities in heart rate variability[229,244,245]. The cardiovascular aberrations and/or mitochondrial dysfunction/damage could plausibly explain reduced oxygen uptake[129] and oxygenation[231] during exercise in ME/CFS (Figure 5, Q).

Neurological aberrations as potential consequences of inflammation, oxidative and nitrosative stress, cardiovascular abnormalities and reduced oxygen uptake
Various neurological abnormalities could be induced by the abnormalities in ME/CFS. First, systemic inflammation can induce neuroinflammation and “sickness behavior”[224] (Figure 5, R). Pro-inflammatory cytokines, induced by peripheral inflammation, can access the central nervous system through various pathways, and induce cytokines, amplify cytokine signals and release secondary messengers, e.g. NO, in the brain thereby influencing virtually every aspect of brain function[247]. Peripheral inflammation affects neuroendocrine function, NMDA receptor activity, neurotransmitter metabolism, and neurogenesis[246,247]. The behavioral effects of peripheral inflammation include depression, “fatigue”, psychomotor slowing, cognitive dysfunction and sleep disruption[247]. In addition to systemic inflammation-induced “sickness behaviour”, other mechanisms by which immunological aberrations affect the nervous system in ME/CFS have been suggested, e.g. an elevated release of cytokines by glial cells[248]; auto-immune pathways, involving vasoactive neuropeptides damaging the blood-brain barrier and blood-spinal barrier[249]; and infections of the nervous system by neurotropic viruses[250]. A recent study established evidence for brain glial activation in patients with chronic pain, a phenomenon repetitively observed in animal models[251]. Activation of microglia or astrocytes, related to neuro-inflammation, in widespread brain area[174] could account for the chronic pain experienced by many patients with ME/CFS.

Second, increased levels of NO-stimulated glutamate release and...
hypersensitivity of NMDA receptors[25,26] could account for “central sensitisation”, manifesting itself in enhanced sensitivity of the central nervous system to various stimuli, e.g. sound, and hyperalgesia (Figure 5, S). Others have proposed an NO-independent O2-mediated pathway to induce hyperalgesia[27,28]. Third, cardiovascular abnormalities, resulting into reduced cerebral blood flow[29] (Figure 5, T1) and cerebral oxygenation[30] (Figure 5, T2), induced or intensified by exertion[31], would account for reduced ATP synthesis in the central nervous system, as implicated by increased ventricular lactate levels[32].

The physiological effects of exercise and stress can explain post-exertional “malaise”

Exercise and psychological stress could amplify pre-existing immunological abnormalities, oxidative and nitrosative stress, and intestinal hyperpermeability (Figure 6). Since these anomalies can plausibly explain various typical symptoms of ME and CFS (next paragraph), the physiological effects of exercise and psychological stress would intensify abnormalities already present in rest. This could explain a (prolonged) aggravation of symptoms after a minor exertion: post-exertional “malaise”.

Exercise has well-known beneficial effects[33,34]. Sustained exercise induces an increase in the pro-inflammatory cytokines TNFα, IL-1β, and IL-8 and the inflammatory cytokine IL-6, produced locally in the skeletal muscle in response to exercise[35,36]. This release is counterbalanced by the release of IL1β and TNFα inhibitors and IL-10[37,38]. In chronic inflammatory diseases, exercise could have adverse effects through a combination of exercise-induced stimulation of immune signals with leukocytes previously affected by other stress, inflammatory, or immune mediators[39]. Deviant effects of exercise on inflammation and immune activation in ME/CFS (Figure 6, X1) are illustrated by the observations that the severity of symptom flare after moderate exercise is directly linked to increased levels of IL-1β, IL-12, IL-6, IL-8, IL-10, and IL-13 8 hours post-exercise[27,31], that travelling from home to the hospital is sufficient for significantly elevated TGF-β levels[27,32], that exercise induces a sustained increase in plasma TNF-α in patients, not in controls[27,32], and that moderate exercise induces a larger 48 hours post-exercise area under the curve for IL-10[33]. In addition, since acute[34] and chronic[35,36] stress can induce inflammation[34,35], psychological stress could amplify pre-existing (low-grade) inflammation in ME/CFS.

Exercise can also have immunosuppressive effects. While moderate exercise seems to stimulate immunity, prolonged strenuous exercise seem to suppress immune function, e.g. NK cell activity and antibody synthesis[37,38,39]. Since the aerobic threshold seems (profoundly) decreased in ME/CFS, “low-level” anaerobic exercise can amplify immunosuppression, e.g. diminished NK cell cytotoxicity and antibody levels, observed in ME/CFS (Figure 6, X2).

In addition, eccentric exercise could induce and/or intensify immune dysfunction in ME/CFS (Figure 6, X3), e.g. inducing or amplifying a Th2-predominance[36,37]. Acute, subacute or chronic stress can suppress cellular (Th1) immunity and boost humoral (Th2) immunity, due to a differential effect of glucocorticoids and catecholamines on Th1/Th2 cells and type 1/type 2 cytokine synthesis[38,39]. In general, physiological and psychological stress may cause a selective suppression of Th1 functions and a shift towards a Th2 response, protecting the host from systemic ‘over-shooting’ with pro-inflammatory cytokines[40].

