

Infection and vaccination in chronic fatigue syndrome: Myth or reality?

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Abstract

Chronic fatigue syndrome (CFS) is characterized by severe disabling fatigue lasting for more than 6 months associated with physical and mental disturbances such as headache, arthralgia, myalgia, memory impairment, sore throat and tender lymph nodes. The exact pathogenesis is still unknown. Several models were proposed to explain its etiology including chronic infection, endocrine dysfunction, autonomic imbalance, depression, decreased immunity states and an aberrant reaction to infection. No convincing evidence was found to support any of the suggested pathogenic mechanisms. The current concept is that CFS pathogenesis is a multi factorial condition in which an infective agent cause an aberrant immune response characterized by a shift to Th-2 dominant response. When the response fails to be switched-off, a chronic immune activation occurs and clinically expressed as the symptomatology of CFS.

Vaccinations are used in order to stimulate the immune system to induce a persistent immunity against the favorable antigens. Several syndromes that contain chronic fatigue as one of their symptoms, such as “Gulf war syndrome” and macrophagic myofasciitis were related to vaccinations.

Can vaccinations induce the aberrant immune response of CFS? Little is known about this issue. There are some reports on CFS occurring after vaccination, but few prospective and retrospective studies failed to find such an association.

A working group of the Canadian Laboratory Center for Disease Control (LCDC) that was founded in order to examine the suspected association between CFS and vaccinations concluded that there is no evidence that relates CFS to vaccination. Further studies are requested to examine this issue since it is very conceivable that if infection can lead to CFS, vaccination may also lead to it in the same immune-mediated pathogenesis.

Keywords: *Chronic fatigue syndrome, infection, vaccination, Th-2 immune response*

Introduction

Fatigue is a very common complaint accompanying many physical disorders (such as hypothyroidism, chronic heart failure and multiple sclerosis) and mental disorders (such as depression).

Chronic fatigue syndrome (CFS), as a distinct medical entity, was first described in the 1980s as a primary persistent or relapsing fatigue. In the past this disorder was known by a number of names depending on the speculated etiology including “post viral fatigue syndrome”, “myalgic encephalomyelitis” and “neuro-myasthnia”.

In 1988 the United State Center for Disease Control and Prevention (CDC) defined this disorder

as the CFS. Its prevalence was reported as 0.2–2.6%, nearly twice in women than in men. Similar prevalence was found in different geographic and ethnic groups [1].

The syndrome is characterized by severe and disabling fatigue associated with headache (90%), difficulty in concentration (90%), sore throat (85%), tender lymph nodes (80%), muscle and joint aches (75%), feverishness (75%), difficulty sleeping (70%), psychiatric problems (65%) and a rapid pulse (10%) [2].

On 1994, the CDC published diagnostic criteria for CFS containing severe fatigue syndrome lasting for at least 6 months accompanying by four or more physical symptoms (as detailed in Table I). The excluding

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Table I. Diagnostic criteria for CFS.

<i>Centers for disease control</i>
Clinically evaluated, medically unexplained fatigue of at least six months' duration that is
Of new onset
Not a result of ongoing exertion
Not substantially alleviated by rest
A substantial reduction in previous levels of activity
Four or more of the following symptoms
Subjective memory impairment
Tender lymph nodes
Muscle pain
Joint pain
Headache
Unrefreshing sleep
Postexertional malaise (>24 h)
<i>Exclusion criteria</i>
Active, unresolved, or suspected disease likely to cause fatigue
Psychotic, melancholic or bipolar depression
(but not uncomplicated major depression)
Psychotic disorders
Dementia
Anorexia or bulimia nervosa
Alcohol misuse or other substance misuse
Severe obesity

criteria include various physical and mental disorders which might cause chronic fatigue such as dementia, obesity and psychotic disorders [3].

Other commonly used criteria were published by the Oxford Group [4]. The main difference between the criteria is that in the Oxford criteria mental impairments are also required in addition to the physical symptoms.

