Review

Fibromyalgia, infection and vaccination: Two more parts in the etiological puzzle

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Abstract

As the pathogenesis of fibromyalgia continues to raise debate, multiple putative triggers have been implicated. The current review summarizes the available data linking fibromyalgia to either infection or vaccination. Multiple infectious agents have been associated with the development of either full-blown fibromyalgia (e.g. hepatitis C), or with symptom complexes extensively overlapping with that syndrome (e.g. chronic Lyme disease). The cases of Lyme disease, mycoplasma, hepatitis C and HIV are detailed. Despite the described associations, no evidence is available demonstrating the utility of antibiotic or anti-viral treatment in the management of fibromyalgia. Possible mechanistic links between fibromyalgia and HIV are reviewed. Associations have been described between various vaccinations and symptom complexes including fibromyalgia and chronic fatigue syndrome. The case of Gulf War syndrome, a functional multisystem entity sharing many clinical characteristics with fibromyalgia is discussed, with emphasis on the possibility of association with administration of multiple vaccinations during deployment in the Persian Gulf and the interaction with stress and trauma. Based on this example a model is proposed, wherein vaccinations function as co-triggers for the development of functional disorders including fibromyalgia, in conjunction with additional contributing factors.

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1. Introduction

Fibromyalgia continues to raise debate. This chronic, distressing disorder affects mainly women in the prime of life and inflicts suffering and of a magnitude comparable to that of rheumatoid arthritis (RA) [1]. A decade and a half after the ACR standardized the definition and classification of fibromyalgia [2], although the syndrome continues to rely on subjective criteria for diagnosis, valuable data has been accumulated regarding the objective neurological variations characteristic of the central nervous system in fibromyalgia, including a decrease in brain stem-initiated pain modulation [3], altered temporal summation of painful stimuli [4] and altered cerebral activation in pain processing areas of the brain [5]. Nonetheless, the etiology of fibromyalgia is yet unclear. Although hypotheses abound, ranging from the genetic, through the neuro-endocrine, traumatic and psychiatric, many authorities assume the condition to be multifactorial in origin. In this context various triggers, which may be cumulative and not mutually exclusive, may be held culpable, stimulating an as yet unidentified cascade of events, culmination in diffuse pain hyper-vigilance characteristic of the central nervous system in fibromyalgia. In this review we have attempted to describe the current knowledge on two related factors within this meshwork, i.e. the association of fibromyalgia with either infection or vaccination. Both infection and vaccination have been linked to the pathogenesis of autoimmunity [6,7]; although fibromyalgia is generally not considered an

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autoimmune disorder, the data reviewed indicates that somewhat surprisingly fibromyalgia may likewise have its links with both infection and vaccination.

2. Infectious factors in the pathogenesis of fibromyalgia

Fibromyalgia gained its formal definition in 1990 as a syndrome characterized by the ongoing presence of widespread pain associated with the finding on physical examination of tenderness on at least 11 of 18 defined points of palpation [2]. Since these classification criteria were stipulated the picture has rapidly broadened and fibromyalgia is currently considered a syndrome of aberrant pain processing with a possible background of an abnormal stress response [8]; it has moreover been integrated into a spectrum of central pain syndromes including, but not limited to, chronic fatigue syndrome, temporomandibular joint disorder, irritable bowel syndrome, and Gulf War syndrome. Besides the syndrome-defining symptom of widespread pain, prominent symptoms of fibromyalgia include disordered patterns of sleep, ongoing fatigue and mild cognitive impairment such as difficulty with memory and concentration.