Another mechanism by which exercise can amplify pre-existing abnormalities is intestinal hyperpermeability[27,28] (Figure 6, X4). Psychological and physiological stress can compromise the intestinal barrier function[38,39]. Intestinal hyperpermeability could result in translocation of enterobacteria to the blood stream, instigating inflammation in response to endotoxins.

An additional pathway by which exercise can amplify pre-existing aberrations is oxidative[27,28] and nitrosative[27,28] stress as a result of exercise (Figure 6, X5). ME/CFS seems to be associated with a prolonged accentuated oxidative stress and reduced heat shock proteins responses to incremental exercise[33]. Several observations suggest an abnormal adaptive response to exercise in ME/CFS[33], the severity of which seems to be related with premorbid physical activity and severe acute infections[33]. Elevated glutamate release and subsequent NMDA receptor activation and induction of nuclear factor kappa-B (NF-κB), psychological distress enhances levels of NO and pro-oxidants in various brain areas[27,28].

Twisk FNM. 4I hypothesis for Myalgic Encephalomyelitis

CONCEIVABLE ETIOLOGY OF CHARACTERISTIC SYMPTOMS

The abnormalities observed in ME/CFS patients or substantial subgroups could explain the presence and variability of various characteristic symptoms (Figure 7 and Table 4). As explained in the previous paragraph the physiological effects of exercise in general and in ME/CFS in particular could account for the post-exertional “malaise”: exercise-induced intensification of symptoms[38].

DISCUSSION

The subjective and ambiguous criteria for CFS define a heterogeneous population of patients with chronic fatigue[2]. While “chronic fatigue” is obligatory for the diagnosis CFS[2], easy muscle fatigueability and cognitive impairment, but above all, post-exertional “malaise” are mandatory for the diagnosis ME, whether defined by the original criteria[30] or the recently proposed new[30] criteria. ME and CFS are two distinct, partially overlapping clinical entities[38].
Based upon observations, it is estimated that 30-60% of people fulfilling the criteria for CFS do not meet the more strict criteria for ME. The majority of the research in the last decades have used the CFS criteria for patient selection, it is unknown how many patients fulfilling the ME criteria don’t meet the case definition for CFS. Despite the confusion created by the use of the CFS criteria, various studies have observed typical abnormalities in the ME/CFS patient group or significant ME/CFS patient subgroups.

Table 4A: A plausible explanation for characteristic symptoms of ME/CFS by abnormalities.

<table>
<thead>
<tr>
<th>Symptom *</th>
<th>Abnormalities</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a “Fatigue” (loss of energy, weakness)</td>
<td>Decreased oxygen uptake, resulting into ATP depletion</td>
<td>[280,281]</td>
</tr>
<tr>
<td>1b</td>
<td>Elevated oxidative and nitrosative stress, resulting into contractile dysfunction</td>
<td>[275,276]</td>
</tr>
<tr>
<td>2a Muscle fatigability and post-exertional muscle weakness and pain</td>
<td>Decreased oxygen uptake, resulting into ATP depletion and increased lactate synthesis, prolongedly aggravated as a consequence of muscle exertion</td>
<td>[282,283]</td>
</tr>
<tr>
<td>2b Intestinal dysbiosis and inflammation</td>
<td>Inflammation, inducing “sickness behavior”, including inflammatory pain, and has an negative impact on nociception</td>
<td>[284,285]</td>
</tr>
<tr>
<td>2c, 3c Widespread muscle and joint pain</td>
<td>Neurological abnormalities / central sensitisation, due to elevated levels of NF-kB, NO, ROS, ONOO-, and NMDA receptor activity</td>
<td>[286-288]</td>
</tr>
<tr>
<td>4 Orthostatic intolerance</td>
<td>Cardiovascular abnormalities / circulatory deficits and autonomic dysfunction, due to increased levels of NO</td>
<td>[245,290]</td>
</tr>
<tr>
<td>5 Depression</td>
<td>Neurological abnormalities / “sickness behaviour”</td>
<td>[291,292]</td>
</tr>
<tr>
<td>6 Headaches</td>
<td>Neurological abnormalities, as part of “sickness behaviour” and/or result of low blood and/or oxygen supply, possibly resulting into increased lactate levels</td>
<td>[293-295]</td>
</tr>
<tr>
<td>7 Hypersensitivity to light, sound and odours</td>
<td>Neurological abnormalities / Central sensitisation due to neuro-inflammation, induced by peripheral inflammation, and/or increased levels of NO</td>
<td>[286,296,297]</td>
</tr>
<tr>
<td>8 Cognitive deficits (brain fog)</td>
<td>Neurological abnormalities / reduced blood flow to and/or oxygenation of the brain</td>
<td>[70,298]</td>
</tr>
<tr>
<td>9 Flu-like feeling</td>
<td>Neurological abnormalities / “sickness behaviour”</td>
<td>[291,299]</td>
</tr>
<tr>
<td>10 Sleep disturbances</td>
<td>Neurological abnormalities / “sickness behaviour”</td>
<td>[300,301]</td>
</tr>
<tr>
<td>11 Stress intolerance</td>
<td>HPA axis abnormalities, including defective stress responses</td>
<td>[27,181]</td>
</tr>
<tr>
<td>12 Abdominal pain / irritable bowel</td>
<td>Intestinal dysbiosis and inflammation</td>
<td>[302,303]</td>
</tr>
<tr>
<td>13 Post-exertional “malaise”; an exercise-/stress-induced increase of symptoms</td>
<td>An increase in abnormalities mentioned above</td>
<td>[279]</td>
</tr>
</tbody>
</table>

