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SPECIAL ARTICLE

Autoimmunity following Hepatitis B vaccine as part of the spectrum of 'Autoimmune (Auto-inflammatory) Syndrome induced by Adjuvants' (ASIA): analysis of 93 cases

Y Zafrir[1]*, N Agmon-Levin[1]*, Z Paz[1], T Shilton[1] and Y Shoenfeld[1,2]
[1]The Zabludowicz Center for Autoimmune Diseases, Sheba Medical Center, Tel-Hashomer, Israel; and [2]Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel

Objectives: In this study we analyzed the clinical and demographic manifestations among patients diagnosed with immune/autoimmune-mediated diseases post-hepatitis B vaccination. We aimed to find common denominators for all patients, regardless of different diagnosed diseases, as well as the correlation to the criteria of Autoimmune (Auto-inflammatory) Syndrome induced by Adjuvants (ASIA).
Patients and methods: We have retrospectively analyzed the medical records of 114 patients, from different centers in the USA, diagnosed with immune-mediated diseases following immunization with hepatitis-B vaccine (HBVv). All patients in this cohort sought legal consultation. Of these, 93/114 patients diagnosed with disease before applying for legal consultation were included in the study. All medical records were evaluated for demographics, medical history, number of vaccine doses, peri-immunization adverse events and clinical manifestations of diseases. In addition, available blood tests, imaging results, treatments and outcomes were recorded. Signs and symptoms of the different immune-mediated diseases were grouped according to the organ or system involved. ASIA criteria were applied to all patients.
Results: The mean age of 93 patients was 26.5 ± 15 years; 69.2% were female and 21% were considered autoimmune susceptible. The mean latency period from the last dose of HBVv and onset of symptoms was 43.2 days. Of note, 47% of patients continued with the immunization program despite experiencing adverse events. Manifestations that were commonly reported included neuro-psychiatric (70%), fatigue (42%) mucocutaneous (30%), musculoskeletal (59%) and gastrointestinal (50%) complaints. Elevated titers of autoantibodies were documented in 80% of sera tested. In this cohort 80/93 patients (86%), comprising 57/59 (96%) adults and 23/34 (68%) children, fulfilled the required criteria for ASIA.
Conclusions: Common clinical characteristics were observed among 93 patients diagnosed with immune-mediated conditions post-HBVv, suggesting a common denominator in these diseases. In addition, risk factors such as history of autoimmune diseases and the appearance of adverse event(s) during immunization may serve to predict the risk of post-immunization diseases. The ASIA criteria were found to be very useful among adults with post-vaccination events. The application of the ASIA criteria to pediatric populations requires further study. *Lupus* (2012) **21,** 146–152.

Key words: ASIA; autoantibodies; autoimmunity; chronic fatigue syndrome; hepatitis B vaccine; SLE; vaccines

Introduction

Vaccines are one of the most significant tools in the delivery of preventive medicine today, as eradication of infectious diseases becomes possible through vaccination programs. The first vaccine was documented in Turkey during 1717 by Mary Wortley Montagu.[1] At that time she observed that inoculation, meaning placing a small quantity of pus collected from victims of smallpox on a skin scratch of a healthy person, resulted in a relative benign disease course.[1,2] The term vaccine was coined later by Louis Pasteur in tribute to Edward Jenner.[2] The latter reported amelioration

*The first two authors contributed equally to this article.

Correspondence to: Yehuda Shoenfeld, MD, FRCP, Zabludowicz Center for Autoimmune Diseases, Chaim Sheba Medical Center, Tel-Hashomer 52621, Israel
Email: shoenfel@post.tau.ac.il

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of smallpox disease in subjects exposed to cowpox, and introduced the first vaccination program.[2] Following those first steps, in the last century a variety of vaccines were developed and have changed the way we now prevent infectious disease.

Hepatitis B virus (HBV) is a common viral infection that affects 350 million people worldwide and is associated with cirrhosis, hepatic failure, and increased risk of hepatocellular carcinoma.[3–5] HBV vaccine (HBVv) was introduced into the market in the early 1980s, and a few years later the first HBVv inoculation program was launched in Taiwan.[6] This is a recombinant vaccine that contains viral surface antigen emulsified within aluminum hydroxide serving as an adjuvant. The HBV antigen is obtained by genetic engineering in the yeast *Saccharomyces* with no addition of preservative. Following the development of HBVv, immunization programs worldwide have revealed that the vaccine efficacy in preventing infection among susceptible children and adults is 80–95%.[7–9] Moreover, HBVv decreases disease load, halts new infections, and was the first vaccine to prevent cancer.[6,10,11]

However, similar to other vaccines, HBVv was associated with immune and non-immune adverse events in post-marketing surveillance studies,[12] case series and case reports.[13–19] These post-immunization phenomena occur rarely, may appear up to 3 years following immunization[17] and are not well defined.

