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## Chronic fatigue syndrome with autoantibodies – The result of an augmented adjuvant effect of hepatitis-B vaccine and silicone implant

Agmon-Levin Nancy<sup>a</sup>, Yehuda Shoenfeld<sup>a,b,\*</sup>

<sup>a</sup> Center for Autoimmune Diseases, Department of Medicine 'B', Sheba Medical Center, Israel

<sup>b</sup> Sackler Faculty of Medicine, Incumbent of the Laura Schwarz-Kip Chair for Research of Autoimmune Diseases, Tel-Aviv University, Israel

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### ABSTRACT

**Background:** Chronic fatigue syndrome (CFS) that defines by prolonged fatigue and other manifestations, was recently integrated into a spectrum of central sensitivity syndromes including several diseases as fibromyalgia. CFS etiology is multi-factorial commonly triggered by infectious agents. Vaccines, induce an immune response similarly to infections, and may trigger just like infections autoimmune diseases, CFS and fibromyalgia. Furthermore vaccines contain an adjuvant which enhances their immune stimulation.

**Case presentation:** A 56-year-old woman was diagnosed with CFS accompanied by fibromyalgia, demyelination and autoantibodies. Her illness begun following the 2nd dose of hepatitis-B vaccine, and was aggravated by the 3rd vaccination. She underwent silicone breast implantation 6 years before vaccination with no adverse events. However, between the 2nd and 3rd vaccination she suffered a breast injury with local inflammation. Upon explanation of her breast implants silicone leak was observed.

**Discussion:** Vaccines have been reported to precede CFS mainly following exposure to multiple vaccinations (e.g. the Gulf war syndrome), or as an adverse response to the vaccine adjuvant (e.g. the macrophagic myofasciitis syndrome). Silicone is considered an adjuvant to the immune system, and may induce “the adjuvant disease”. Silicone implant, especially silicone leak relationship with autoimmunity and CFS has been the focus of considerable debates.

**Conclusion:** Our patient illness started following hepatitis-B vaccine, suggesting that it was caused or accelerated by vaccination. In parallel to vaccination our 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. To the best of our knowledge this is the first case of combined adverse effect to vaccine and silicone. Vaccine safety in individuals with silicone implants requires further studies.

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\* Corresponding author. Department of Medicine 'B' & Center for Autoimmune Diseases, Chaim Sheba Medical Center, Tel-Hashomer 52621, Israel. Tel.: +972 3 5302652; fax: +972 3 5352855.

E-mail address: [shoenfel@post.tau.ac.il](mailto:shoenfel@post.tau.ac.il) (Y. Shoenfeld).

## 1. Introduction

Chronic fatigue syndrome (CFS) is defined by a prolonged fatigue an un-refreshing sleep and post-exertional malaise accompanied by additional manifestations [1]. CFS has recently been integrated into a spectrum of central sensitivity syndromes that includes fibromyalgia, temporomandibular joint disorder, irritable bowel syndrome, and the Gulf War syndrome [2,3]. The etiologies of CFS and fibromyalgia are multi-factorial and commonly triggered by an aberrant reaction to an infectious agent [4–5]. Vaccines, which trigger an immune response similarly to infections [6,7] have also been associated with the development of CFS [2,8–10]. Furthermore vaccines contain an enhancer to their immune stimulation effects which stems from the fact that the infective particles in vaccines are emulsified in adjuvant [11]. Several adjuvant, such as alum and silicone were found to be independently associated with aberrant immune responses and the emergence of CFS [11,12]. The role of silicone, used for cosmetic purposes, as the cause of “adjuvant disease” has been evaluated in recent years [12,13].

We present a case of a 56 years old woman, who developed CFS following Hepatitis-B (HBV) vaccination, and exposure to silicone from her breast implants. The co-exposure to vaccine and silicone created an augmented adjuvant effect, leading to CFS as well as to the appearance of several autoantibodies.

## 2. Patient history

A 56 years old woman was evaluated for CFS beginning 13 years earlier following vaccination with HBV-vaccine. Her medical history prior to vaccination was unremarkable besides recurrent urinary tract infections and silicone breast implantation performed 6 years before vaccination with no adverse events. Her breast implants were made of silicone capsule filled with saline. The patients received the recommended HBV-vaccine while studying to become a nurse. Following the second vaccination she became ill with fatigue, weakness and headaches. At the same period of time she suffered from breast injury accompanied by local inflammation and a lymph node enlargement that required medical therapy. Upon the third HBV-vaccine, performed 6 months later, her symptoms worsened. Thereafter she became chronically ill, with a drastic decline in her overall health characterized by chronic fatigue, un-refreshing sleep, post-exertional malaise, concentration difficulties, short term memory impairment, fainting spells, body aches (head, muscle and joints), aberrant sensation suggestive of a demyelization illness, and depression. Her physical examination was remarkable for tender points suggestive of fibromyalgia, Raynaud phenomena and lymphadenopathy. During the years her laboratory tests for complete blood count, chemistry, TSH, T4 and sedimentation rate were constantly within normal limits, but serological tests demonstrated polyclonal gammopathy, high levels of anti-adrenal, anti-striated muscle and anti-smooth muscle antibodies, increased rheumatoid factor titers and elevated IgG, IgM, and IgA, immune-complexes. An MRI of the brain performed several years after vaccination demonstrated multiple scattered T2 signal hyperintensities in the frontal and parietal occipital deep white matter and sub-cortical white matter. Lumbar puncture re-

vealed elevated IgA and albumin in the Cerebral Spinal Fluid. During the years to follow her disease became almost incapacitating, she had to quit her regular job, as well as her house hold duties. Four years after the vaccination the patient had both breast implants removed with their surrounding capsules. On histological examination leaking of silicone and extensive calcification in both breasts were observed. The patient’s symptoms persisted for years, and treatments with anti-depressant helped her depressive symptoms but not her fatigue and other complains.