The symptoms of fibromyalgia would appear to overlap considerably with those of a viral or atypical infection. First and foremost, widespread myalgia, the hallmark of fibromyalgia, is a prime symptom of many infections, ranging from the common cold to HIV [9]. Fatigue, an additional leading symptom, is likewise common to both fibromyalgia and viral infections. It is not surprising therefore that early research on both fibromyalgia and the related syndrome of chronic fatigue attempted to identify evidence of infection with pathogens such as EBV among these patients. Thus, a study by Buchwald et al. [10] described 50 patients with fibromyalgia who exhibited symptoms considered typical of “chronic Epstein-Barr virus infection”. These included sore throat, recurrent rash, adenopathy and recurrent low grade fever. All patients described an acute onset which appeared typical of a viral disorder. Nonetheless, antibody titers to Epstein-Barr virus were no different among the patients compared to controls. Similarly, patients with chronic fatigue were found to have no evidence of chronic EBV infection [11]. This finding failed to support previous observations by Moldofsky [12] concerning the effect of acute viral infection on development of sleep disorders considered to be harbingers of fibromyalgia. Despite these early observations, which cast doubt upon the role of EBV infection in fibromyalgia and chronic fatigue, research in this field has continued. Recent publications [13] have discussed the capacity of early nonstructural EBV-encoded protein to cause immune dysregulation as well as instigating clinical symptoms such as fatigue.

Early researches of the fibromyalgia syndrome attempted to find associations with additional infectious agents besides EBV. Thus, anecdotal evidence linked chronic Coxsackie B infection with widespread pain and fatigue “mimicking fibromyalgia” [14]. Subsequently, three patients were described who developed fibromyalgia after serologically proven acute Parvovirus infection [15]. Classical fibromyalgia-like sleep disturbances, such as alpha-wave intrusion into non-REM sleep were documented in these patients. The significance of this observation became questionable, however, shortly afterwards with a study testing for Parvovirus IgM antibodies among 15 fibromyalgia patients who recalled an acute “viral” onset of their symptoms. When compared to patients who recalled no such episode (and to healthy controls) no increased prevalence of positive Parvovirus serology was demonstrated [16]. Another rigorous effort was made to identify evidence of Parvovirus B19 infection in a selected group of seven patients suffering from chronic fatigue syndrome (CFS) who additionally demonstrated mild hematological abnormalities such as leucopenia and thrombocytopenia. In view of the known hematological injury caused by Parvovirus B19, these patients were considered particularly likely to show evidence of such infection. All patients underwent bone marrow aspiration, and Parvo viral infection was sought both by serology, bone marrow PCR and morphological examination. No evidence of marrow involvement with Parvovirus B19 was found in any patient, although one patient had antibody evidence of transient viral infection. There thus appears to be no evidence of an association between Parvovirus B19 infection and fibromyalgia or chronic fatigue.

3. The tale of Lyme disease

Lyme disease is an infectious disorder caused by *Borrelia burgdorferi* which is endemic in more than 15 states in the USA as well as in areas of Europe and Asia. Originally confused with juvenile RA [17], Lyme disease subsequently came to be recognized as a major confounder in the diagnosis of fibromyalgia, particularly in areas where both prevalence of Borreliosis and anxiety concerning the disease run high. Since Lyme disease causes both diffuse arthralgia, cognitive difficulties such as impaired concentration and memory, as well as fatigue, and since serological testing for Lyme disease is complex and not in all cases conclusive [18], it is not surprising that patients suffering from fibromyalgia were diagnosed as cases of “chronic Lyme disease”. In effect, before recognition of this clinical conundrum, Lyme disease came to be considered almost a diagnosis of exclusion in cases with unexplainable clinical symptoms of this nature. This often led to repeated administration of unwarranted antibiotic treatment.

