

# Infection, Vaccination, and Autoantibodies in Chronic Fatigue Syndrome, Cause or Coincidence?

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Chronic fatigue syndrome (CFS) is a heterogeneous syndrome of unknown etiology and physiopathology. CFS patients complain about disabling fatigue, depression, difficulty with memory, and concomitant skeletal and muscular pain. Interestingly enough, there is certain overlap between CFS symptoms, autoimmune rheumatic disease, and infectious diseases. Certain neuroendocrine-immune abnormalities have also been described, and autoantibodies commonly described in some autoimmune diseases have been found in CFS patients as well. An increasing number of autoantibodies, mainly directed against other nuclear cell components, have been illustrated. Likewise, an association between some infectious agents, antibody production, and later CFS onset has been reported. Similarly, vaccination is depicted as playing an important role in CFS onset. Recently, a case report pointed toward a causal association between silicone breast linkage, hepatitis B virus vaccination, and CFS onset in a previous healthy woman. Such findings suggest that there is a likely deregulation of the immune system influenced by specific agents (infections, vaccination, and products, such as silicone). Evidence suggests that CFS is a complex disease in which several risk factors might interact to cause its full expression. Thus, although different alterations have been found in CFS patients, undoubtedly the main feature is central nervous system involvement with immunological alterations. Therefore, a new term *neuro-psycho-immunology* must be quoted. New studies based on this concept are needed in order to investigate syndromes, such as CFS, in which immunological alterations are thought to be associated with concomitant psychological and health disturbances.

**Key words:** chronic fatigue syndrome; infectious agents; vaccination; autoantibodies; neuropsychological disturbances; immunological alterations; psychiatric disorders

## Introduction

Chronic fatigue syndrome (CFS) is a heterogeneous syndrome of unknown etiology. Patients with CFS complain about disabling fatigue, depression, difficulty with memory, and concomitant skeletal and muscular pain last-

ing for at least 6 months.<sup>1,2</sup> CFS affects more than 267 per 100,000 people.<sup>3</sup> The reported prevalence is 0.2–2.6%, with women being affected almost twice as often as men.<sup>4</sup> In association with CFS physiopathology, immune imbalance, abnormal cytokine profile or cytokine genes,<sup>5</sup> and decreased serum concentrations of complement components have been reported.<sup>6</sup> Other studies have shown an association between infection and later CFS onset.<sup>7–9</sup> With regard to infection, diverse viruses have been associated with the onset of CFS symptoms.<sup>8–12</sup>

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Likewise, vaccination has also been associated with ultimate onset of CFS in some patients.<sup>13,14</sup> Most recently, a case of CFS onset following the double effect of exposure to silicone and hepatitis B vaccine was reported. It was suggested that the breast implants and vaccination acted as specific adjuvants for the CFS onset in that patient.<sup>15</sup> Thus, the possibility of molecular mimicry in CFS between some molecular components of infectious microorganisms and the production of specific autoantibodies in susceptible subjects cannot be neglected.<sup>16</sup> Many studies have shown the presence of several autoantibodies in CFS patients. Antibodies to diverse cell nuclear components,<sup>17</sup> phospholipids,<sup>18</sup> neuronal components,<sup>19</sup> neurotransmitters,<sup>20-22</sup> as well as antibodies against some neurotransmitter receptors of the central nervous system (CNS) have been described.<sup>23</sup> However, it is still unclear if CFS represents a kind of autoimmune process rather than a mixture of several common features overlapping.<sup>24</sup> There is conflicting information about the role of autoantibodies, infections, and vaccine in the pathogenesis of CFS. In this study, we review infectious agents, vaccines, and autoantibodies reported as being related in CFS patients.