## 3. Discussion

Chronic fatigue syndrome (CFS) was first described in the 1980s as a primary persistent or relapsing fatigue. Later on the CFS diagnostic criteria were defined as severe fatigue, lasting for at least 6 months accompanied by four or more physical symptoms as subjective memory impairment, tender lymph nodes, muscle pain, joint pain, headache, un-refreshing sleep and post-exertional malaise lasting more than 24 h. CFS prevalence in the general population is 0.2–2.6%, it is nearly twice as common in women, and lacks differences among geographic and ethnic groups [2–4]. The etiologies of CFS and fibromyalgia are multi-factorial including hormonal, autonomic dysfunction, and aberrant immune reaction [5]. However, it seems that all these contributors to induction of CFS are “triggered” by infections [4]. Infectious agents, namely viruses, bacteria and parasites can trigger a variety of autoimmune diseases [7,14,15], CFS and fibromyalgia [2–5,10,16–18]. Different mechanisms as molecular mimicry, polyclonal activation, epitope spreading, bystander activation and the presence of super-antigens are responsible for the induction of immune mediated diseases following infections [7,14,19]. These mechanisms of immune response are similarly induced by vaccines; thereby vaccines exert their protective immune response. Alas, the same mechanisms may trigger in some susceptible individuals an autoimmune response, regardless if exposure was to infectious agent or to a vaccine [20–22]. Moreover, vaccines contain an enhancer to these mechanisms which stems from the fact that the infective particles are emulsified in an adjuvant [11].

Vaccines have been reported to precede the development of CFS and fibromyalgia [2,8–10,16]. It was postulated that the Gulf war syndrome which combines CFS and other manifestations, is the result of multiple vaccinations induced chronic Th-2 immune response [8]. The macrophagic myofasciitis syndrome characterizes by post-vaccination CFS and a muscle lesion at the site of vaccine injection. Electron microscopy of the muscle lesion demonstrates a persistent immune reaction to aluminum hydroxyl, the adjuvant used in different vaccination as Hepatitis-A, Hepatitis-B and toxoid vaccines [9]. The recombinant hepatitis-B vaccine is a highly purified, genetically engineered, single antigen vaccine, which is considered by the medical community as safe [23]. A causal relationship between hepatitis-B vaccine and several autoimmune disorders have been described [20,24,25] In a case-control study, Geier and Geier [26] prospectively analyzed the occurrence of autoimmune adverse events among recipients of the Hepatitis-B vaccine and found significantly increased odd ratios for the development of multiple sclerosis, optic neuritis, vasculitis, arthritis, alopecia, SLE, rheumatoid

arthritis, and thrombocytopenia compared to patients vaccinated for tetanus. This increased risk for autoimmune diseases among recipients of hepatitis-B vaccine stem from several constituents of the vaccine, which, besides antigenic epitopes, contains yeast, adjuvant and preservative as aluminum and thimerosal [20]. Fatigue has been observed in 1/3 of hepatitis-B vaccinated subjects [27] and at least 30 cases of CFS were associated with hepatitis-B vaccine within 3 months post-vaccination [28]. However, several studies failed to demonstrate a correlation between HBV-vaccine and CFS in the general population. A retrospective Canadian study of CFS patients found a similar prevalence of hepatitis-B vaccination within a time frame of 3 months, compare with controls [29]. Another study followed 700 students who were vaccinated with hepatitis-B vaccine, 12% of them complained of tiredness that was self limited and did not evolved into CFS [29,30]. Thus it may be suggested that in susceptible individuals hepatitis-B vaccine can trigger autoimmune phenomena and fatigue, while an additional trigger might be required for the development of CFS such as multiple vaccinations or an augmented adjuvant reaction.

Adjuvant is an agent that stimulates the immune system, preferably without having any antigenic effect by itself [19]. Adjuvants have been called the “the immunologists dirty little trick”, as they are simultaneously administered with vaccines in order to induce a more vigorous immune response to the vaccinated antigens [11]. Many adjuvants have been used including oils, aluminum salts, Freund's adjuvant and virosomes. The mechanisms of adjuvancy are not fully elucidated, as adjuvant mimick specific sets of conserved molecules such as bacterial lypopolysaccharides, endocytosed nucleic acids and unmethylated CpG-DNA that activate the innate immune response [31]. Adjuvants effect is not restricted to the innate immune response, as adaptive response is closely associated. Recently, enhancement of Th2 cell response by the adjuvant alum was observed in a mouse model. The addition of alum to OVA-peptide injected to mice increased the number and efficiency of dendritic cells and monocytes, thus improving the antigen presentation and T cell activation [19].

