Latent viral immune inflammatory response model for chronic multisymptom illness

CDR Sean R. Maloney\textsuperscript{a,}\textsuperscript{b}, Susan Jensen\textsuperscript{b}, Virginia Gil-Rivas\textsuperscript{c}, Paula Goolkasian\textsuperscript{c,}\textsuperscript{*}

\textsuperscript{a}Deployment Processing Command-EAST, PCS Box 20086, Building 309, Camp Lejeune, NC 28542, United States
\textsuperscript{b}W.G. (Bill) Hefner VA Medical Center, 1601 Brenner Avenue, Salisbury, NC 28144, United States
\textsuperscript{c}University of North Carolina, Charlotte 9201, University City Blvd., Charlotte, NC 28223, United States

A latent viral immune inflammatory response (LVIIR) model is presented which integrates factors that contribute to chronic multisymptom illness (CMI) in both the veteran and civilian populations. The LVIIR model for CMI results from an integration of clinical experience with a review of the literature in four distinct areas: (1) studies of idiopathic multisymptom illness in the veteran population including two decades of research on Gulf War I veterans with CMI, (2) new evidence supporting the existence of chronic inflammatory responses to latent viral antigens and the effect these responses may have on the nervous system, (3) recent discoveries concerning the role of vitamin D in maintaining normal innate and adaptive immunity including suppression of latent viruses and regulation of the immune inflammatory response, and (4) the detrimental effects of extreme chronic repetitive stress (ECRS) on the immune and nervous systems.

The LVIIR model describes the pathophysiology of a pathway to CMI and presents a new direction for the clinical assessment of CMI that includes the use of neurological signs from a physical exam, objective laboratory data, and a new proposed latent viral antigen–antibody imaging technique for the peripheral and central nervous system. The LVIIR model predicts that CMI can be treated by a focus on reversal of immune system impairment, suppression of latent viruses and their antigens, and healing of nervous system tissue damaged by chronic inflammation associated with latent viral antigens and by ECRS.

In addition, the LVIIR model suggests that maintaining optimal serum 25 OH vitamin D levels will maximize immune system suppression of latent viruses and their antigens and will minimize immune system inflammation. This model also emphasizes the importance of decreasing ECRS to improve immune system function and to minimize nervous system injury from excess serum glucocorticoid levels. The proposed model supports growing evidence that increasing omega 3 essential fatty acid levels in nervous system tissues may decrease inflammation in the nervous system and improve neural plasticity and recovery from neuronal injury.

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tissues of the body, it may become an idiopathic multisystem illness. This paper proposes that a CMI may be influenced by the interaction of several simultaneous factors such as; non viral antigenic stimulation of the immune system, neural toxins, medications that suppress the immune system, CNS post concussive changes, nutritional deficiencies, and pre-morbid mental health conditions.

The latent viral immune inflammatory response (LVIIR) model was developed as the result of combining clinical experience with a review of the literature in four distinct areas. (1) A brief review of idiopathic multisymptom illness in the veteran population since the US Civil War including two recent decades of research on veterans involved in conflicts in Western Asia including Kuwait, Iraq and Afghanistan. (2) New evidence supporting chronic inflammatory responses in the nervous system to latent viral antigens including those of the herpetic family of viruses and the effect that these responses may have on the nervous system. (3) Recent discoveries concerning the role of vitamin D in maintaining normal innate immunity, normal adaptive immunity, and the suppression of latent viruses. (4) The detrimental effects of extreme chronic repetitive stress (ECRS) on the immune system and the nervous system. In addition, the LVIIR model's explanation of CMI is based on the extensive clinical experience of the first two authors in treating service members deploying to and returning from the war zones in Afghanistan and Iraq, in veterans at a Department of Veterans Affairs, VA Medical Center, and in civilian populations including children.

CMI & other idiopathic multisystem illnesses

Idiopathic and disabling war related illnesses with similar symptoms and signs have been documented since the US Civil War [3]. They are often described as clinical syndromes for which the underlying causes of the signs and symptoms are not well understood. There are multiple factors associated with CMI and other idiopathic war related illnesses including ECRS, trauma, and some factors unique to specific conflicts [4]. Examples of unique factors might include infection and malnutrition during the US Civil War, exposure to chlorine and mustard gases during World War I, malnutrition and exposure to harsh weather during World War II and the Korean War, exposure to “agent orange” during the Vietnam War, and exposure to concussions from improvised explosive devices, numerous potential toxins, vaccines, and medications during recent wars in Kuwait, Iraq and Afghanistan.