### Infectious Agents and CFS Etiology

Numerous researchers have tried to correlate infection by several microorganisms with CFS onset. Among them, the human parvovirus (HPV)-B19 has been the most reported associated virus. Although several studies have tried to show that CFS may follow acute parvovirus B19 infection,<sup>25-27</sup> the evidence supporting this hypothesis is not convincing; the main difficulty is associating the onset of CFS with presence of antibodies to HPV-B19.<sup>26</sup> Acute viremia is not associated with the onset of CFS symptoms either<sup>25</sup> and attributing a case of CFS to B19 infection is extremely difficult in the absence of serological confirmation of acute infection at fatigue onset.<sup>26</sup> One study suggested that, in subjects with a background

of preexisting psychological stress, the infection by HPV-B19 could have precipitated the onset of CFS.<sup>27</sup> Other studies have suggested that infection by another virus, the human herpes virus-6 (HHV-6), a neurotropic, gliotropic, and immunotropic virus, is more often found in patients with CFS than in healthy controls.<sup>28-30</sup> Some researchers suggest that a reactivation of the HHV-6 virus may be related to CFS onset.<sup>30</sup> However, HHV-6 virus is not found in all patients at the time of testing.<sup>28</sup> Another study attempted to show an association between infection by dengue virus and postinfection onset of CFS.<sup>31</sup> Although, some clinical features were associated with the onset of chronic fatigue, a significant association between chronic fatigue and dengue severity could not be found.<sup>31</sup> In a recent prospective study evaluating postinfective and chronic fatigue syndromes precipitated by viral and nonviral pathogens was performed.<sup>32</sup> The postinfective fatigue syndrome phenotype was stereotyped and occurred at a similar incidence after infection by Epstein-Barr virus (EBV),<sup>33</sup> Ross River virus (RRV),<sup>32</sup> and *Coxiella burnetii*, which causes Q fever.<sup>32,33</sup> CFS was predicted largely by the severity of the acute illness rather than by demographic, psychological, or microbiological factors in that study. Similar findings have been reported concerning infection by hepatitis B virus (HBV) and the onset of a similar condition to CFS, fibromyalgia (FM).<sup>34</sup> FM is characterized by diffuse musculoskeletal pain, fatigue, morning stiffness, and sleep disturbance. It was recently integrated into a spectrum of central sensitivity syndromes that include several diseases, such as CFS.<sup>35</sup> Thus, as has been suggested in CFS, chronic viral infections might trigger FM symptoms as well. One study suggested that chronic hepatitis B carriage appears to increase the risk of FM and many of the typically associated symptoms.<sup>34</sup> Likewise, in a recent case report, a woman developed CFS after HBV vaccination. She underwent silicone breast implantation 6 years before vaccination with no adverse events. However, between the second and third HBV vaccination, she suffered a breast

injury with local inflammation and later development of CFS.<sup>15</sup> At the same time of vaccination, the patient suffered from breast injury, which might represent the time of silicone leak. The exposure to the adjuvant, silicone, might have augmented her immune response to the vaccine and subsequent onset of CFS symptoms.<sup>15</sup> Concerning this, 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 not enough evidence that associates CFS and vaccination.<sup>4,36</sup> By contrast, other studies have documented chronic microbial infections in patients with CFS or myalgic encephalomyelitis (ME), including those caused by *Chlamydia pneumoniae*, hepatitis C, enteroviruses, and human retroviruses. Other studies have included virus reactivations in CFS/ME, such as varicella zoster virus, herpes simplex virus, and Epstein–Barr virus.<sup>37</sup> However, for many years another group of viruses has also been associated with CFS. Using a monoclonal antibody, enterovirus VP1 protein was detected in the circulation of 44 of 87 patients with CFS/ME.<sup>38</sup> In view of the tropism of enteroviruses for skeletal and cardiac muscle, research focused on enterovirus infection of skeletal muscle in CFS has been undertaken. Studies have demonstrated a higher frequency of enterovirus infection of skeletal muscle in patients with CFS/ME compared to that seen in normal controls;<sup>39,40</sup> enterovirus infection of skeletal muscle was therefore proposed as the likely disease mechanism. However, several negative studies<sup>41,42</sup> combined with the rise of the psychiatric “biopsychosocial model” of CFS/ME have led to a diminished interest in this area. Infectious agents involved in CFS onset are summarized in Table 1.