Recently an enigmatic post-immunization syndrome, termed 'Autoimmune (Auto-inflammatory) Syndrome Induced by Adjuvants' (ASIA) was identified.[20] This syndrome encompasses symptoms which appear following chronic exposure to silicone, tetramethylpentadecane, pristaine, aluminum and other adjuvants.[21–23]

Thus, in the current study we analyzed the clinical characteristics of patients who developed post-HBVv immune/autoimmune-mediated disease, aiming to find common denominators, regardless of their defined disease, as well as the relevancy of the ASIA criteria in this cohort.

Patients and data analysis

Patients

The medical records of 114 patients who experienced immune or autoimmune-mediated diseases following HBVv were evaluated. Immunizations took place in different centers in the USA between 1990 and 2008, and were performed according to the CDC protocol. All patients approached legal consultation. Only patients who experienced the appearance of a new immune-mediated phenomenon following vaccination and who were diagnosed by a specialist before applying for a legal consultation were included in this study. Of the 114 evaluated medical records, 93 fulfilled these inclusion criteria.

The study received the approval of the ethics committee and fulfilled the ethical guidelines of the recent declaration of Helsinki.

Methods

In this retrospective study the medical records of patients were evaluated for demographics (age, sex, employment) and past medical history (personal and familial). In addition, dates and number of inoculations, and local and immediate adverse events, as well as clinical manifestations and their temporal relation to HBVv doses were collected. All available blood tests (complete blood counts, chemistry, serology, etc.), imaging modalities (x-rays, computed tomography (CT) and magnetic resonance imaging (MRI) scans, etc.), treatments and outcome were also recorded. The ASIA criteria were applied to each patient.

Results

Characteristics of the 93 patients who presented following HBV vaccination

At the time of first HBVv inoculation, 59 (63.5%) patients were adults (>18 years of age) and 64 (69.2%) were females. Their mean age was 26.5 ± 15 years (range: days to 67 years). Autoimmune susceptibility, defined as having personal or familial history of autoimmunity (hypothyroidism, diabetes mellitus type 1, multiple sclerosis, etc.) was documented in 21% of our cohort, of which 14 (15%) had a personal and 18 (19%) a familial history of autoimmunity. In this study eight individuals (8.4%) were health-related personnel (two medical doctors, three nurses, two paramedics and one speech therapist). HBVv immunization was conducted between the years 1990 and 2008 according to the recommended CDC protocol (three doses at month 0, 1, and 6). The post-vaccination follow-up period ranged from 1–17 years. Eleven patients (12%) received one dose of HBVv, 27 patients (29%) received two doses, and 55 (59%) received all three inoculations. On average, 2.5 doses of HBVv were administrated

and 44 (47%) of patients continued with the immunization program despite experiencing adverse events. The mean latency period from last HBVv immunization and onset of symptoms was 43.2 days (ranging from 1 day to 2 years). Early post-vaccination adverse events such as rash, flu-like symptoms, serum sickness and angioedema were reported by five (5%) patients within 3 weeks (mean, 15 days).

Clinical manifestations of 93 patients following the HBVv

Various systemic and local clinical manifestations were described and grouped according to the involved organs or systems as depicted in Table 1.

Neuro-psychiatric manifestations were documented in 70% of patients. Neurological manifestations were documented in 60% of the group, including numbness 30%, paresthesia 23%, short-term memory loss 15%, dizziness 14%, gait disturbance 8.6%, burning sensation 7.5%, paralysis 7.5%, optic neuritis 7.5%, cognitive dysfunction 7.5%, neurogenic bladder and bowel 6.5%, ataxia 6.5%, seizure 5%, nystagmus 4%, vertigo 4%, hyporeflexia 4%, Lhermitte's phenomenon 3%, hyperesthesia 3%, urinary retention 2%, dysarthria 2%, tinnitus 2%, nuchal rigidity 1%, myoclonic jerks 1% and tics 1%. Psychiatric disturbances were experienced by 16% patients and included sleep disturbances 19.3%, depression 9.6%, irritability 8.6% and obsessive compulsive disorder 1%.

