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Chronic fatigue syndrome and fibromyalgia following immunization with the hepatitis B vaccine: another angle of the 'autoimmune (auto-inflammatory) syndrome induced by adjuvants' (ASIA)

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Abstract The objectives of this study were to gather information regarding demographic and clinical characteristics of patients diagnosed with either fibromyalgia (FM) or chronic fatigue (CFS) following hepatitis B vaccination (HBVv) and furthermore to apply the recently suggested criteria of autoimmune (auto-inflammatory) syndromes induced by adjuvants (ASIA), in the aim of identifying common characteristics that may suggest an association between fibromyalgia, chronic fatigue and HBV vaccination. Medical records of 19 patients with CFS and/or fibromyalgia following HBVv immunization were analyzed. All of which were immunized during 1990–2008 in different centers in the USA. All medical records were evaluated for demographics, medical history, the number of vaccine doses, as well as immediate and long term post-immunization adverse events and clinical manifestations. In addition, available blood tests, imaging results, treatments and outcomes were analyzed. ASIA criteria were applied to all patients. The mean age of patients was 28.6 ± 11 years, of which 68.4 % were females. 21.05 % had either personal or familial background of autoimmune disease. The mean latency period from the last dose of HBVv to onset of symptoms was 38.6 ± 79.4 days, ranging from days to a year. Eight (42.1 %) patients continued with the immunization program despite experiencing adverse events. Manifestations that were commonly reported included neurological manifestations (84.2 %), musculoskeletal (78.9 %), psychiatric (63.1 %), fatigue (63.1 %), gastrointestinal complains (58 %) and mucocutaneous manifestations (36.8 %). Autoantibodies were detected in 71 % of patients tested. All patients fulfilled the ASIA criteria. This study suggests that in some cases CFS and FM can be temporally related to immunization, as part of ASIA syndrome. The appearance of adverse event during immunization, the presence of autoimmune susceptibility and higher titers of autoantibodies all can be suggested as risk factors. ASIA criteria were fulfilled in all patients eluding the plausible link between ASIA and CFS/FM.

Keywords Autoimmune (auto-inflammatory) syndromes induced by adjuvants (ASIA) · Vaccines · Autoimmunity · Hepatitis B vaccine · Fibromyalgia · Chronic fatigue syndrome

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Table 1 Demografic and clinical characteristics of CFS/FM patients who presented following HBVv HBV vaccination

Pt. no.	Gender	Age	Defined disease	Time from the last vaccine to the appearance of symptoms (days)	*Constitutional and systemic symptoms*	Neurological	Psychiatric	Musculoskeletal	Gastrointestinal	Mucocutaneous manifestations	Ophthalmic
1	F	14	CFS	4	1	1	0	0	1	0	1
2	M	27	CFS	7	1	1	1	1	0	1	0
3	M	28	CFS	30	1	0	1	0	1	1	0
4	M	15	CFS	30	1	1	1	0	1	0	0
5	F	52	CFS	12	1	1	0	0	1	1	1
6	M	17	CFS	25	1	1	1	1	1	1	0
7	F	12	CFS	108	0	1	1	1	0	0	0
8	F	30	CFS	3	1	1	1	1	1	1	0
9	M	35	FM	350	0	1	0	1	0	0	0
10	F	45	FM	14	1	1	1	1	1	0	0
11	F	40	FM	1	1	1	1	1	1	1	0
12	F	35	FM	6	1	1	1	1	1	0	0
13	F	26	FM	44	0	1	0	1	0	0	0
14	F	28	FM	3	1	0	0	1	0	0	0
15	M	35	FM	2	1	1	1	1	1	0	1
16	F	33	FM	7	0	1	0	1	0	0	0
17	F	33	FM	21	1	1	0	1	0	1	1
18	F	29	FM	41	1	1	1	1	0	0	0
19	F	11	FM	21	1	0	0	1	1	0	1