### Vaccination and CFS

Several studies have been conducted intended to examine either the risk for CFS on-

**TABLE 1.** Infectious Agents Associated with Chronic Fatigue Syndrome Onset

Microorganism	Possible mechanism of association	Ref.
HPV-B19	Postinfection	25–27
HHV-6	Reactivation	28–30
Dengue	Postinfection	31
EBV	Postinfection	33, 37
RRV	Postinfection	32
HBV	Postinfection	15, 34
HVC	Postinfection	37
Enterovirus	Postinfection	37
Retrovirus	Postinfection	37
VZV	Reactivation	36
HSV	Reactivation	37
<i>Coxiella burnetii</i> (Q fever)	Postinfection	32, 33

HPV-B19, human parvovirus B19; HHV-6, human herpes virus-6; EBV, Epstein–Barr virus; RRV, Ross River virus; HBV, hepatitis B virus; HCV, hepatitis C virus; VZV, varicella zoster virus; HSV, herpes simplex virus.

set associated with vaccination or the effect of using vaccines in patients diagnosed as having CFS.<sup>43</sup> One study performed by Moraq *et al.* tested the likely association between specific psychological variables, raised titers of antibodies against rubella, and later onset of CFS.<sup>44</sup> They concluded that specific psychological variables could be used to predict raised levels of postvaccination fatigue.<sup>44</sup> Regarding other vaccines, vaccination against Q fever, although safe, could provoke acute disabling disease and, in its late course, could be complicated by fatal (e.g., endocarditis) or debilitating disorders, such as CFS onset.<sup>45</sup>

While some studies have suggested that vaccination against HBV might be associated with CFS onset (most of the published articles are written in French),<sup>15,46,47</sup> others have rejected this possibility, arguing that the vaccine is safe with minimal adverse effects.<sup>36,48</sup> A case series has also shown that after weighing the small risks of the adverse effects of HBV vaccination against the risk of exposure to deadly hepatitis B virus, vaccination is always the best choice (Table 2).<sup>49</sup> In a recent case-control study performed by Magnus

**TABLE 2.** Vaccination and Chronic Fatigue Syndrome Onset

Vaccine	Risk	Protection	Vaccination recommended	Ref.
Rubella	Yes	No	Yes	44
Q fever	Yes	No	Yes	45
HBV	Yes	No	Yes	45–47
Meningococcal vaccine	No	No	Yes	50
Poliovirus	No	No	Yes	52
Staphylococcus toxoid	No	Yes	Yes	53
Influenza virus	No	No	Yes	54, 55

*et al.*<sup>50</sup> to evaluate the risk of CFS and multiple sclerosis (MS) according to meningococcal vaccine history in teenagers, no statistically significant association between vaccination and occurrence of CFS/MS could be observed.<sup>50</sup> Another study suggested that vaccination involving aluminum-containing adjuvants could trigger the cascade of immunological events, which are associated with immune-disrupting conditions, including CFS and macrophagic myofasciitis.<sup>51</sup> Concerning the effect of vaccination on patients having CFS, several studies have shown the safeness of vaccination use.<sup>52</sup> Noteworthy, polio virus vaccination was not found to be clinically contraindicated in CFS patients; however, there was evidence of minimally altered immune reactivity and virus clearance.<sup>52</sup> By contrast, other researchers have shown that the effect of vaccination with a staphylococcus toxoid in patients with FM and CFS is somehow beneficial (Table 2).<sup>53</sup> A significant improvement in psychometric assessment, self-rating depression scales, clinical global impression of the disease, as well as in the visual analogue scale (VAS) used to measure pain levels after vaccination was observed.<sup>53</sup> A beneficial effect was also confirmed when pre-treatment values of overall punctuation scales were compared to posttreatment values. However, the small sample size limits the validity of the results.<sup>53</sup> Regarding immunization against influenza,<sup>54</sup> vaccination appears to provide protective antibody levels without worsening CFS symptoms or causing excessive adverse effects (Table 2).<sup>55</sup> Efforts to motivate patients

with CFS to obtain annual influenza immunization are recommended to mend illness perception.<sup>54,55</sup>