Silicone may be considered as an adjuvant to the immune system. Adverse events to silicone were termed in the 1990s “the adjuvant disease” and included weakness, fatigue, myalgia, arthralgia, memory loss and loss of myelinated nerve fibers [32]. Silicone decreases NK cells activity and increases autoantibodies production in animal models with a genetic susceptibility to autoimmunity, as well as in humans [33,34]. The silicone breast implants relationship with autoimmunity and CFS has been the focus of considerable debates. In addition to the symptoms of “the adjuvant disease”, induction of autoantibodies production and connective tissue disorders mainly systemic sclerosis and sicca syndrome have been described in association with silicone [32,34]. In many cases a defined connective tissue disease could not be diagnosed, yet patients presented with a combination of autoimmune manifestations associated with silicone exposure [13]. The presence of multiple autoantibodies could be demonstrated in our patient including anti-adrenal, anti-striated muscle, anti-smooth muscle antibodies, increased rheumatoid factor titers and elevated immune-complexes. In a meta-analysis published in 2000 [35], the association between silicone breast implants and classical connective tissue diseases could not be confirmed, and

the effect on the number of women in whom a definite connective tissue disease developed was minimal. However, this may not be the case for an atypical presentation of autoimmune disorders or even for yet an “unidentified silicone-associated autoimmune disease” [13,36,37]. In 2001 a study of 28 self reported symptoms among 1546 silicone breast implanted women versus 2496 reduction mammoplasty women showed significantly more symptoms in the breast implant cohort [38]. In the mid 1990s Borenstein [12] summarized the symptoms of silicone exposure and described the overlap of symptoms between chronic fatigue, fibromyalgia and “siliconeosis”. Thereafter CFS was documented in up to 71% of women with silicone breast implant, and the vast majority of women with silicone-associated disorder had chronic fatigue/fibromyalgia like syndrome [13].

Furthermore, histology studies of breast prostheses demonstrated a mild local foreign body response with a granulomatous reaction, and a high frequency of implant rupture. The loss of envelope integrity allows capsular silicone or silicone gel to escape into the surrounding tissues, regional lymph nodes and the circulatory system [13]. Silicone leakage can pass unnoticed for years by both patient and physician and be diagnosed only upon examination of the capsular material on explantation of prosthesis. On the other hand the leak of silicone can be presented with a range of symptoms from a mild local inflammation and lymph node enlargement, to gross changes in breast size and silicone leakage to other body parts. Systemic effects of silicone leak were studied by Vermeulen and Scholte in 2003, and by others [13,36,37]. A strong correlation between implants envelope rupture and chronic systemic symptoms as fatigue, impaired memory, headache, muscle and joint pains were observed and they persisted for years. Both CFS and FM were associated with a rupture of the breast implant [37–38]. Systemic symptoms might be improved after implants removal, but improvement delay is associated with the age of the implant, the presence of local symptoms of inflammation [13].

Thus, although the association between silicone exposure and define connective tissue disorder was difficult to establish, the induction of silicon-associated disease that combines autoimmune manifestations and central sensitivity syndromes is strongly supported by numerous studies. These adverse events are further aggravated by leak of the silicon beyond the capsular boundaries.

In the case presented here CFS, autoimmune and neurological manifestation presented abruptly after the second dose of the hepatitis-B vaccine and continued thereafter. Vaccines although generally safe, may rarely cause in susceptible individuals autoimmune phenomena, CFS and other diseases. Our patient exposure to silicone was uneventful before vaccination; however silicone leak was documented afterwards and might have occurred between the second and third doses of hepatitis-B vaccination. Therefore this unique case represents a susceptible condition, in which exposure to a double adjuvant effect (e.g. the adjuvant effect of silicone and adjuvant encompasses in the hepatitis-B vaccine) combined, augmented and preceded the appearance of CFS. To the best of our knowledge this is the first described case of the combined adverse effect of vaccine and silicone. In the future one might consider avoidance of certain vaccinations in individuals with silicone prosthesis. Furthermore HLA typing might be also

considered in order to diagnose individuals that are prone to develop autoimmune diseases before vaccination [39,40].

#### 4. Disclosure

An informed consent has been received from the patient to present her case. Yehuda shoenfeld has served as an expert witness in cases (including the one reported in this article) involving adverse vaccine reaction in the no-fault U.S. National Vaccine Injury Compensation Program.

#### Take-home messages

- Vaccines are most important illustrious achievements of modern medicine.
- Vaccines may induce or aggravate autoimmune diseases as well as fatigue, and hepatitis B virus is notorious among vaccines.
- Silicone implants are a required tool for cosmetic surgeries, which improve the implanted individual well being.
- Silicone implants may act as an adjuvant and induce fatigue and autoimmune phenomena termed siliconeosis.
- A novel augmented co-effect of silicone and hepatitis B vaccine, as triggers of the chronic fatigue syndrome with autoimmune features, is presented.

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