Pt. no.	Gender	Age	Defined disease	Time from the last vaccine to the appearance of symptoms (days)	ANA	RF	SM	MBP	RO/LA/RNP	TPO	Tg
1	F	14	CFS	4	NA	0	0	NA	NA	0	0
2	M	27	CFS	7	NA	NA	NA	NA	NA	NA	NA
3	M	28	CFS	30	NA	NA	NA	NA	NA	NA	NA
4	M	15	CFS	30	NA	NA	NA	NA	NA	NA	NA
5	F	52	CFS	12	1	1	NA	NA	NA	NA	1
6	M	17	CFS	25	NA	NA	NA	NA	NA	NA	NA
7	F	12	CFS	108	1	NA	NA	NA	NA	1	1
8	F	30	CFS	3	NA	NA	NA	NA	NA	NA	NA
9	M	35	FM	350	1	1	NA	1	1	NA	1
10	F	45	FM	14	0	1	1	0	NA	NA	NA
11	F	40	FM	1	NA	1	NA	1	NA	NA	NA
12	F	35	FM	6	0	1	0	NA	0	NA	NA
13	F	26	FM	44	1	0	NA	NA	NA	NA	NA

Table 1 continued

Pt. no.	Gender	Age	Defined disease	Time from the last vaccine to the appearance of symptoms (days)	ANA	RF	SM	MBP	RO/LA/RNP	TPO	Tg
14	F	28	FM	3	0	NA	NA	NA	NA	NA	NA
15	M	35	FM	2	1	NA	1	NA	0	NA	NA
16	F	33	FM	7	0	0	NA	NA	NA	NA	NA
17	F	33	FM	21	1	NA	0	NA	0	NA	NA
18	F	29	FM	41	NA	1	1	0	NA	NA	1
19	F	11	FM	21	0	0	0	NA	NA	0	0

Introduction

Chronic fatigue syndrome (CFS) and fibromyalgia (FM) are part of a wider spectrum of the 'central sensitivity syndromes,' which also includes irritable bowel syndrome and temporomandibular joint disorders [1]. CFS and FM may share several clinical manifestations including fatigue, sleep disturbances, headache, impaired memory, reduced ability to concentrate, psychiatric symptoms and musculoskeletal pain [2, 3]. Both are rather difficult to diagnose due to the nonspecific nature of the patient's complaints and thus pose a diagnostic dilemma to the clinician, with a few differential diagnoses [4, 5]. Those unfortunate enough to acquire either of these syndromes can suffer from a significant impairment in their life and daily activity [2, 6].

The estimated prevalence of CFS varies between 0.2 and 2.5 % [7, 8] and of FM is about 2 % [9]. Both occur more frequently among young women, and the mean age at onset ranges from 20 to 50 years [7, 10]; however, these conditions may affect children as well [11, 12]. While the pathogenesis of both diseases is yet to be elucidated, many etiologies have been proposed, including genetic predisposition, such as polymorphism of the COMT gene (Val158Met) [13, 14], endocrine abnormalities, immune dysregulation, psychological and psychosocial factors and more. Other studies have suggested a relation with infections, adjuvants and various vaccines [15–18] including hepatitis B virus vaccine [19–24]. Recently, the term 'autoimmune (or auto-inflammatory) syndromes induced by adjuvants' (ASIA) was suggested for symptoms which appear following vaccination, silicone implantation, or exposure to tetramethylpentadecane, pristane, aluminum and other adjuvants [25–28]. ASIA syndrome includes four major and four minor criteria, and in order to diagnose ASIA, fulfillment of either two major, or one major plus two minor criteria is required [25].