In the earliest report on the association of fibromyalgia with chronic Lyme disease, 100 consecutive patients at a Lyme disease clinic were analyzed [19]. Lyme disease was found to be responsible for symptoms of only 37 of these patients. Twenty-five patients met criteria of fibromyalgia. Among these patients three were found to have active Lyme disease while 17 had a history suggestive of previous Lyme infection. The authors stressed the concern that ongoing mild fatigue and malaise following adequate antibiotic treatment, as well as *bona fide* fibromyalgia, may be misdiagnosed as chronic Lyme disease and lead to unnecessary antibiotic therapy. A subsequent rigorous study conducted at a Lyme disease clinic in a university hospital attempted to clarify the relationship between...
Lyme disease and fibromyalgia [20]. In this observational cohort study, 8% of 287 patients with Lyme disease were found to have fibromyalgia over a 3.5 year period. Fifteen of these patients underwent evaluation which included clinical assessment, immunodiagnostic tests for Lyme disease and neurological evaluation. In nine patients symptoms, including widespread pain, tender points, memory difficulty and fatigue, developed a mean duration of 1.7 months after the onset of acute Lyme disease. In another six patients such symptoms developed together with Lyme arthritis. At the time of evaluation, 11 patients had positive immunoglobulin (Ig) G antibody responses to _B. burgdorferi_ by enzyme-linked immunosorbent assay (ELISA), one had a positive Western blot, and three had positive cellular immune responses to Borrelial antigens. Four patients had mild CSF abnormalities. Signs of Lyme disease responded to courses of antibiotics (4 weeks of Ceftriaxone). Fourteen of the 15 patients, however, continued to suffer from symptoms of fibromyalgia. It thus was concluded that Lyme disease may indeed trigger fibromyalgia and may even coexist with that syndrome in a chronic form; however, antibiotic treatment usually fails to resolve the symptoms of fibromyalgia. The relative futility of treating patients with symptoms of fibromyalgia and positive serological results for Lyme disease with antibiotics was further demonstrated by a cost-analysis study which demonstrated that in endemic areas the risks and costs of empirical parenteral antibiotic therapy exceed the benefits [21]. Moreover, in a retrospective analysis of 800 cases of persisting nonspecific musculoskeletal or neurological symptoms thought to represent chronic Lyme disease, 77 patients were found to suffer from fibromyalgia per se and to have received recurrent courses of antibiotics [22]. Thus, it now seems rather clear that Lyme disease may trigger fibromyalgia on the one hand but may also frequently be confused with that diagnosis. Moreover, the anxiety tied to Lyme disease may in itself have deleterious effects on patients, leading both to exacerbation of other symptoms and to the creation of implicit pressure on physicians to institute antibiotics which may be both costly as well as associated with side effects. A recent meta-analysis examining symptoms such as fatigue, musculoskeletal pain, and neuro-cognitive impairment in patients with a previous diagnosis of Lyme disease [23] found these symptoms to be significantly more prevalent among such patients as compared with control, while identifying symptom patterns which differed from those seen in fibromyalgia, depression and chronic fatigue. Whether “post-Lyme widespread pain and fatigue” can really be considered separate from other more classical cases of fibromyalgia remains to be established.

The case of Lyme and fibromyalgia can be viewed to some extent as a test case for the practical application of uncovering the relationship between fibromyalgia and infection. Unlike many other infectious agents which have been tied to fibromyalgia, Lyme disease has effective treatment. The failure of patients treated with adequate antibiotic regimes for Lyme to improve vis-à-vis the symptoms of fibromyalgia tends to imply that in the case of fibromyalgia infection serves as trigger for a chain of events which, once initiated, will run its course without necessity of ongoing infection.

4. _Mycoplasma_, fibromyalgia and chronic fatigue

Similar to _Borrelia_, _Mycoplasma_ are infectious agents responsible for chronic disease in humans with characteristics such as protracted fatigue. Due to their elusive nature _Mycoplasma_ agents appear to be attractive candidates in the search for an infectious pathogen in conditions such as chronic fatigue syndrome, particularly when a “viral” onset is apparent with such manifestations as fever, sore throat and adenopathy as well as a sudden onset. For this reason several attempts have been made to identify evidence of such infection in patients with both CFS and in overlapping cases of fibromyalgia. Initial attempts using serology for _Mycoplasma_ yielded negative results [24]. Studying a group of 91 patients diagnosed with either fibromyalgia or chronic fatigue, Nasralla et al. [25] used PCR on circulating peripheral cells in order to identify evidence of infection with _Mycoplasma pneumoniae_, _Mycoplasma fermentans_, _Mycoplasma hominis_ and _Mycoplasma penetrans_. High prevalence of mycoplasmal infection was detected, with 30.8% showing evidence of double infection and 22% having triple infections. The presence of multiple Mycoplasmal infections was associated with a more protracted illness. No control group was described. Endresen [26], however, in a subsequent review, pointed out that the incidence of _Mycoplasma_ infection among patients with CFS was around 50%, and was much higher than the rate in healthy controls which was around 10%. This review also pointed out that many patients with CFS appear to improve after antibiotic treatment aimed against _Mycoplasma_. Another study supporting these observations reported a high 52% prevalence of mycoplasmal infection among 200 patients with CFS; simultaneously 7.5% of the same patients were found to show evidence of infection with _Chlamydia pneumoniae_ and 30.5% infection with Human Herpes Virus-6 (HHV-6) [27]. Prevalence of infection among 100 control patients in this study was low: 6% were infected with _Mycoplasma_, 1% with _Chlamydia_ and 9% were infected with HHV. Patients with co-infections tended to suffer from more severe signs and symptoms.