### Autoantibodies in CFS

Several types of antibodies have been reported in CFS patients (Table 3).<sup>17,21,22</sup> However, their pathological role remains largely unexplored, primarily because of the many conflicting results that have been found in antibody studies of CFS patients and the lack of reproducible and convincing evidence. Because most of the symptoms and alterations commonly described in CFS patients have been related to physiological alterations, such as enhanced pain perception and musculoskeletal involvement, the study of autoantibodies has been mainly focused on antinuclear cell components and antineurotransmitters. The intent to correlate the presence of certain antibodies and symptoms has also revealed conflicting results. Although certain clinical characteristics of CFS overlap with those commonly described in autoimmune rheumatic disorders, certain autoantibodies widely described as hallmarks of autoimmune rheumatic diseases, such as the anti-double-stranded (ds)DNA antibodies, have not yet been found in CFS patients.<sup>17,19</sup> Likewise, no association between CFS and anti-Sm, U1-ribonucleoprotein (RNP), SS-A/Ro, SS-B/La, Scl-70, or centromere antibodies has been uncovered (Table 3).<sup>19</sup> Where one of these associations has been described in CFS

**TABLE 3.** Antibodies Associated with Chronic Fatigue Syndrome

Antibody	Reported	Ref.
<i>Antibodies in AIDs</i>		
Anti-dsDNA	No	17, 19
Anti-Sm	No	19
Anti-RNP	No	19
Anti-SS-A/Ro	No	19
Anti-SS-B/LA	No	19, 24
Anti-Scl-70	No	19, 24
ANA	Yes	57
<i>Nuclear components</i>		
Laminin B1	Yes	17, 56
68/48-kDa nuclear protein <sup>a</sup>	Yes	58
p80-coilin nuclear protein <sup>b</sup>	Yes	59
<i>Phospholipid antibodies</i>		
Antiphosphatidylinositol <sup>c</sup>	Yes	21, 61, 62
<i>Antibodies to CNS components</i>		
Serotonin	Yes	20, 21, 61
ACTH	Yes	22
CHMR1	Yes	23
MAP2	Yes	19
<i>Antibodies to diverse microorganisms</i>		
Gram-negative enterobacteria <sup>d</sup>	Yes	65
<i>Coxiella burnetii</i> (Q fever) <sup>e</sup>	Yes	66

AIDs, autoimmune rheumatic diseases; dsDNA, double-stranded DNA; ACTH, adrenocorticotrophic hormone; ANA, anti-nuclear antibodies; CHMR1, muscarinic cholinergic receptor 1; MAP2, microtubule-associated protein 2; RNP, ribonucleoprotein.

<sup>a</sup>Clinically associated with hypersomnia and cognition complaints.

<sup>b</sup>Found in Japanese patients, mainly the IgG 1 and 2 subclasses.

<sup>c</sup>Antiphosphatidylinositol IgM and IgG antibodies.

<sup>d</sup>Both IgM and IgG antibodies against enterobacteria were reported.

<sup>e</sup>Both IgM and IgG antibodies against *Coxiella burnetii* were reported.

patients, there has been concomitant Sjögren's syndrome, which could be responsible, in the case of one patient, for a listing of anti-SS-A/Ro, SS-B/La positive.<sup>24</sup>

### Antibodies to Nuclear Components in CFS

Fifty-two percent of CFS patients are reported as having autoantibodies to compo-