Pathogenesis models

The exact pathogenesis of CFS is still unknown. During the last years several etiologies were examined:

Endocrine dysfunction

The presence of a significant fatigue in different endocrine disorders like hypothyroidism and Addison's disease led the investigators to look for endocrine pathogenesis for CFS.

Suppressed hypothalamic–pituitary–adrenal (HPA) axis

(1) Poteliakhoff et al. [5] had found low cortisol levels in CFS patients' blood. In several other studies reduced-cortisol level in the blood and urine of CFS patients was reported [6,7].

Challenge tests with corticotropin releasing hormone (CRH) led to a blunted adreno cortico tropin hormone (ACTH) response indicating a down regulation of the HPA axis probably due to an increased negative feedback that suppresses the HPA axis response [8].

Treatment with low-dose hydrocortisone reduced the fatigue levels in the short term in

some patients with CFS [9]. These data indicates that fatigue in patients with CFS is a result of low cortisol level due to suppression of the HPA axis.

(2) Dehydroepiandrosterone (DHEA) and dehydroepiandrosterone sulfate (DHEA-S) are glucocorticoids which are secreted from the zona reticularis of the adrenal's cortex. DHEA-S have physiological properties, such as neurosteroids, which are associated with such psychophysiological phenomena as memory, stress, anxiety, sleep and depression [10]. Measurement of DHEA and DHEA-S in Japanese CFS patients found low level of these hormones that may explain the fatigue and high prevalence of depression in CFS patients [11].

Suppressed growth hormone (GH) axis. Despite preliminary data that described low basal level of A trial of GH replacement on CFS patients did not show any improvement in their symptoms [12].

Immune system dysfunction

Many immunological deficiencies are associated with fatigue, like the prominent fatigue reported by AIDS patients.

The CFS expresses several immune dysfunctions both in the cellular and humoral components.

Despite the increased number of activated T cell lymphocytes including cytotoxic T cells, the immune cells function poorly. There is an increased neutrophil apoptosis, low level of NK cell and decreased response of lymphocytes to mytogenic stimuli in culture [13] and the immunoglobulin level is decreased (especially the IgG1 and IgG3) [14].

Cytokine imbalance. Alternation in the cytokines profile with a shift towards a Th-2 pro-inflammatory response was observed in CFS patients (low levels of TGF β , high levels of IL-4 and INF γ). The high level of the pro-inflammatory cytokines may explain some of the manifestations such as fatigue and flu-like symptoms seen at CFS patients [14].

Autonomic dysfunction

Different autonomic symptoms have been found in CFS patients such as hypotension, brady-tachycardia and hemodynamic instability in head-tilt test, representing an autonomic dysfunction [15]. Naschitz et al. [16] proposed a diagnostic test for CFS based on the degree of heart rate and blood pressure as an expression of the autonomic dysfunction, but the test has not been accepted in common practice. It is probable that the autonomic dysfunction is only a part of the clinical image since it can not explain symptoms such as myalgia and lymphadenopathy.

Mental disorder

Although some studies have not found objective cognitive impairment, CFS patients tend to present psychiatric problems such as depression and low self estimation and the Oxford criteria for the diagnosis of CFS requires the presence of mental disturbances in order to determine this diagnosis. Some physicians believe that CFS is basically, a psychiatric disorder (depressive or somatic disorder) and the other physical symptoms (endocrine, immunological) are secondary to it [17]. The use of cognitive behavioral therapy (CBT) in CFS patients is based on this theory and was found to be effective [18].

Infections as a cause of CFS

The first reports of CFS were described in patients following an infection, and were related to a chronic infection, but no convincing data of persistence of infection was confirmed [19]. It was not clear whether the infection was the cause of the syndrome or the infection was secondary to the decreased immunity in CFS patients [20].

The current concept is that CFS is an aberrant chronic post-infection immune response and was given the name of chronic fatigue and immune dysfunction syndrome (CFIDS).

This concept also explains the immunological finding in CFS patients. The following pathogens were suspected to cause CFS:

Viral infections

Herpes virus family. Epstein-barr virus (EBV) was one of the first suspected pathogens to induce CFS due to the significant fatigue accompanying EBV infection like in mono nucleosis.