Even with variations in experiences and exposures during different conflicts, chronically disabled veterans have presented with CMI and other idiopathic multisystem illnesses that have similar but perplexing characteristics. Symptoms are present in these illnesses that do not have an apparent medical explanation and laboratory tests, which measure severity and identify the causes of CMI and other multisystem idiopathic illnesses are notably absent. At times, there is progressive disability and, occasionally, signs and symptoms resolve spontaneously. Idiopathic syndromes have been identified in varied locations in the world at different times for at least the past one and one-half centuries. Most of the veterans afflicted with CMI or other idiopathic war related illnesses (i.e., chronic pain syndromes) have sustained some known form of ECRS from exposure to traumatic and stressful experiences. CMI and other idiopathic multisystem illnesses, however, have also appeared in non-deployed service members and in civilian populations [1–6].

The LVIIR model presents one plausible pathway to idiopathic multisymptom illnesses or clinical syndromes that have occurred in different locations and following different conflicts for the past one and one-half centuries. The LVIIR model may also prove to be consistent with many recent epidemiological, neuropsychological (including PTSD [7]), toxicological, and immunological studies of idiopathic war related illnesses [6–9].

Role of latent herpetic viruses in the nervous system

Latent herpetic viruses have been infecting people for thousands of years [10]. The inflammatory nature of latent herpes zoster and herpes simplex I & II viruses in tissues of the nervous system and in other tissues of the body has been well documented [11–15]. The LVIIR model proposes that inflammation caused by the interaction of the immune system and latent herpetic viral antigens may be associated with hyper-excitability of sensory ganglia (i.e., herpes zoster neuritis) and of other neurons of the nervous system (i.e., herpes simplex I vestibular neuritis, etc.) with or without clinically significant replication of either entire latent viruses or their DNA/RNA and with or without recurrent latent viral infection or nerve cell death. Latent herpetic viruses (and possibly latent viral antigens alone) have the ability to travel between sensory ganglia and innervated tissues of the body [16] and may also migrate from neurons of peripheral sensory ganglia to other neurons of the central nervous system.

This hypothesis that latent viral antigens may be present and trigger an immune inflammatory response is supported by a recent study involving varicella zoster virus, glycoprotein E-Specific, CD4+ T cells. Circulating gE-specific CD4 + T cells were detected at a relatively high frequency in healthy donors with normal immune systems. This finding would be compatible with frequent exposure to replicative cycle antigens in these healthy donors [17]. Varicella zoster virus (VZV) specific T cell responses may be vital in the prevention of latent viral reactivation.

In a mouse model, cytotoxic (killer) CD8 T cells have been shown to block HSV I reactivation from latency in sensory neurons (trigeminal ganglia). HSV I infected trigeminal ganglia cells, infiltrated with CD8+ T cells, were able to produce HSV I immediate and early proteins, but did not produce HSV I late proteins or infectious virions. CD8+ T cells prevented reactivation of HSV I without destroying the infected neurons [18].

Elevated IgG levels to cytomegalovirus have also been implicated in rapid cognitive decline in older individuals (age 60–100) over a 4 year period [19]. Persistent latent viral DNA/RNA, in the presence or absence of infectious virus replication, can result in the loss of normal cell homeostasis and in an inflammatory response associated with antigenic viral proteins. The antigenic inflammatory response could result in demyelination or oligodenrogli cell death [20].

Considerable time may be required to reverse synaptic or possibly neural network long-term potentiation and depression changes even after the latent viral immune inflammatory response has resolved. Reversal of changes may also be incomplete in severe cases of a latent viral immune inflammatory response due to irreversible neuronal changes, injury, or even cell death. The role of inflammatory responses in pain was also highlighted in a recent review [21] of sensory neuron function. Specifically, the researchers concluded that “recent evidence suggests that up regulated expression of inflammatory cytokines in association with tissue damage or infection triggers the observed hyper-excitability of pain sensory nerves”. Furthermore, chemokine and chemokine receptor expression in sensory ganglia may contribute significantly to virus-associated neuropathic pain syndromes [21]. Application of prolonged or intense noxious stimulation to sensory ganglia is thought to rearrange synaptic strength as in long term potentiation [22]. Chronic pain associated with hyperalgesia to pin prick and/or allodynia to touch may be a result of or related to detrimental synaptic plasticity at the sensory, spinal cord, or higher level. Chronic excessive indirect (through the cortex) somatosensory or autonomic afferent nerve input to the limbic system may result in...
detrimental long term potentiation or long term depression of synapses especially in the hypothalamus, hippocampus, and amygdala. The resulting detrimental neural plasticity changes in the CNS may play a significant role in symptoms (i.e., pain, fatigue, increased startle reflex, sleep problems, rage, PTSD, anxiety, depression, decreased concentration, and decreased short term memory) experienced by veterans with CMI’s or other idiopathic war multisystem illnesses [23–26].