nents of the nuclear envelope, in particular to the nuclear envelope laminin B1 molecule.<sup>17</sup> The same authors suggested that autoantibodies to insoluble cellular antigens are a unique feature that might help to distinguish CFS from other rheumatic autoimmune diseases.<sup>56</sup> The presence of antinuclear antibodies (ANAs) was also described in 13% of 114 CFS Chinese patients, without evaluating any likely pathogenic role<sup>57</sup> (Table 3). Nishikai *et al.*<sup>58</sup> showed that autoantibodies to a 68/48-kDa nuclear protein were present in 13.2 and 15.6% of patients with CFS and primary FM, respectively. As a group, the anti-68/48-kDa-positive CFS patients presented more frequently with hypersomnia ( $P < 0.005$ ), short-term amnesia ( $P < 0.07$ ), or difficulty in concentration ( $P < 0.05$ ) than those CFS patients without such antibodies. Nishikai and colleagues concluded that the presence of the anti-68/48-kDa protein antibodies might be useful as possible markers for a clinico-serological subset of CFS/FM patients with hypersomnia and cognitive complaints.<sup>58</sup> Another study has described an additional antibody to the p80-coilin nuclear protein in a large sample of Japanese patients who had systemic scleroderma, Sjögren's syndrome, and other rheumatic disorders in parallel with CFS (Table 3).<sup>59</sup> p80-Coilin is a nuclear autoantigen that strongly accumulates in Cajal bodies (CB) and is considered a marker for CBs.<sup>60</sup> CBs are noncapsular nuclear bodies with a diameter of 0.3–1 micron and appear to be composed of coiled fibrils. Human autoantibodies to CBs recognize an 80-kDa nuclear protein highly enriched in CBs, leading to the name p80-coilin.<sup>60</sup> CBs are known to assemble and disassemble during the cell cycle, with the highest number of CBs occurring middle to late G1, when p80-coilin is assembled into several small nuclear body-like structures.<sup>60</sup> Noteworthy, in the group of CFS Japanese patients,<sup>59</sup> the sera had a predominant distribution of subclass IgG(1) anti-p80-coilin antibodies with five sera having concomitant subclass IgG(2) (Table 2).<sup>59</sup>

### Antibodies to Phospholipids in CFS

Several years ago, antiphospholipid antibodies that had previously been detected in CFS patients were postulated as possibly also having a pathogenetic role. Antiphospholipid antibodies were found in CFS patients in 1995 by Klein and Berq,<sup>61</sup> and this was confirmed in 1998 by Heller and team.<sup>21</sup> Recently, increased serum levels of IgM antibodies directed against phosphatidyl inositol (Pi) in CFS and major depression were found. There was evidence that an IgM-mediated immune response against Pi is one factor underpinning the comorbidity between both CFS and depression (Table 3).<sup>62</sup> The authors suggested that anti-Pi antibodies may have biological effects, for instance, by altering inositol 1,4,5-triphosphate, phosphatidylinositol-4,5-bisphosphate, diacylglycerol, and phosphatidylinositol-3,4,5-triphosphate production, thus interfering with intracellular signaling processes in both depression and CFS.<sup>62</sup>

### Antibodies to Neurotransmitters and Receptors in CFS

There is some evidence that antibodies to neurotransmitters, such as serotonin (5-HT),<sup>20,21</sup> adrenals,<sup>63</sup> adrenocorticotropin hormone (ACTH),<sup>22</sup> and receptors like muscarinic cholinergic receptor 1 and  $\mu$ -opioid receptor 1, might play an important role in the pathogenesis of CFS.<sup>23</sup> The most prominent autoantibodies reported are anti-serotonin,<sup>21,61</sup> antimuscarinic cholinergic receptor 1 (CHRM1),<sup>23</sup> and anti-microtubule-associated protein 2 (MAP2) (Table 2).<sup>19</sup> Indeed, levels of anti-MAP2 and anti-CHRM1 were significantly higher in CFS patients than in controls ( $P = 0.003$ ),<sup>19</sup> ( $P < 0.0001$ ) respectively,<sup>23</sup> and antiserotonin antibodies were found in 62% of CFS patients.<sup>21,61</sup> The CFS patients with positive autoantibodies to muscarinic receptors have been reported as presenting a significantly higher mean score of feeling "muscle weakness" than CFS patients

without autoantibodies to muscarinic receptors ( $P < 0.01$ ).<sup>23</sup> In another study, the presence of autoantibodies to 5-HT was found to be closely related to FM/CFS than to other conditions, whereas antibodies to gangliosides and other phospholipids were also detected in other disorders.<sup>20</sup> The observation that family members of CFS and FM patients also have these antibodies is an argument in favor of a genetic predisposition. Those data allowed us to suggest the concept that FM and CFS may belong to the same clinical entity and may manifest themselves as psychoneuro-endocrine autoimmune diseases.<sup>20</sup> Another interesting finding supporting this concept is that fatigue of the CSF type is characterized by a significantly higher incidence of autoantibodies against the adrenals and a higher cholesterol level.<sup>63</sup> Increased fatigue of CFS patients has been associated with a lower melatonin level, a higher serotonin level, and a lower melatonin/serotonin ratio compared to patients without fatigue.<sup>63</sup> Dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis has also been a commonly recognized feature of many pathological conditions, including CFS.<sup>64</sup> Some evidence indicates that this interfering factor is ACTH autoantibodies (Table 3).<sup>63</sup> The resulting effect of chronic ACTH autoantibody interference might be the manifestation of adrenocortical insufficiency symptoms and psychological disturbances, which have been reported in CFS patients.<sup>64</sup>