While these results seem temptingly straightforward it must be pointed out that the evidence of mycoplasmal infection in CFS as well as fibromyalgia has not been universally corroborated. Thus, Vernon et al. [28] found no evidence of infection with _Mycoplasma_ species among 34 patients with CFS, using _Mycoplasma_ species-specific primer pairs for direct amplification of microbes from plasma DNA. Most important from a practical viewpoint is the utility of antibiotic treatment aimed against _Mycoplasma_ in this clinical spectrum. This issue was addressed in a rigorous, placebo-controlled double-blind study conducted on patients suffering from Gulf War syndrome, an entity which shares many overlapping characteristics with fibromyalgia and CFS, including pain, fatigue and cognitive symptoms [29]. The study focused on 491 patients with detectible blood _Mycoplasma_ DNA. These patients...
were randomized to receive doxycycline, 200 mg per day or placebo for 12 months. No statistically significant difference was found between doxycycline and placebo groups, while side effects such as nausea and photosensitivity were more common among patients receiving doxycycline. Although direct extrapolation can obviously not be made between Gulf War syndrome and fibromyalgia, this study focusing on a highly selected group of patients positive for Mycoplasma DNA yet still failing to demonstrate clinical utility of prolonged antibiotic treatment tends to undermine the rational for the empirical use of such treatment in the spectrum of functional disorders.

5. The case of hepatitis C

The association between hepatitis C infection and fibromyalgia was recognized in a study comparing 90 patients with HCV to 128 healthy controls and 32 patients with non-HCV related cirrhosis [30]. Fourteen of the HCV infected patients (16%) were found to meet ACR criteria for the diagnosis of fibromyalgia as well as one patient among the cirrhosis patients. None of the control patients met ACR criteria. Patients with HCV were also found to have higher tender point counts.

It was thus established that a high prevalence of fibromyalgia exists among patients with HCV (particularly women). A concurrent study analyzed the frequency of HCV infection among patients with fibromyalgia in comparison with patients suffering from RA [31]. HCV antibodies were found in 15.2% of the patients with fibromyalgia as compared with 5.3% of RA patients. A substantial proportion of these patients had normal alanine aminotransferase levels. The authors concluded that HCV infection should be actively searched for in patients with fibromyalgia even in the absence of liver enzyme abnormalities. Interestingly, another study described fibromyalgia as one of a group of misleading rheumatic manifestations among patients in whom HCV was identified, additionally including carpal tunnel syndrome, palmar tenosynovitis and non-erosive polyarthritis [32]. Thus, HCV workup appears to be called for in the context of various and multiple musculoskeletal symptoms. A similar conclusion was reached based on a review of rheumatological manifestations of hepatitis C infection, which ranked fibromyalgia as a common complication, diagnosed in no less than 16% of patients in an Israeli sample [33]. In apparent contradiction with these results, a recent study conducted in Spain found no increase in the prevalence of hepatitis C among patients diagnosed with fibromyalgia as compared with healthy controls [34]. Whether this difference reflects local geographic variation or differences in methodology remains to be seen.