Further support for a latent viral immune inflammatory response model for CMI comes from our recent retrospective study conducted at a veteran’s hospital [27]. The study reviewed the successful use of long term (6 to 18+ months) antiviral therapy (acyclovir and valacyclovir) in the treatment of US veterans with chronic, often disabling, pain syndromes attributed to atypical herpetic viral reactivation. These pain syndromes were associated with the presence of hyperalgesia to pinprick, subtle or atypical rashes, pain, and burning or itching sensation. The veterans had elevated/positive antibody titers to at-least one herpetic virus including varicella zoster and herpes simplex I & II. One or more of these latent viruses were suspected of causing the veteran’s pain syndromes. Reported improvement in signs and symptoms ranged from 78% to 97% with moderate dose, long term, antiviral therapy (6–18 months)[27].

In another study [28], twelve patients with central nervous system dysfunction including long-standing fatigue were treated with Valganciclovir for 6 months. The patients had symptoms for 1–8 years and had high IgG antibody titers to Human Herpes-6 virus and Epstein Barr Virus. Nine of the 12 patients experienced near resolution of their symptoms and were able to return to full-time work or normal activity levels. IgG antibody titers, in those patients who responded, dropped significantly with treatment.

Also, a case study [29] of three children/adolescents with disabling chronic pain syndromes (greater than 1 year duration) reported such significant improvement in symptoms when treated with long term antiviral therapy (acyclovir or valacyclovir) that they were able to return to school. All three children had elevated IgG antibody titers to varicella zoster and one had elevated IgG antibody titers to HSV I. Two had chronic prominent but atypical