### Antibodies to Diverse Microorganisms and Their Correlation with CFS

Studies have suggested that infection with gastrointestinal pathogens could be related to CFS onset. Raised serum concentrations of IgA and IgM to LPS of gram-negative enterobacteria, such as *Pseudomonas aeruginosa*, *Morganella morganii*, *Proteus mirabilis*, *Pseudomonas putida*, *Citrobacter koseri*, and *Klebsiella pneumoniae*, in CFS patients have been reported (Table 1).<sup>65</sup> Interestingly, the prevalence and median values for serum IgA against the LPS of enterobacteria were significantly greater in patients with CFS

than in normal volunteers. Serum IgA levels were significantly correlated to the severity of illness, as measured by the fibro-fatigue scale and to symptoms, such as irritable bowel, muscular tension, fatigue, concentration difficulties, and failing memory.<sup>65</sup> The results showed that enterobacteria might be involved in the etiology of CFS and that an increased gut-intestinal permeability could cause a deregulated immune response to the LPS of Gram-negative enterobacteria.<sup>65</sup> In Japanese patients with CFS,<sup>66</sup> indirect immunofluorescence tests demonstrated that six of 20 patients who had had Q fever were positive for *Coxiella burnetii* IgM antibody to phase II antigen, and 18 were positive for IgG antibody. Antibody titers of both IgM and IgG decreased markedly after treatment. All six patients who had been positive for *C. burnetii* DNA became negative together with an improvement in subjective symptoms.<sup>66</sup> In another explorative study the repeated administration of the Staphypan Berna vaccine in patients with FM/CFS resulted in significant serological changes in the group receiving active treatment, whereas no significant changes were found in treated controls (Table 2).<sup>67</sup> Such findings suggest that immune modulation with a staphylococcal preparation might be used as a potential treatment to improve CFS symptoms.<sup>53,67</sup>

### Concluding Remarks

CFS is still a scientific challenge with regard to understanding its etiology and physiopathology. However, new insights have provided some clues, which we should focus on. Although CFS shares several clinical and pathological similarities with several autoimmune rheumatic and infectious diseases, such as the presence of diverse antibodies and alterations in some immunological markers. Nevertheless, there is still a lack of evidence for designating CFS as an autoimmune phenomena. In addition, many problems have arisen in trying to define CFS as a syndrome itself.<sup>2,68</sup> However, the most recent evidence points toward an ongoing autoimmune

phenomenon in such patients that, although not fully understood, is likely to be enhanced by the presence of certain infectious agents and other adjuvants.<sup>15</sup> Because the endocrine system has also been reported as being altered in CFS patients,<sup>22,63</sup> CFS has been identified as a complex disease in which more than one system may play an important role in its physiopathology, and this could include some type of CNS involvement. Another possibility to define CNS involvement in this syndrome is as a combination of psycho-endocrine-autoimmune phenomena, a new and different immunological approach for explaining some diseases with a large psychological component and with several immunological disturbances.<sup>61,69</sup> Some examples supporting such statements are the finding of antibodies producing CNS involvement in patients with systemic lupus erythematosus, a well-defined autoimmune rheumatic disease,<sup>70,71</sup> and also the finding of immunological alterations in patients with “non-autoimmune disorders” classified as psychiatric ones, such as schizophrenia.<sup>72</sup> More recent knowledge has shown that the immune system may influence and interact with other systems of our body, in both physiological and pathological scenarios. Thus, it is not surprising that a disturbance in the normal physiology of the immune system in the brain might cause an alteration in the perception of the sensation of pain, as well as other psychological alterations seen in CFS patients. New studies on CFS physiopathology should be undertaken, taking into account that CFS is a complex disease in which several systems, including the immune system, are undoubtedly involved.

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### Conflicts of Interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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