Evidence for this theory came from studies on EBV infection in CFS patients such as high titers of antibodies to the EBV viral capsid antigen (EBV VCA IgM) in the sera of CFS patients compared to controls [21]. Another Herpes virus member that has been implicated in CFS is the cytomegalo virus (CMV). High titers of antibodies to CMV were found in CFS patients [21].

In a case control study high titers of anti human herpes virus 6 (HHV 6) antibodies (IgM and IgG) were detected in the sera of CFS patients and DNA copies of HHV 6 were detected by PCR [22].

In contrast, another study that was carried out in order to confirm those observations failed to show an elevation in antibodies titers to EBV, CMV or HHV 6 in CFS patients [23].

Enterovirus. Enteroviruses are known to causes respiratory and gastrointestinal disease accompanies by fatigue. Evidences for a persistent enterovirus

infection in CFS patients come from studies that found RNA copies of enterovirus in muscle biopsies from CFS patients (20% in CFS patients vs. 0% in the control group) [24], and persistent viremia detected by PCR in two serum samples taken at least 5 months apart [25]. In contrast, other studies failed to find an association between enteroviruses and CFS in serological, antigenic tests or PCR tests [26,27].

Parvovirus. Fatigue and arthralgia are common complaints during parvovirus B19 infection.

There are some case-reports describing post-parvovirus B19 infection patients who developed a chronic and prominent course of fatigue that fulfilled the criteria for CFS diagnosis [28]. Post-parvovirus CFS was treated successfully with IV immunoglobulin [29].

Bacterial infection

Mycoplasma. Several studies found a high prevalence of Mycoplasma infection in CFS patients compared to healthy control (50 vs.10%). This high prevalence of Mycoplasma infection from different species (*Mycoplasma fermentans*, *Mycoplasma hominis*, *Mycoplasma pneumoniae* or *Mycoplasma penetrans*) is similar in different studies done on different populations of CFS patients [30]. The diagnosis of Mycoplasma-induced CFS is very important because most patients with CFS who have Mycoplasma infection appear to recover after long antibiotic course with doxycycline [31].

Borrelia. Fatigue is a common complain in Lyme disease. Several case-reports studies examined the hypothesis suggesting a relationship between *Borrelia burgdorferi* and CFS. Most of the studies did not find an association between Lyme disease and CFS [32,33] except for one study on 68 patients with a history of diagnosis of borreliosis or tick-borne encephalitis that developed significant fatigue that met the CFS criteria in 50% of the patients [34].

Chlamydia. Fatigue is a common symptom reported by patients with upper respiratory tract infection with positive sputum culture for *Chlamydia pneumoniae* (*C. pneumoniae*) [35]. A study on 171 CFS patients found 10 patients with a high titer of anti *C. pneumoniae* antibodies. In those patients an antibiotic long course of azitromycin improved their symptoms and their serology [36]. High prevalence of co-infection with *C. pneumoniae* and Mycoplasma were found by PCR employing CFS patients' sera [37]. However, some studies failed to find a high prevalence of *C. pneumoniae* infection in CFS patients [38].

Can vaccinations induce CFS?

As discussed above, the exact pathogen of CFS is unknown, but the leading theory is that an aberrant immunological response to infection causes a chronic activation biased toward a Th-2 dominant reaction. This theory raises the suspicion that vaccinations that are given in order to trigger an immunological defense reaction, may cause in distinct cases an aberrant reaction that will be expressed as CFS by the mechanism discussed above. The main adverse reactions to vaccinations are usually local at the site of injection (erythema and pruritus) but systemic flue-like reaction (fever, myalgia, fatigue and lymph nodes tenderness) and allergy may occur [39]. Those adverse reactions are usually mild and self-limited. Several reports associate distinct vaccinations with the induction of autoimmune disease [40,41]. Rheumatoid arthritis, reactive arthritis, vasculitis, encephalitis, thrombocytopenia and multiple sclerosis relapse have been documented after hepatitis B virus (HBV) vaccination. Acute arthritis or arthralgia, chronic arthritis and thrombocytopenia appeared after mumps and rubella vaccine (MMR). Guillain–Barre syndrome (GBS) and vasculitis after influenza, and GBS that appeared after polio-immunization.