![Fig. 1. Low vitamin D and vitamin 25(OH)D stores in immune system function.](https://dx.doi.org/10.1016/j.mehy.2012.11.024)
cytes are activated by these cells and proliferate, both B and T presenting processed antigens to them and stimulate resting B lymphocytes and T lymphocytes by pre-
system are able to process antigens and then are able to activate
Vitamin D and immune system function
The immune system’s response to latent viruses and their viral antigens may be adversely affected by vitamin D insufficiency and deficiency. Fig. 1 provides a detailed exploration of the different forms of vitamin D in the serum and other tissues of the body in order to explain the relationship between the immune system and vitamin D. Vitamin D₃, cholecalciferol, is formed in the basal layer of the skin under the influence of ultra violet B sunlight. Cholecalciferol is stored in adipose tissue of the body. Vitamin D₃ and its metabolites are also present in the blood serum and are attached to vitamin D binding protein (DBP). As vitamin D₃ passes through the liver, it is converted to 25 OH D₃ and stored in the liver.
Vitamin D₃ is poorly soluble in an aqueous environment and highly soluble in a lipid environment. When vitamin D₃ in the diet and production of vitamin D₃ from skin exposure to ultra violet B sunlight are low, body fat may sequester vitamin D₃ from the serum due to vitamin D₃’s high lipid solubility. Thus a higher percent of body fat may contribute to lower serum vitamin D₃ levels when intake and production of vitamin D₃ are low. Vitamin D₃ is transported in vascular and interstitial tissues attached to vitamin D binding protein (DBP) [30]. Plasma concentration of DBP is approximately 20 times greater than the total concentration of vitamin D₃ and its metabolites.
Low serum 25 OH vitamin D₃ levels can lead to secondary hyperparathyroidism [31]. Parathyroid hormone is known to stimulate the kidney’s conversion of serum 25 OH vitamin D₃ to serum 1,25(OH)₂ vitamin D₃, the active form of vitamin D₃ [31]. This may explain why serum 1,25(OH)₂ vitamin D₃ levels can be variable (including paradoxically normal to elevated) in patients with chronic vitamin D deficiency and are an unreliable measure of vitamin D status.
The presence of 1 alpha hydroxylase in many vitamin D target cells of the body (in addition to proximal renal tubular cells) is consistent with autocrine, intracrine, and paracrine functions for 1,25(OH)₂D₃ in the regulation of cell proliferation and differentiation. Both vitamin D activating (25-hydroxylase and 1 alpha-hydroxylase) enzymes and vitamin D metabolizing (24-hydroxylase) enzyme are present in some cells of the immune system including macrophages and mature dendritic cells. Strict regulation of these enzymes within immune system cells is consistent with an autocrine and paracrine role of vitamin D₃ in the immune system [32].
Macrophages and mature dendritic cells of the innate immune system are able to process antigens and then are able to activate and stimulate resting B lymphocytes and T lymphocytes by presenting processed antigens to them [33]. When B and T lymphocytes are activated by these cells and proliferate, both B and T lymphocytes express a 1,25(OH)₂D₃ vitamin D receptor (VDR). When extracellular 25(OH)D₃ levels are normal, macrophages and mature dendritic cells are able to convert adequate 25(OH)D₃ to 1,25(OH)₂D₃ (active vitamin D₃) within their cells. After exportation of the newly processed 1,25(OH)₂D₃ out of these cells, the increased extracellular 1,25(OH)₂D₃ levels provide negative feedback to activated B and T lymphocytes to limit the proliferation of B lymphocytes, IgG, T lymphocytes and associated inflammatory cytokines of the adaptive immune system [33]. The production of active vitamin D, 1,25(OH)₂D₃, at the site of inflammation permits higher concentrations of active vitamin D than might be achieved through normal diffusion from the serum. This partial uncoupling of interstitial serum 1,25(OH)₂D₃ from serum 1,25(OH)₂D₃ may explain why serum 25(OH)D₃ (rather than serum 1,25(OH)₂D₃) may be the controlling factor for limiting inflammation due to negative feedback by extracellular paracrine 1,25(OH)₂D₃.
When normal serum and interstitial 25 OH vitamin D₃ levels are present, antigenic stimulation of the macrophage/macocyte toll-like receptor 2/1 (TLR2/1) up-regulates these cell’s expression of vitamin D receptor (VDR) and 25 OH vitamin D-1a-hydroxylase (1-OHase). Intracellular 25 OH vitamin D₃ 1a-hydroxylase converts intracellular 25 OH D₃ to 1,25(OH)₂ D₃ which then stimulates the intracellular production of a cathelicidin in monocytes/macrophages. Human cathelicidin is a peptide that induces the destruction of infectious agents and improves innate immunity [34,35]. Cathelicidin has been shown to have direct antiviral activity against adenovirus and herpes simplex virus in vitro [36].
When serum, interstitial, and monocyte/macrophage intracellular 25 OH vitamin D₃ levels are lower (vitamin D insufficiency/deficiency states), the intracellular production of cathelicidin is decreased and the effectiveness of monocyte/macrophage suppression of infectious agents is compromised. Impaired monocyte/macrophage function combined with an increased but ineffectual, antigen stimulated, B lymphocyte and T lymphocyte response may result in impaired suppression of latent viral antigens/viruses and an increased and chronic latent viral immune inflammatory response.
Dendritic cells of the innate immune system are important for immune system surveillance and dendritic cells also have a vitamin D (VDR) receptor [37]. Cell culture experiments support the hypothesis that vitamin D has significant anti-viral effects especially against enveloped (including herpetic) viruses [38]. Low vitamin D status and the presence of Epstein Barr virus appear to have a detrimental synergistic effect on the immune system facilitating the activation of auto-reactive T cells and increasing the inflammatory reaction to Epstein Barr virus [39].
In August of 2008, an article [40] reviewed a growing body of literature describing the low vitamin D₃ stores in patients with chronic pain and the need for vitamin D₃ supplementation in these patients. A retrospective study [41] of veteran’s charts at the Salisbury, NC. VA Medical Center examined the rate of vitamin D insufficiency in a sample of 400 veterans, including those who had chronic disabling pain syndromes. A majority (70.5%) had serum 25 OH vitamin D₃ levels below Lab Corp of America’s lower limits of normal (<32 ng/ml), and 34% were vitamin D deficient (<20 ng/ml). Within the African American subset of veterans in this study, 93% were below the lower limits of normal and 68% were vitamin D deficient. The increased pigmentation in the skin of African Americans may have resulted in greater blocking of ultra violet B sunlight and reduced production of vitamin D₃. In this study, veterans with low serum vitamin D₃ levels were almost twice as likely to develop a chronic pain syndrome compared to veterans with normal vitamin D levels.
A second large study of veterans in six Dept. of Veterans Affairs, medical centers in the Southeastern United States demonstrated wide spread vitamin D deficiency that resulted in high medical costs [42]. This study also reported an especially high risk of vitamin D deficiency in African American veterans. Both studies [41,42] are consistent in reporting high rates of low serum 25 OH
vitamin D levels in the veteran population, thus, chronically low vitamin D levels may be one factor that could contribute to impairment of the immune system and to the development of a latent viral immune inflammatory response.

Stress, immune system function, and PTSD

The effect of severe acute and ECRS on vitamin D metabolism, consumption and storage is not known. Severe acute stress and ECRS with increased glucocorticoid production, however, may impair vitamin D metabolism as has been demonstrated with the use of exogenous corticosteroids including prednisone [43]. ECRS may have particular relevance in the case of idiopathic CMI’s and other idiopathic multisystem illnesses due to its independent negative effects on immune system functioning and on the central nervous system [44,45].

Overtime, ECRS is known to cause hyperplasia of the adrenal gland, increased glucocorticoid secretion, and atrophy of the thymus gland, which is one source of T lymphocytes [44]. Fig. 2 demonstrates how ECRS may relate to immune system function. Sympathetic fibers of the autonomic nervous system innervate bone marrow, thymus, spleen, and lymph nodes. All lymphocytes have adrenergic receptors. Stimulation of the hypothalamic–pituitary–adrenal axis or of the sympathetic–adrenal–medullary axis by ECRS results in the secretion of adrenal hormones including epinephrine, norepinephrine, and cortisol [46,47]. Exposure to ECRS, in contrast to acute stress, has been shown to have negative effects on almost all functional measures of the innate and adaptive immune systems [46]. Impairment of the cellular immune response has been shown to often result in higher antibody levels against latent viruses [46–48].