Other manifestations included ophthalmic manifestation, which evolved in 32% patients: eye field visual change 20.4%, diplopia 6.5%, visual loss 6.4%, uveitis 3%, conjunctivitis 2%, gaze disturbance 2% and retinopathy 1%. General symptoms were reported in 60%, and included fatigue 41.9%, weakness 20.4%, fever 18%, chills 7.5% and lymph node enlargement 5%. Mucocutaneous manifestations were reported in 30% and included rash 17.2%, malar rash 7.5%, photosensitivity 6.5%, Raynaud's phenomenon 6.5%, edema 6.5%, systemic rash 6.5%, hair loss 5%, sicca syndrome 4%, mucosal ulcer 4%, itching 2% and skin pigmentation 1%. Musculoskeletal manifestations were reported in 59% of cases, and they included arthralgia 36.5%, myalgia 25.8%, joint stiffness 19.3%, back pain 14%, arthritis 10.7%, muscle spasm 7.5%, muscle tone 3% and muscle wasting 3%. Gastrointestinal complaints were found in 50% of the patients, and included weight loss 24.7%, nausea 18%, abdominal pain 17%, vomiting 13%, loss of appetite 13%, diarrhea 10.7%, jaundice 4% and constipation 2%.

Table 1 Clinical manifestation among patients with post-HBVv disease arrayed according to organ and systems

Manifestations	*No. of Pt (%)*
Neurological	62 (66.6%)
General Symptoms	56 (60.2%)
Musculo-skeletal System	56 (60.2%)
Gastrointestinal	47 (50.5%)
Fatigue	39 (41.9%)
Ophthalmologic	30 (32.2%)
Muco-cutaneous	28 (30.1%)
Sleep disturbance	18 (19.35%)
Psychiatric	15 (16.12%)
Local reaction	10 (10.75%)

Serological and other laboratory tests

In this cohort 49 patients were serologically evaluated for the presence of autoantibodies, and 39/49 (80%) demonstrated seropositivity. Out of the entire group, anti-nuclear antibodies (ANA) were demonstrated in 28/49 (57%) of patients. Specific antibodies were also present, such as rheumatoid factor (28%), anti-smooth muscle (16%), immune complex (8%), anti-dsDNA (8%), anti-RNP (6%), anti-Smith (2%), and anti-SSA/Ro and anti-SSB/La 4% each. Other autoantibodies were also reported, such as anti-myelin basic protein (IgM) 8%, adrenal autoantibodies 8%, anti-cardiolipin 4%, anti-thyroglobulin 6%, anti-thyroid peroxidase 2% and anti-mitochondrial 2%.

Decreased NK cell activity was observed in six sera of six patients evaluated. Lumbar puncture was performed in six patients, of whom five demonstrated cerebrospinal fluid oligoclonal bands.

Imaging and other studies

Some 44 patients underwent imaging procedures by CT or MRI. Evidence of demyelinating lesions was recorded in 25/44 (56%) evaluated patients. Single photon emission computed tomography was performed in 2% of patients, showing asymmetry of the temporal lobes. On electroencephalogram, bilaterally decreased activity was documented in four patients, decreased nerve conduction velocity in 10 patients, and four nerve biopsies demonstrated demyelinating neuropathy.

Diagnosed diseases following the administration of HBVv and the correlation of ASIA criteria to our results

In this cohort, various post-HBVv autoimmune and immune-mediated conditions were diagnosed

as specified in Table 2, of which 76% may be categorized as autoimmune and 24% as immune-mediated.

ASIA criteria[21] were applied to all 93 patients, of whom 71% were adults and 28.7% were children. In this cohort 80/93 patients (86%), comprising 57/59 (96%) adults and 23/34 (68%) children, fulfilled the required criteria for ASIA (Table 3). All patients in our cohort had a prior exposure to the vaccine, and 82% experienced the appearance of 'typical' manifestations of ASIA and therefore fulfilled the first two major criteria. Minor criteria were experienced by four patients. Among 13 patients who did not fulfill the ASIA criteria, 7/13 were males and 11/13 were children, nine of whom were diagnosed with type 1 diabetes mellitus.