In our present study, we have evaluated the clinical files of 19 patients who were diagnosed with either fibromyalgia or chronic fatigue following HBVv. We have analyzed their demographic and clinical characteristics and applied the recently suggested criteria of ASIA. We hypothesized that both syndromes are part of ASIA syndrome following HBV vaccination

Patients and data analysis

Patients

We analyzed a large cohort of 114 American patients suffering from post-immunization adverse events between the years 1990 and 2008 [19]. The vaccination was performed according to the CDC protocols, and all patients

Table 2 The suggested criteria of 'ASIA' among 20 patients who developed FM or CFS following HBVv

Major criteria	Present in post-HBVv group
Exposure to an external stimuli (infection, vaccine, silicone, adjuvant) prior to clinical manifestations	100 %
The appearance of 'typical' clinical manifestations[a]	100 %
Removal of inciting agent induces improvement	Not relevant
Typical biopsy of involved organs	Not assessed
Minor criteria	**Present in our post-HBVv group**
The appearance of autoantibodies or antibodies directed at the suspected adjuvant	71 %[b]
Other clinical manifestations (i.e., irritable bowel syn.)	Not assessed
Specific HLA (i.e., HLA DRB1, HLA DQB1)	Not assessed
Evolvement of an autoimmune disease (i.e., MS, SSc)	Non

[a] Typical manifestations of ASIA in the current cohort included: myalgia, myositis or muscle weakness, arthralgia and/or arthritis, chronic fatigue, non-refreshing sleep or sleep disturbances, neurological manifestations, cognitive impairment, memory loss, pyrexia, dry mouth

[b] Out of the 14 patients that underwent a laboratory test for autoantibodies

approached legal consultation, following their diagnosis. Among them, we identified 19 who developed CFS of FM (by the ACR criteria) up to 1 year following HBVv immunization, and their medical records were gathered. This study received approval of the ethical committee and fulfilled the ethical guidelines of the recent declaration of Helsinki.

Methods

All medical records of patients were evaluated for demographic (age, sex, employment) and past medical history (i.e., personal and familial). In addition, dates and number of inoculations, local and immediate adverse events, as well as clinical manifestations and their temporal relation to HBVv were collected. All available blood tests (i.e., complete blood counts, chemistry, serology, etc.), imaging modalities (i.e., X-rays, C.T. and MRI-scans, etc.), treatments and outcome were also analyzed. The ASIA criteria were applied to each patient.

Results

Characteristics of CFS and FM patients who presented following HBV vaccination are specified in (Table 1) of which 11 were diagnosed with FM and eight with CFS. Thirteen of the 19 patients in our cohort (68.4 %) were females (nine from the FM group). At the time of first HBVv injection, 14 (73.6 %) were above the age of 18 years old (mean age 28.6 ± 11). Autoimmune susceptibility, defined as having personal or familial history of autoimmunity, was documented in four (21.05 %) of the patients, of which two had a personal (hypothyroidism, hyperthyroidism) and two family (inflammatory bowel disease and multiple sclerosis) history of autoimmunity. Notably, seven patients (36.8 %) were health personnel. The HBVv immunization was conducted according to the recommended CDC protocol (i.e., three doses at 0, 1 and 6th months). Three patients (15.7 %) received only one dose of HBVv, four patients (21.05 %) received two doses, and 12 (63.1 %) received all three inoculations (average: 2.47 doses). Eight (42.1 %) patients continued with the immunization program despite experiencing adverse events. The mean latency period from the last HBVv immunization to onset of symptoms was 38.6 ± 79.4 days (ranging from a day to 1 year).

Clinical manifestations and autoantibodies of FM/CFS patients, following the HBVv

Various systemic and local clinical manifestations were described and grouped according to the involved organs or systems:

Constitutional and systemic symptoms were reported in 15 patients (78.9 %) and included fatigue 63.1 %, malaise 31.5 %, fever 26.3 %, chills 15.7 % and lymph node enlargement 10. 5 %.

Neurological manifestations were documented in 84.2 % of the group including sensory change (paresthesia, numbness burning sensation, hyperesthesia) 42.1 %, short term memory loss 36.8 %, dizziness 26.3 %, cognitive dysfunction 21.05 %, headache 10.5 %, vertigo 10.5 % and urinary retention 10.5 %.

Psychiatric disturbances were experienced by 63.1 % of patients and included sleep disturbances 47.3 %, depression 21.05 %, irritability 21.05 % and obsessive compulsive disorder 5.2 %.