Delayed-type hypersensitivity reactions have been examined in human participants to evaluate cellular immunity. T lymphocytes recognize an antigen introduced into the skin, then proliferate, secrete cytokines, and start an acute cellular immune system inflammatory reaction to clear the antigen from the skin. Chronic stress has been shown to impair or decrease delayed-type hypersensitivity reactions [49].

It is difficult to directly explain PTSD with its behavioral and psychological manifestations by employing a LVIIR model based on physical signs, laboratory tests, and proposed imaging techniques. However, physical factors, which appear to increase the risk of PTSD may be consistent with the multi-factor LVIIR model. Factors from epidemiological studies [7] that appear to increase the risk of PTSD in veterans and others include: sex (female), age (younger age greater than older age), race and ethnicity (African American and Hispanic individuals).

Specifically, in states of insufficient vitamin D production or intake, a higher percent body fat in females may lead to a greater amount of vitamin D dissolved in lipid tissue thus lowering serum and interstitial 25(OH)D levels available for immune system function and regulation. African American and Hispanic individuals often have greater protection from ultra violate B sunlight due to increased pigmentation in the skin. As a result of this natural sun block, they produce vitamin D slowly and generally have low serum vitamin D levels when overall sun exposure to skin is inadequate for sufficient vitamin D production. Finally, there may be two or more possible explanations for the higher risk of PTSD in younger versus older individuals, which are consistent with the LVIIR model. One possible explanation is that there is greater capacity for neural plasticity in the brains of younger individuals making them more susceptible to detrimental synaptic long-term potentiation or depression effects of ECRS or a LVIIR. A second possible explanation is that younger individuals may experience greater glucocorticoid production detrimental to the central nervous and immune system function as part of a response to ECRS or to stress associated with a LVIIR.

The LVIIR model

The proposed LVIIR model hypothesizes that latent viral antigens may trigger a latent viral immune inflammatory response in the setting of an impaired immune system often associated with low vitamin D stores and psychological/physical stressors. This new model is presented in Fig. 3 and is described by the following statements.

(a) A host cell containing latent viral DNA/RNA is able to produce antigen glycoproteins and other antigen molecules with or without clinically significant RNA/DNA or complete virus replication [18].

(b) A LVIIR can be triggered by latent viral antigens and an impaired immune system. Two significant factors that may adversely affect immune system function include: vitamin D insufficiency or deficiency and extreme chronic repetitive stress.

(c) Extreme chronic repetitive stress can overstimulate the hypothalamic–pituitary–adrenal (HPA) axis [44,50,51] resulting in atrophy of the thymus gland and reduction in the production and population of T lymphocytes [44].

(d) A LVIIR may include increased production of B lymphocyte IgG immunoglobulin and other immune system inflammatory molecules (i.e., certain cytokines) with or without significant latent viral replication, and with or without clinically significant total white blood cell count elevation or other clinical signs of infection.

Fig. 2. Extreme chronic repetitive stress (ECRS) and immune system function.
(e) A LVIIR can be amplified by or made worse by a second inflammatory antigen, allergen, or other inflammatory chemical [52].

(f) Latent viral antigens and their accompanying inflammatory response are proposed to spread in many ways to tissues of the body including: from the host cell to nearby cells, through the blood circulation, and through axonal transport from the peripheral nervous system to the CNS and from the peripheral nervous system to other tissues of the body innervated by these latent viral host cells [16].

(g) The antigens of any latent or combination of latent viruses at the same time can stimulate a LVIIR. Due to the prevalence of latent herpetic viruses in the human population and particularly in the nervous system, herpetic viruses are proposed to be the most common viruses (but not necessarily the only latent viruses [52] capable of causing a LVIIR.

(h) The tissue locations of latent viral antigens causing the inflammatory response determine the initial clinical symptoms and signs.

Varicella zoster and herpes simplex I & II are scattered in latent form in nervous system tissue. The scattered nature of these herpetic latent viruses in the nervous system may explain the variations in symptoms and signs experienced by individuals with CMI. These herpetic latent viruses also provide a ready source of antigens in the setting of immune system impairment. Likewise, latent Epstein Barr virus contained in B Lymphocytes [16] may spread viral antigen and an immune system mediated inflammatory response to the central nervous tissue and other tissues of the body.

CMI and other idiopathic multisystem illnesses are progressive and disabling. Extreme chronic repetitive stress and vitamin D insufficiency/deficiency are proposed to be two common predisposing and perpetuating factors for a CMI or other idiopathic multisystem illness due to a LVIIR. They may not, however, be the only predisposing factors for impaired immune system function and the development of these conditions in otherwise healthy individuals.