* The numbers refer to the cause-and-effect relationships between abnormalities and symptoms in fig. 7.
Twisk FN. 4I hypothesis for Myalgic Encephalomyelitis

Figure 7 The abnormalities observed in ME/CFS could account for characteristic symptoms.
enhanced glucocorticoid sensitivity of the Th1 arm of the immune system. Finally, inflammation/immune activation, cardiovascular impairment and low oxygenation/oxygen uptake could account for various neurocognitive and neuropsychological abnormalities found in ME/CFS.

Other authors have proposed alternative explanatory models for ME/CFS. The ONOO-model, with a key role for the self-perpetuating vicious circle of elevated oxidative and nitrosative stress, resulting into peroxynitrite (ONOO-), proposed by Pall et al.[305] is incorporated within the 4I explanatory model. The 4I explanatory model is also in line with the NO-induced central sensitisation-model of Meeus et al.[306] The 4I model has commonalities with the neuro-immunological (NI) model for ME/CFS, put forward by Morris and Maes[307]. However, there also some relevant differences. In essence, the NI model is a linear model in which a non-peristent infection induces a vicious circle of oxidative and nitrosative stress and inflammation, neo-epitopes (induced by oxidative and nitrosative damage to proteins) and autoimmunity. The 4I hypothesis embodies key roles for reactivating and chronic infections, immune dysfunction and Th2-dominated immune activation (next to inflammation), HPA axis dysfunction, e.g. hypocortisolism and blunted adrenal responses, enhanced sensitivity of the HPA axis and the (cellular) immune system to the suppressive effects of cortisol, and circulatory deficits[308]. In contrast with the hypothesis that maladaptive stress responses, either due to a stress crash[309] or “allostatic overload”[310], are causing the immunological abnormalities seen in ME/CFS, the 4I hypothesis is based upon the premise that the immunological aberrations and oxidative/nitrosative stress can induce and sustain the endocrine abnormalities and defective stress responses through various pathways. The 4I hypotheses is consistent with the “alternate homeostatic state”-hypothesis of Craddock et al.[309], although, the 4I incorporates an opposing cause-and-effect-relationship between the immunological and endocrine abnormalities in ME/CFS.

LIMITATIONS

While the abnormalities incorporated in the 4I model have been observed in ME/CFS patients or major patient subgroups repetitively, the cause-and-effect relationships between these abnormalities have often been established in general, non-ME/CFS-specific circumstances. However, the causal relations underpinning the 4I hypothesis, although speculative, collectively offer a plausible explanation for various abnormalities frequently observed in ME/CFS and characteristic symptoms.

Due to the heterogeneity of the CFS[302] patient group, the duration of the illness of the patients investigated, and the essential role of exertion-induced abnormalities, none of the abnormalities will be present in all CFS patients at all times and it is unlikely that here will ever be one abnormality present in all CFS[302] patients. In order to establish which abnormalities and causal relationships are applicable to specific patients, it is also essential to make a distinction between patients with post-exertional “malaise”, cognitive deficits and other characteristic symptoms of ME[311], and CFS[302] patients without these typical symptoms and to investigate well-defined biological and symptomatic ME and CFS patient subgroups in more detail.

The 4I hypothesis can be tested by investigating the abnormalities in biological and clinical subgroups defined by biomarkers and objective measures of the clinical status[312], by applying correlational analyses on the abnormalities present in patient subgroups, and by testing interventions aimed at reversing specific aberrations in patients, e.g. infections, immunological aberrations and oxidative/nitrosative stress.

CONCLUSIONS

Immunologic abnormalities frequently observed in ME/CFS, inflammation (I1), Th2-biased immune activation (I2), immunosuppression (I3) and immune dysfunction (I4) seem to play a crucial role in the etiology and pathophysiology of ME/CFS. These immunological aberrations, combined with three potential immunological stimuli, can explain various other abnormalities observed in ME/CFS and underpin the 4I explanatory model for ME/CFS, which accounts for several characteristic symptoms.

Future research should confirm various abnormalities and explore the alterations in more detail in specific clinical and biological subgroups. Correlational analysis of co-existing abnormalities in patient subgroups and the outcomes of interventions aimed at specific abnormalities could be used to accept, refine or reject the cause-and-effect relationships incorporated in the 4I explanatory model for ME/CFS.

CONFLICT OF INTERESTS

The Author has no conflicts of interest to declare.

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21348064. doi: 10.1017/CBO9780511545313.048.