What is the mechanism through which hepatitis C may cause fibromyalgia? Some insight into this connection is provided by the effect various inflammatory cytokines have on the hypothalamic-pituitary-adrenal axis, which is activated by IL-1, IL-6 and TNF-α, while being down-regulated by IL-2 and interferon-α. Fibromyalgia has been associated with many cytokine abnormalities including increased levels of IL-2, IL-8, IL-1 and IL-6. Aberrant cytokine profiles have been implicated by some researchers as etiologic in fibromyalgia [35] and chronic widespread pain has been recently linked to a lack of anti-inflammatory and analgesic Th2 cytokine activity [36]. Cytokine profile alterations are additionally known to be involved in sleep disturbances and chronic fatigue [37], thus forming another possible link with symptoms inherent in fibromyalgia. IL-8 elevation has likewise been associated with depression in fibromyalgia [38]. Stress is an important background factor which may cast its effect on various players in this intricate network, relating to hypothalamic-pituitary-adrenal function, depression, and cytokine profiles.

Cytokine changes seen in fibromyalgia as well as hepatitis C may be responsible for hyperalgesia through cytokine receptors present on glial cells and through opiate receptors on lymphocytes [39]. Thus, in the case of HCV, a mechanistic link may be established between inflammatory changes in the immune system and the development of changes in neuro-endocrine function typical of fibromyalgia.

Recently, fibromyalgia symptoms have been described in increased prevalence among patients suffering from hepatitis B as well, adding another hepatotrophic viral pathogen to the putative infectious agents linked with fibromyalgia [40].

6. The case of HIV

As the myriad clinical manifestations of infection with HIV were delineated, a broad spectrum of rheumatologic manifestations became evident [41–43]. Thus, it came as no great surprise that fibromyalgia as well was increased in prevalence among patients infected with HIV. In a first report on this issue 15 of 51 (29%) patients suffering from HIV infection were found to fulfill criteria for fibromyalgia (compared with 57% of patients with RA) [44]. In a subsequent study of 140 patients infected with HIV, 11% were found to have fibromyalgia, comprising 41% of patients with musculoskeletal symptoms [45]. HIV patients with fibromyalgia were more frequently male and had an increased prevalence of depression. More than a decade later, the prevalence of fibromyalgia and other musculoskeletal complications was evaluated once more in HIV patients [46]. Despite the dramatic improvement in treatment and prognosis of HIV ushered during this period by the introduction of highly active anti-retroviral therapy (HAART), the prevalence of fibromyalgia remained relatively steady at 17% of the sample of 75 HIV patients.

6.1. How does HIV cause fibromyalgia?

Although no clear answer is currently available to the question above, various hypothetical links may be suggested based on what we know about the pathogenesis of these two seemingly unrelated conditions. In order to avoid undo speculation we shall focus on three possible mechanistic connections, namely, the role of hypothalamic-pituitary-adrenal dysfunction, sleep disturbances and depression.

Alterations in function of the hypothalamic-pituitary-adrenal axis have been well documented in HIV infection, including
blunting of the ACTH and cortisol response to stress [47] or to a CRH challenge [48]; increased basal ACTH/Cortisol levels have also been documented [49].

Fibromyalgia has similarly been associated with various perturbations of the hypothalamic-pituitary-adrenal axis (HPA) [50] such as an impaired ability to activate the hypothalamic-pituitary axis in response to induced hypoglycemia [51]. An intriguing recent study has associated levels of pain in fibromyalgia patients with momentary cortisol secretion upon awakening [52]. Although the precise role played by HPA alterations per se (as opposed for instance with the effect of stress) in the pathogenesis of fibromyalgia is still incompletely understood, a possible mechanistic link with the endocrine results of HIV appears plausible.

HIV infection is known to be associated with significant sleep disturbances [53] and these have been found to be associated with levels of pain and stress in these patients [54]. Some highly active anti-retroviral drugs are known to cause significant neuro-psychiatric side effects, including sleep disturbances [55]. Interestingly, such disturbances have been shown to respond to treatment modalities known to be effective in the treatment of fibromyalgia such as amitryptiline [56] and cognitive behavioral therapy [57]. Since disturbed sleep patterns are classical manifestations of fibromyalgia [58], it is possible that disturbed sleep constitutes another mechanistic link between HIV infection and the development of fibromyalgia.