Gastrointestinal complaints were reported in 58 % of the patients and included weight loss 26 %, nausea 26 %, vomiting 26 %, abdominal pain 21.05 %, diarrhea 15.7 % and loss of appetite 10.5 %.

Musculoskeletal manifestations were reported in 78.9 % of the cases, and they included arthralgia 57.8 %, back pain 42 %, myalgia 27.5 %, joint stiffness 21.05 %, arthritis 10.5 % and muscle spasm 10.5 %.

Mucocutaneous manifestations were recorded in 36.8 % and included photosensitivity 21.05 %, rash 21.05 %, edema 10.5 %, alopecia 5.2 %, mucosal ulcer 10.5 % and hair loss 5.2 %.

Ophthalmic manifestation evolved in 21 % of patients and included eye field visual changes

Autoantibodies were measured in 14 patients, out of which 10 (71 %) patients (2 CFS and 8 FM) had detectable autoantibodies, 6 had anti-nuclear antibodies, 6 had anti-rheumatoid factor, 4 had anti-thyroglobulin, 1 had anti-thyroperoxidase, 3 had anti-Sm antibodies, 2 had anti-myelin basic protein, and 1 had antibodies directed at RO, LA and ribonucleoprotein antigens.

ASIA criteria and FM/CFS following the HBVv

ASIA criteria [25] were applied to all patients. In this group, all patients fulfilled two major criteria, required to define ASIA (Table 2): one major criterion is the prior exposure to external stimuli (HBV vaccine); the second major criteria are the 'typical' ASIA manifestations, which were all experienced by the patients. In addition, ten patients had a positive serology for autoantibodies therefore fulfilled a minor criterion.

Discussion

In the current study, we describe a series of patients diagnosed with CFS or FM following HBVv; both CFS and FM are conditions with an unclear pathophysiology.

Various environmental factors have been linked with these diseases including the exposure to vaccines, infectious agents, as well as adjuvants [17, 23, 24, 26, 29–31].

HBVv is composed of recombinant viral antigens expressed in *Saccharomyces cerevisiae* bacterial cells coupled with aluminum adjuvant. Chronic HBV infection has been associated with FM; therefore, this may suggest that the exposure to the antigen found in the vaccine may itself induce FM [32]. Furthermore, high levels of anti-*Saccharomyces cerevisiae* antibodies were found in patients with autoimmune diseases including anti-phospholipid syndrome, systemic lupus erythematosus, type 1 diabetes mellitus and rheumatoid arthritis [33]. In the past adjuvants, incorporated in most vaccines, were considered inert to the immune system. In recent years, their ability to induce immune or autoimmune reactions has been clearly documented [18, 26–28, 34–37]; furthermore, one study showed that immunization with an adjuvant induces high level of anti-phospholipid antibodies [38]. In addition, animal studies have demonstrated the ability of vaccines to cause immune-mediated manifestations including central and peripheral nervous system ones [37, 39].

The association between autoimmune diseases and either FM or CFS is still not well defined; however, there are some reports which support this view: several studies demonstrated that patients suffering from autoimmune diseases like systemic lupus erythematosus, rheumatic arthritis and psoriatic arthritis were also diagnosed with FM [40–44]. Out of our cohort, four had either a personal or a family history of autoimmunity; this further strengthens an association between autoimmune background CFS and FM. Several different studies showed higher levels of cytokines, such as IL-6, IL-8 and IL-1RA, in patients with fibromyalgia syndrome, suggesting that an immune process takes part in the pathogenesis of this disease [45]. Another link that supports the autoimmune nature of CFS and FM is the presence of autoantibodies documented in several studies. For instance, an association between autoantibodies against 68/48 kDa protein was documented [46]. While in another study, the presence of anti-thyroperoxidase antibodies in euthyroid patients diagnosed with FM was reported [47]. Notably, in this cohort, different autoantibodies were documented in 71 % of sera tested. This observation may support further investigation of a large profile of autoantibodies among CFS/FM patients and particularly among those diagnosed following immunization.