Table 2 Defined diseases diagnosed following HBVv immunization

Diagnosed diseases:	*No. of patients*
Neurological diseases*	24 (25.8%)
Diabetes mellitus	10 (10.7%)
SLE	9 (9.6%)
Rheumatoid arthritis	8 (8.6%)
Autoimmune hepatitis	4 (4.3%)
Crohn's diseases	3 (3.2%)
Scleroderma	3 (3.2%)
Central pain syndrome**	19 (20.5%)
Other immune-mediated diseases	13 (13.9%)

*Neurological diseases include: multiple sclerosis, chronic inflammatory demyelinating polyneuropathy, neuromyelitis optica (Devic's syndrome), Guillain-Barre syndrome, transverse myelitis and cervical myelitis.
**Central pain syndrome includes chronic fatigue syndrome and fibromylagia.

Discussion

Autoimmune diseases affect 5–8% of the population, with a strong female predominance.[24–34] The prevalence of autoimmune diseases is determined by a mosaic of genetic susceptibilities, loss of immune regulation, changes in the hormonal milieu and exposure to environmental factors.[35] The latter include various causes such as UV light, toxins, drugs, infectious agents, vaccines and adjuvants.[36–39]

Immune adjuvants, such as those incorporated in human and animal vaccines, were considered in the past to be inert. Alas, their ability to induce, by themselves, immune-mediated or autoimmune reactions has now been established.[21–23]

The HBVv is composed of a recombinant viral antigen as well as an aluminum adjuvant. Hence, in the current study we analyzed the clinical manifestations of 93 patients who presented with immune/autoimmune conditions following HBVv administration. Of note, as this cohort was retrospectively analyzed and was composed of patients who sought legal assistance, only patients diagnosed with a defined condition following immunization were included. Recently a new syndrome was defined and termed ASIA, 'Autoimmune (Auto-inflammatory) Syndrome induced by Adjuvants'. This syndrome encompasses a wide variety of adjuvant-induced conditions, from vague non-specific

Table 3 The suggested criteria of 'ASIA' among 93 patients diagnosed with post-HBVv immune-mediated diseases

Major criteria:	Present in post-HBVv group
Exposure to an external stimulus (infection, vaccine, silicone, adjuvant) prior to clinical manifestations.	100%
The appearance of 'typical' clinical manifestations*	82%
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	80%
Other clinical manifestations (e.g. irritable bowel syndrome)	Not assessed
Specific HLA (e.g. HLA DRB1, HLA DQB1)	Not assessed
Evolvement of an autoimmune disease (e.g. multiple sclerosis, systemic scleroderma)	76%

*Typical manifestations of ASIA in the current cohort included:
- Myalgia, myositis or muscle weakness (43%).
- Arthralgia and/or arthritis (43%).
- Chronic fatigue (42%) non-refreshing sleep or sleep disturbances (19%).
- Neurological manifestations (66%).
- Cognitive impairment (7.5%), memory loss (15%).
- Pyrexia (18%).
- Dry mouth (4%).

manifestations to well-defined autoimmune diseases. Thus, our study represents only one side of the spectrum of the ASIA; nevertheless, it may serve as a validation cohort for the suggested criteria for this syndrome.

In this study, the typical gender bias was observed, and similar to most autoimmune diseases, 70% of the patients were female.[24] Most of these were diagnosed with a post-vaccination immune-mediated condition within a mean of 43 days, although the range of latency periods from the last dose of HBVv was between days and 2 years. Traditionally, a latency period of 3–6 weeks from exposure to a stimulus and the appearance of an immune-mediated disease was accepted.[38] However, variable latency periods have been documented in the current medical literature, such as the detection of autoantibodies years before diagnosis of a full-blown autoimmune disease.[40] Others have documented increment in titers of anti-cardiolipin antibodies years after exposure to infection stimuli,[41] or the appearance of autoimmunity months or years following immunization.[42] For instance, in a very large cohort a significant correlation between influenza vaccine and rheumatoid arthritis was observed 6–12 months following immunization,[42] as well as an association between HBVv and immune-mediated neuronal damage 3 years post-vaccination.[17]

Several plausible risk factors have been observed in our cohort. Interestingly, 47% of patients continued with the immunization protocol despite experiencing variable adverse events. One may raise the question of whether halting the immunization protocol would have been beneficial for this group. Another plausible risk factor is the personal or familial history of immune-mediated diseases, documented in 21% of our cohort. As the estimated prevalence of autoimmunity in the general population is smaller (5–8%), we may speculate that our cohort is genetically more susceptible to develop adverse immune responses. Moreover, in this study the data were collected retrospectively and therefore may represent an underestimation of the true prevalence of autoimmunity among family members.