Several syndromes that are related to vaccinations contain chronic fatigue as a part of the syndrome. The Gulf war syndrome was described in 4–8% of the soldiers who participated in the Gulf war and few months–years later suffered from illness that included impaired cognition (distractibility, memory problems), fatigue, arthromyoneuropathy (joints and muscle pains) and post-traumatic stress disorder [42]. The syndrome was related to chronic Th-2 biased immune response. Rook and Zumla [43] raised the hypothesis that the multiple vaccinations given to the troops during their deployment induced a systemic Th-1 to Th-2 switched immune response and cause to the symptoms above. Four features of the vaccination protocol used in this war led them to this theory:

- (1) The vaccination against anthrax that was given to the soldiers used Pertussis derivate as an adjuvant agent, which is known to induce a Th-2 dominant response.
- (2) The soldiers were exposed to large burden of vaccinations which tend to shift the immune response to a Th-2 dominant response.
- (3) The vaccinations were given after the deployment of the troops, while being in stressful condition. Under this condition the cortisol level is reduced, the DHEA level is increased and the immune response is shifted to Th-2 dominant profile.
- (4) The troops were exposed to carbamate and organophosphate insecticides which inhibits IL-2—a pivot cytokine of Th-1 response.

Support for this theory came from a cross sectional study of 923 UK Gulf war veterans who still had their vaccinations records [44]. The study found an association between multiple vaccinations given during the conflict and later evolution of Gulf war syndrome.

Another syndrome that was related to vaccinations is macrophagic myofasciitis. This syndrome is a post-vaccination disorder characterized by stereotypic lesion on the deltoid muscle (site of injection) associated with prominent fatigue that fulfills the CFS criteria. Electron microscopy and experimental studies show that the lesion is due to persistent immune reaction to aluminum hydroxyl used in different vaccination as an adjuvant agent including HAV, HBV and toxoid vaccinations. The aluminum hydroxyl is known to induce a shift of the immune response toward a Th-2 profile reaction and if it persists—a chronic inflammatory activation may occur. The persistent elevated levels of the Th-2 cytokines induce the systemic symptoms of chronic fatigue, muscle and joints pain [45].

An association between vaccination and CFS is much less documented. In 1992 several reports claimed that CFS was evolved after immunization to HBV was published in Canada. A working group of the Laboratory Center for Disease Control (LCDC) of the Canadian National Health and Welfare (NHW) was founded in order to examine the suspected association between anti-HBV vaccination and CFS. The working group gathered 30 cases of patients with CFS that appeared within 3 month after immunization against HBV—the great majority after the first dose of the vaccine [46]. The working group examined several studies dill with this question. A retrospective study on 134 CFS patients found that 2.2% of them received anti-HBV vaccine within the 3 month before the beginning of the disease. When they compared this figure to the occurrence of anti-HBV vaccination in the matched Canadian population (1.9%), no significant different was found. A prospective study followed after 700 students who were vaccinated with anti-HBV vaccine. About 12% of the students complained on tiredness that was self limited and none of them evolved to CFS. Those studies brought the members of the working group to a conclusion that there is no evidence that show an association between CFS and anti-HBV vaccine. Updated studies that checked the relationship between CFS and vaccination came to the same conclusion [47,48].

The use of vaccinations in CFS patients did not exacerbate their symptoms. A study that examined CFS patients vaccinated with anti-influenza vaccination found no significant difference between the CFS patients and the control healthy group. Although CFS patients reported on adverse affects four times more then the healthy vaccines, those adverse effects

were related to common post-influenza vaccination symptoms and to constitutional CFS symptoms [49].

We can summarize carefully that except for several case-reports, there is no study that found induction of CFS by vaccination, but only few studies concerning this issue have been published. Further studies examining this question should be carried out and the physician's index of suspicion should be raised because this possibility of vaccination-induced CFS is reasonable in view of the ability of vaccinations to cause Th-2 dominant response.

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