In our cohort, 75 % of patients were females, which is another typical autoimmune phenomena, and in particular among patients diagnosed with ASIA [19]. Interestingly, although CFS and FM are considered rare in childhood [48, 49], in our cohort, 26.4 % were younger than 18 years old, which may further support the link between exposure to the vaccine at young age as part of the vaccination program and appearance of CFS/FM.

In our study, the latency period from the last HBVv to overt manifestations was 38 days, although the range was between few days and a year. Traditionally, only a latency period of 3–6 weeks from exposure to the appearance of an immune-mediated disease was considered [50]. However, accumulating data suggests that a broader latency period, from immunization or exposure to other external stimuli, exits. For example, the association between HBVv and immune-mediated neuronal damage was documented 3 years post-vaccination [24], and macrophagic myofasciitis was diagnosed up to 8 years following inoculation with vaccine [51]. Herein, our observation further supports the idea that the latency period is variable and clinical symptoms may appear long after exposure to stimuli.

Several risk factors for the relation between vaccine and autoimmunity have been observed in our cohort: 21.05 % percent had personal or familial history of immune-mediated diseases and 36.8 % continued with the immunization protocol despite experiencing variable adverse events. Thus, we can speculate that patients who experience an adverse event after exposure to the first dose of HBVv or recall a history of post-vaccination adverse effect, and perhaps those with personal of familial autoimmunity, may be regarded as 'high risk' patients.

Neuro-psychiatric manifestations were present in 89.4 % of patients, while exclusive neurological or psychiatric symptoms were reported among 84.2 and 73.6 % of patients, respectively. Both the HBV antigen and adjuvants, especially alum, were found to be neurotoxic [24, 52–58]. Hence, several studies performed on animals demonstrated impaired learning and memory as well as hippocampal neuronal loss following exposure to aluminum [59–61]. Our observation further supports the link between ASIA and neuro-cognitive impairments.

In our cohort, all patients fulfilled two major criteria (i.e., they were exposed to an external stimulus, the vaccine and experienced the appearance of 'typical' manifestations of ASIA) and 71 % exhibited sera-positivity for different autoantibodies thus fulfilling an additional minor criteria. This may allude to the notion that many patients diagnosed with CFS–FM may suffer from ASIA, which may be diagnosed as a high index of suspicion is present and following a meticulous history intake.

Some limitations to our study should be addressed. This is a retrospective study that lacks a control group and therefore cannot prove causal association between immunization and the final outcome. The vast majority of the patients approached legal consultation, representing a very biased group. This bias represents subjects who seek for legal compensation and thus overestimate the association of their symptoms to immunization. Another limitation rose from our decision to include only patients that experienced a new onset of autoimmune phenomena; by this, we have excluded cases of patients that experienced exacerbation of previously diagnosed diseases. These limitations should be addressed in the future by larger and prospective studies, as well as in animal models to evaluate causality.

Conclusion

This study suggests an association between immunizations with HBVv or to one of its components to CFS and FM, as part of the ASIA syndrome. Although a causal association could not be proven, a temporal association was clearly evident in this cohort. An important point to stress is that this temporal association may last longer than is usually expected and in our cohort was observed up to a year following immunization. Several risk factors were noted such as the appearance of adverse event during immunization which may imply an increased risk of developing post-immunization diseases or the presence of autoimmune susceptibility documented by personal or family history or the presence of autoantibodies. Last but not least, the ASIA criteria were fulfilled in all patients eluding the plausible link between ASIA and CFS/FM. Further studies are needed to support our observation and possibly shed more light on genetic, autoimmune and vaccine ingredient related risk factors.

Conflict of interest Prof. Yehuda Shoenfeld has served as an expert witness in cases involving adverse vaccine reactions in the no-fault U.S. National Vaccine Injury Compensation Program. All other authors have no conflict of interest.

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