Severe chronic pain associated with a LVIIR herpetic sensory neuritis/ganglionitis may produce a secondary, ongoing, source of ECRS resulting in chronic stimulation of the hypothalamic–pituitary–adrenal axis and increased glucocorticoid production. Chronic increased production of glucocorticoids may have adverse effects on limbic system function (particularly the amygdala, and hippocampus) and the frontal lobe of the brain independent of any direct LVIIR effect [45].

The presence of hyper-excitability of nerve cells due to a LVIIR as well as neuroplasticity changes in the nervous system due to long-term synaptic potentiation and depression could physiologically explain exaggerated responses to painful or other stimuli in nervous system cells. Hyper-excitability in sensory nerves or the spread of an antigen driven immune inflammatory response to nearby motor nerves could explain exaggerated peripheral motor responses or other exaggerated nervous system efferent responses in the parasympathetic and sympathetic autonomic nervous system. A very severe immune inflammatory response could result in nervous system tissue injury and cell death.

Clinical assessment

Objective methods for the clinical assessment of idiopathic CMI's and other idiopathic multisystem illnesses are important. To determine a diagnosis of LVIIR, it may be helpful during the initial medical history and physical exam to record symptoms and to test for signs of possible neuronal hyper excitation due...
to inflammation in the peripheral nervous system (including cranial, spinal, and peripheral nerves). Examples of pertinent symptoms and signs in sensory nerves include: neuropathic pain, itching and burning sensations associated with hyperalgesia to pin prick and allodynia to touch in the skin. Examples in a cranial nerve might include ringing in the ears and episodes of dizziness associated with decreased balance on heel to toe walking with the eyes closed in the absence of peripheral neuropathy and cerebellar dysfunction; and examples involving the autonomic nervous system might include increased or decreased peristalsis of the bowel (diarrhea or constipation associated with irritable bowel syndrome), exaggerated hyperhidrosis (sweating) in the palms and soles, and tachycardia or bradycardia of the heart with exaggerated sympathetic or parasympathetic stimulation. The presence of physical symptoms and signs consistent with neuronal inflammation and secondary hyper excitability in scattered parts of the nervous system provides one possible physiological explanation for CMI and other idopathic stress related multisystem illnesses based on the LVIIR model.

When possible, symptom improvement should be assessed objectively and if monitored, patients can easily recognize resolution of chronic tinnitus and improvement in fatigue level, endurance. Similarly, improvement in psychological and cognitive issues such as irritability, anxiety, PTSD symptoms, decreased concentration, and decreased short term memory are often noted by spouses and other family members first and can be measured through psychological and cognitive testing. Chronic pain symptoms are often the last to resolve and are the most difficult to quantify. Pointing out resolution of easily monitored signs often encourages compliance with treatment regimens that must continue for 6–18 months for significant improvement and to up to 36 months to reach maximum medical benefit.

The LVIIR model and some previous research findings [28–29,46–48] predict that monitoring fluctuations in specific latent viral IgG antibody concentrations in the blood serum may help to identify the primary latent virus(s) stimulating the immune inflammatory response and may be useful in monitoring responses to specific treatments. Monitoring of other non-specific pro-inflammatory cytokine molecules (especially IL-1, IL-6, and TNF alpha [46] participating in an immune inflammatory response) before, during, and after treatment may also help in identifying the presence and severity of a LVIIR and in documenting successful treatment of this response [53].

Monitoring specific viral antigen or antigen–antibody complex levels in the blood serum (if present) or in immune system cells may also provide a way to identify and quantify the latent viruses that are contributing to an inflammatory response. It may also provide specific information concerning the effectiveness of the immune system in suppressing a latent virus and its antigens, and the effectiveness of a specific treatment. Exposing blood serum, blood cells, or other tissue samples to specific viral antibodies tagged with a fluorescent dye [54] or with a radionuclide may permit the identification and quantification of specific latent viral antigens present in the blood serum, blood cells or other tissue samples.

Although imaging techniques for the diagnosis of LVIIR is unavailable, the potential to develop such a technique already exists. To verify the presence and location of a LVIIR, an imaging test that connects a specific viral antigen to a latent viral immune inflammatory response in a specific location of the nervous system (or other tissue in the body) is needed. Engineered antibody type molecules, including bivalent antibody fragments tagged with radioactive nuclides, have been used previously to locate antigens on tumor cells [55].

Radionuclide tagged, specific latent viral antibody type, molecules could be engineered that would migrate to target nervous system or other body tissues/cells which are experiencing a LVIIR. Once there, the molecules with antibody characteristics (but of smaller size that typical IgG antibodies) could bind to specific latent viral antigens, which are triggering the immune inflammatory response. Increased concentrations of the radionuclide tagged antibody-antigen complexes in affected tissues could be imaged [55]. The identified structures/locations from viral antigen–antibody complex imaging must correlate with the patient’s signs and symptoms. The technique must also verify that the inflammatory process has resolved when the patient’s signs and symptoms resolve and the patient recovers.