Lastly, depression is common among patients infected with HIV, with a lifelong prevalence which has been estimated at 22–45% [59] while the frequency of a major depressive event is nearly twice as high in HIV positive individuals as compared with negative controls [60]. Depression is also classically associated with conditions of chronic pain, though a cause-and-effect relationship remains tentative [61]. Recent research, utilizing the functional MRI modality, has indicated that in fibromyalgia, depression is associated with the magnitude of neuronal activation in brain regions processing the affective-motivational dimension of pain, rather than with the sensory-discriminative aspects of pain processing [62]. It thus appears that similar to neuro-endocrine perturbations and to sleep disturbances, depression could thus serve as a putative link between fibromyalgia and HIV infection. Obviously, none of these factors are mutually exclusive and all three may well coexist in the overlapping spectrum between these conditions.

7. Is fibromyalgia associated with vaccination?

As can readily be discerned from the above discussion, the etiology of fibromyalgia in general, as well as the association between fibromyalgia and infection, remains obscure to a considerable degree. Consequently, it is not surprising that the possible relationship of this syndrome with vaccination similarly remains to be established. Nonetheless, a number of intriguing lines of evidence have evolved implicating a possible role for vaccination as we shall describe in the remainder of this review.

The possibility of fibromyalgia (then term fibrositis) and chronic fatigue representing a reaction to prior immunization against Rubella was raised by Allen [63] almost two decades ago as a medical hypothesis. Pointing out significantly elevated serum IgG antibodies directed against Rubella in patients with these conditions, the author noted an apparent epidemiological association between the introduction of a new Rubella vaccine (strain RA27/3) in 1979 and the debut of publications regarding chronic fatigue in the subsequent three years. Chronic fatigue and fibromyalgia appear not to be the only complications attributed to Rubella vaccination; the US federal court of claims eventually came to recognize a casual relationship between this vaccine and a spectrum of musculoskeletal complications including fibromyalgia, arthralgia, arthritis and various non-specific symptoms not restricted to the skeleton [64]. Rubella seronegativity is often screened for early in pregnancy and the rubella vaccine administered in the post-partum period in order to prevent seronegativity in subsequent pregnancies. A randomized, placebo-controlled trial has compared complications developing after this procedure with the outcome after administration of placebo [65]. RA27/3 Rubella vaccine in this study was significantly associated with the development of acute arthralgia and arthritis; the increase in frequency of chronic arthralgia and arthritis was marginally significant. A small difference was found in the frequency of persistent myalgia between recipients of the RA27/3 vaccine (15%) and recipients of placebo (9%). This difference fell just short of statistical significance (p = 0.051). No difference was observed in the frequency of acute myalgia. A follow-up study indicated that the risk of developing post-RA27/3 vaccine arthralgias may be higher among women who had very low pre-vaccination levels of antibody [66].

Thus, although current data are insufficient in order to establish a casual relationship between Rubella vaccination and fibromyalgia, it appears clear that this vaccine is capable of causing acute musculoskeletal symptoms, while a mild increase in the frequency of chronic myalgia cannot be ruled out.

Utilizing the vaccine adverse event reporting system (VARES) Lathrop et al. [67] screened all adverse events related to vaccination with Lyme vaccine in the USA between December 1998 and July 2000. Arthralgia, myalgia and pain were the most common reactions, accounting together for over 66% of adverse events altogether. As in the case of native Lyme disease, the reported symptoms were thus of a nature reminiscent of fibromyalgia.