Clinical manifestations reported by this group of 93 patients involved different organs and systems (neurological, musculoskeletal, gastrointestinal) as well as common constitutional ones (fatigue, fever). Several systems were commonly involved regardless of the defined diagnosis, such as neuro-psychiatric manifestations which were present in 70% of patients, although only 25% of this cohort were actually diagnosed with a neurological diseases such as multiple sclerosis, Guillain-Barré syndrome, transverse myelitis, etc. The association of HBVv with the development of post-immunization neuronal damage has been previously observed,[17,43–46] and may result either from the viral antigen or from the adjuvant.[13] Aluminum-associated neuronal toxicity has been suggested in humans and documented in animal models.[47] Other common manifestations were documented in this cohort, including musculo-skeletal and gastrointestinal complaints that may easily be ignored or regarded as not relevant by patients and physicians, but which were recently included in the ASIA criteria. The role of adjuvants in muscle inflammation and necrosis was described in macrophagic myofasciitis syndrome, and included in ASIA.[48]

ASIA includes four major and four minor criteria, and in order to diagnose ASIA, fulfillment of either two major or one major and two minor criteria is required.[21] These criteria enable the inclusion of patients with non-defined and well-characterized diseases under the spectrum of ASIA. Our cohort is composed only of patients who presented with various distinct diseases, although they share common clinical manifestations. A very similar list of manifestations was specified as a criterion of ASIA, termed 'typical' clinical manifestations, thus further supporting a common denominator for all patients diagnosed with ASIA.[21] Among our group of patients, 86% fulfilled the criteria of ASIA; 11/13 patients that did not fulfill the criteria were children, and of these, nine were diagnosed with type 1 diabetes. This raises the question of whether the ASIA criteria can be applied to children, especially those diagnosed with type 1 diabetes.

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. In addition, the 93 patients evaluated here had approached legal consultation, representing a very biased group. This bias may work both ways; on one hand, this may represent subjects who seek legal compensation and thus overestimate the association of their symptoms to immunization. On the other hand, non-defined conditions that are more frequently associated with ASIA maybe underestimated and rejected by legal representatives and thus be under-represented herein. Another limitation arose from our decision to include only those patients who experienced the appearance of a new autoimmune phenomena confirmed by a specialist. These inclusion criteria, although required while collecting retrospective

data, exclude patients with post-immunization exacerbation of previously diagnosed diseases. These limitations may be addressed in future larger prospective studies, as well as by utilizing animal models to evaluate causality.

Conclusion

This study, although limited by its retrospective and biased nature, is also, to the best of our knowledge, the largest case series to suggest a probable association between HBVv and immune-mediated diseases. Although causality can not be addressed in this study, several aspects of the link between immunization and autoimmunity have been enlightened. A temporal association of up to 2 years has been observed and stands in agreement with other prospective studies. Common clinical characteristics were present regardless of diagnosed disease, suggesting a common denominator in post-vaccination immune-mediated phenomena. Moreover, those clinical manifestations (neurological, musculoskeletal, gastrointestinal, fatigue, etc) may be regarded as 'typical' for ASIA, and thus can be addressed individually by the medical community in everyday practice as well as in future studies. Several risk factors have been put forward by our observations, such as the occurrence of early adverse event(s) or a personal/familial history of autoimmunity.

A rigorous attempt to estimate personal risk factors such as the correlation between early and late events, personal history and genetic profile should be addressed in future studies. Last but not least, 86% of our patients fulfilled the criteria of the newly diagnosed syndrome, ASIA. In our cohort the criteria were useful when put into clinical practice for evaluation of adults. The application of ASIA criteria and/or diagnosis to children, especially those diagnosed with type 1 diabetes, requires further study.

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Conflict of interest

The authors declare that they have no conflicts of interest except for Y Shoenfeld who has appeared in court for subjects afflicted by vaccines as a medical consultant.

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