In recent years, functional imaging techniques including positron emission tomography and functional MRI have enabled researchers to explore brain neuroplasticity and to examine remodeling of neural systems and their components changed by disease or injury. Functional neuroimaging may also complement behavioral assessments by allowing the observations of novel networks controlling perceptions, cognition, and short-term memory [56,57].

Correlation of the locations of viral antigen–antibody inflammatory responses in the nervous system (through radionuclide imaging) with functional MRI or other new imaging techniques of the central nervous system may help to explain many of the behavioral changes seen in CMI and other idiopathic multi-system illnesses and may assist in monitoring central nervous system recovery from these disorders.

The LVIIR model suggests that resolution of these illnesses can be objectively monitored by the gradual decrease in the following: clinical symptoms and signs of these illnesses, participating latent viral antigen production, latent virus antibody–antigen complexes in affected tissues, latent viral IgG antibody titers in the serum that are specific to any participating latent viruses, and the quantity of immune system molecules including cytokines participating in the inflammatory response.

**Predictions from the LVIIR model**

Based on the LVIIR model, treatment of CMI and other idopathic multisystem illnesses requires reversing the latent viral immune inflammatory response. This might be accomplished by restoring the innate and adaptive immune systems’ ability to suppress latent viruses and their antigens and by eliminating detrimental immune system hyperactivity, if present. Achieving these two goals will require the early recognition and reduction of treatable predisposing or perpetuating factors for immune system impairment. Possible treatable predisposing or perpetuating factors for a LVIIR include vitamin D insufficiency/deficiency, chronic extreme repetitive stress, and other nutritional factors, medications, infections, toxins, or diseases that might adversely affect the immune system.

The LVIIR model predicts that maintaining optimal serum 25(OH)D3 levels for immune system health may be one of the most important methods to treat and prevent a CMI and other idiopathic multisystem illnesses. Treatment of chronic low vitamin D states can be challenging especially in individuals with a high percent body fat or poor vitamin D absorption. Treatment can also be challenging in individuals without adequate sun exposure and in those individuals who are intolerant to ultra violet B sunlight.

The body’s production of vitamin D3 varies during the year based on sun exposure. Factors influencing exposure include distance of the sun from the earth and duration of daylight (time of year), atmospheric conditions (cloud cover, pollution in the air, etc.), percentage of skin exposed, duration of sun exposure, and use of sun blocking agents. Dietary intake of vitamin D fortified foods and vitamin D supplements can also affect serum 25(OH)D3 levels.

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Serum concentration levels of 25(OH)D$_3$ are quite small and are commonly measured in the United States in nanograms (10$^{-9}$ g) per ml. In our clinical experience [41] stopping over the counter vitamin D, multi-vitamin, and fish oil supplements, and avoiding increased sun exposure (sun bathing) for 2–3 days before testing for serum 25(OH)D$_3$ levels produces consistent levels that represent body stores of vitamin D. Avoiding vitamin fortified foods for 12–24 h before the blood test is also helpful. The threshold and optimal levels of serum 25(OH)D$_3$ levels for immune system health is not known and will have to be determined by further studies. In our clinical experience, CMI’s and other idiopathic multisystem illnesses do not improve significantly or resolve in affected individuals until serum 25(OH)D$_3$ levels are maintained at threshold level of approximately 50–60 ng/ml for at least 6–18 months. Effectiveness of and compliance with a treatment regimen (combination of increased sun exposure, when possible, and vitamin D supplementation) to raise serum 25(OH)D$_3$ levels can only be determined by monitoring serum 25(OH)D$_3$ levels.

Long term oral vitamin D supplementation in most CMI patients with normal bowel absorption and body weight can be limited to 3000–4000 IU per day of D$_3$, cholecalciferol, to avoid vitamin D toxicity [58]. The LVIIR model also suggests that treatment with oral 25(OH)D$_3$ or a combination of D$_3$ and 25(OH)D$_3$ may be more effective than treatment with vitamin D$_3$ alone in quickly improving innate and adaptive immune system function including the suppression of latent viruses and the reduction of immune system inflammation without causing hypercalcemia. The use of oral 25(OH)D$_3$ would bypass factors which might interfere with the conversion of D$_3$ to 25(OH)D$_3$ by the liver.

Treatment of the psychological manifestations of CMI’s and other idiopathic multisystem illnesses (anxiety, depression, PTSD, sleep disturbances, decreased short term memory and decreased concentration, etc.) with medical and psychological treatments is also very important. According to the LVIIR model, the path to recovery from a well established CMI or other chronic idiopathic multisystem illness takes a considerable amount of time (6–18 months for significant improvement and up to 36 months to reach maximum medical improvement). The body must recover optimal immune system function, suppress latent viruses and clear their antigens from tissues of the body including the nervous system, and finally undo any detrimental neural plasticity changes including synaptic long-term potentiation and depression.