8. The case of Gulf War syndrome

Gulf War syndrome is a unique clinical entity associated with the military conflict occurring in 1990–1991 in the Persian Gulf. Characterized by chronic fatigue, general malaise, irritability and cognitive impairment as well as musculoskeletal symptoms [68,69] and overlapping with post-traumatic stress disorder [70], the syndrome clearly carries attributes of a functional disorder (alternatively — a syndrome of
“Medically unexplained symptoms” [71]) and holds obvious similarities with fibromyalgia and chronic fatigue syndrome. Due to its specific historical and geographical characteristics, however, Gulf War syndrome offers an opportunity to study the association between such symptoms and specific exposures, thus potentially illuminating etiological factors which may be relevant for additional functional disorders, such as fibromyalgia. Thus, comparing servicemen deployed in the Persian Gulf in 1990–1991 with those participating in the Bosnian conflict or with contemporary service outside theaters of military conflict, revealed an excess prevalence of symptoms such as fatigue, post-traumatic stress and psychological distress among those servicemen deployed in the Persian Gulf [72]. This study identified multiple vaccinations administered to servicemen in the Gulf War as a relatively unique exposure characteristic to this conflict. In addition to multiple routine vaccinations administered, the concern regarding use of unconventional weapons of mass destruction led to administration of vaccinations directed against biological agents. In a cross-sectional study analyzing the relationship between ill health after the Gulf War and administration of vaccines before and during deployment in the Gulf [73] multiple measures were assessed, including fatigue, post-traumatic stress reaction, psychological distress, health perception, physical functioning and the presence of “multi-symptom illness”. The results indicated that the administration of multiple vaccinations prior to deployment in the gulf was associated with only one of these six measures (post-traumatic stress reaction), while administration of vaccines during deployment in the Gulf was associated with five out of the six (all but post-traumatic stress reaction). The authors concluded that while multiple vaccinations in themselves did not appear to be harmful, the combination between administration of such vaccinations and the concurrent stress associated with deployment in the combat zone (and possible other factors) may increase the risk of developing ongoing ill-health, including fatigue and multiple additional symptoms. A follow-up study indicated that while multiple vaccinations were important in initiating Gulf War syndrome, risk factors more important in perpetuation of symptoms over the long run were the severity of initial experience of the related Gulf War syndrome, it appears that however, Gulf War syndrome offers an opportunity to study the association between such symptoms and specific exposures, thus potentially illuminating etiological factors which may be relevant for additional functional disorders, such as fibromyalgia. This load was associated in some cases (particularly in British troops) with the administration of pertussis vaccine as an adjuvant, which is a known Th2 inducer [78]. Additional factors such as the stress associate with deployment in an area of combat could have Th2 inducing effects mediated thorough an increase in levels of cortisol and a fall in levels of androgens such as DHEA [79,80]. In interpreting these results it must be pointed out that although increased Th2 activation has been reported in CFS unrelated to Gulf War syndrome [81], differences in the immunological profile of these conditions undoubtedly exist [82]; moreover the application of these profiles to fibromyalgia is definitely not self-evident.

9. Conclusion

Elucidating the etiology of fibromyalgia continues to pose a challenge. In addition to the classic triggers such as physical trauma, emotional stress and genetic predisposition, an infectious cause has been suggested by many anecdotal reports, although evidence of causation remains tentative. In particular, cases such as Lyme disease and HIV, obvious overlap of clinical manifestations can be described; nonetheless, evidence of the utility of antibiotic or anti-viral treatment in fibromyalgia or CFS is lacking. As for the role of vaccination, based on the experience of the related Gulf War syndrome, it appears that not the mere exposure to one or another particular vaccine but rather the combination between various vaccines, adjuvant, and additional moderating factor such as stress may govern the effect of vaccination on the immune system and on the eventual development of chronic unexplained symptoms including fatigue, mood and cognition disturbances and pain.

Will the future uncover a greater role for infection and or vaccination in the pathogenesis of fibromyalgia? The history of medicine teaches us that serious and common disorders, such as peptic ulcer disease, which for many years were attributed to multifactorial causes (including a predominant psycho-somatic element), were eventually found to have a major infectious etiology. Finding such a factor in fibromyalgia would indeed be a “holy grail” of revolutionary implications regarding diagnosis and treatment. Currently though, it seems more likely that as we come to better understand and sub-classify fibromyalgia, various infections, through interaction with genetic and environmental factors, will be assigned their precise role in the syndrome’s pathogenesis and etiology.

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