Omega 3 fatty acids have been proposed as a safe anti-inflammatory treatment of neuropathic pain [59], to improve psychiatric health, and to increase resilience of the brain including modulation of the inflammatory cascade following traumatic brain injury [60–62]. Based on some pilot data from the first two authors, the threshold for successful treatment of nervous or other tissue inflammation in veterans and active duty personnel with idiopathic CMI’s or other idiopathic multisystem illnesses is 1800 mg of omega 3 essential fatty acid per day in 2–3 divided doses with food.

Medications that interfere with vitamin D metabolism [43] (corticosteroids and prednisone) and neuroleptic medications, which have been shown to increase hepatic metabolism of vitamin D [63] (including phenytoin and phenobarbital), should be used sparingly and avoided if possible. There may be other medications such as newer neuroleptic medications that also interfere with vitamin D metabolism.

The use of antiviral medication may be helpful when the latent viruses causing a latent viral immune inflammatory response (LVIIR) can be identified [27–29]. Based on pilot data in adolescents and adult veterans with normal kidney function, the threshold doses for successful treatment of CMI or other idiopathic multisystem illnesses associated with herpes zoster and simplex 1 & II was approximately 400 mg PO 5 times a day for acyclovir and approximately 1500 mg per day in divided doses for valacyclovir. Treatment lasted 6–18 months or longer, and antiviral treatment was used prior to the realization of chronic low vitamin D stores in these patient populations.

In spite of generally good responses to antiviral therapy, relapses in the symptoms of CMI and other idiopathic multisystem illnesses were not uncommon when antiviral therapy was stopped [27,29]. Nine years after initial evaluation, the pediatric case with relapsing symptoms (when antiviral therapy was discontinued) was diagnosed with chronic vitamin D deficiency with a serum 25 OH vitamin D$_3$ level of 12.9 ng/ml (normal range 32–100 ng/ml – Lab. Corp. of America, 2008). The relapses of symptoms that occurred in this pediatric case and in many of our veterans may have resulted from a continued immune system impairment from low vitamin D stores. Other limitations of antiviral treatment included GI side effect of nausea with acyclovir treatment and difficulty with compliance to multiple dosing when taking long-term acyclovir (400 mg PO 5 times per day).

Summary and conclusions

A LVIIR model is proposed explain multi-factor CMI’s, other idiopathic multisystem illnesses, and some associated mental health disorders. War environments expose soldiers and often civilians to adverse weather, toxic substances, insects, infectious diseases, extreme chronic repetitive stresses, and injury. The use of uniforms that cover the body from head to toe, have been a main method of protection for soldiers from adverse environmental exposures throughout the last two centuries. During the current conflicts in Iraq and Afghanistan, protective clothing, frequent or prolonged deployments, working long hours in doors or in vehicles, and night operations keep the skin out of contact with ultra violate B light. The avoidance of sun exposure to skin in the civilian population has also become prevalent in recent years. The lack of sun exposure poses a significant risk for vitamin D depletion and immune system dysfunction in both the civilian and military populations.

Those exposed to war frequently experience severe anxiety over possible injury. They may also experience ECRS associated with actual injury or illness, the witnessing of severe violence and injury, and isolation from family. ECRS associated with war environments and particularly with combat exposure can lead to over stimulation of the hypothalamic–pituitary–adrenal axis [44,50,51] and to impairment of the immune system and the CNS. Central nervous system impairment, associated with ECRS and a LVIIR, may mimic or confound symptoms of a post concussive syndrome or mild traumatic brain injury. The natural course of a concussion or mild brain injury is improvement over a relatively short period of time. The natural course over time of a CMI or other idiopathic multisystem illnesses is often no improvement or worsening until major perpetuating factors of immune system dysfunction are resolved and detrimental neuroplastic changes in the nervous system are reversed. Finally, a latent viral immune inflammatory response may be compounded by other factors particular to specific conflicts.

The proposed LVIIR model will require verification through further testing and evaluation. New diagnostic studies based on antibody–antigen complex laboratory testing and imaging technologies will have to be developed and tested. The optimal serum 25 OH vitamin D$_3$ level for immune system health will have to be determined and the optimal treatments for LVIIRs will have to be verified.

The most immediate and perhaps most important change to our evaluation and treatment of veterans and other civilians with, disabling, chronic multi-symptom illness and other idiopathic multi-symptom illnesses may be the testing for and treatment of low
vitamin D states, treatment of nervous system inflammation if present, and the elimination of ECRS in order to restore normal immune system function and to minimize any ongoing damage to the nervous system from a LIVIR.

Conflict of interest

None of the authors or co-authors have any financial or personal relationships that could influence appropriately their work.

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