Hepatitis B: Infection, Vaccination and Autoimmunity

Maya Ram MD[1] and Yehuda Shoenfeld MD[1,2*]

[1]Center for Autoimmune Diseases and Department of Medicine B, Sheba Medical Center, Tel Hashomer, Israel
[2]Sackler Faculty of Medicine, Tel Aviv University, Ramat Aviv, Israel

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The idea that infectious agents in general, and viruses in particular, could trigger the development of autoimmune diseases in genetically susceptible individuals has been raised in various clinical and epidemiological studies [1]. Also included in the medical literature are case reports, ecological association studies, as well as some animal studies relating to a wide range of autoimmune diseases temporally associated with vaccination [2]. In addition, vaccines contain peptides that are homologous to viral antigens. Therefore, it is not surprising that the question of whether vaccination could lead to autoimmune illness has been the focus of many scientific debates [3]. However, there is no conclusive evidence for a causal link between vaccination and the development of autoimmune diseases [4] since it has not been determined whether available epidemiological tools are sensitive enough to detect such a link [5]. The debate rages on.

Different studies have linked hepatitis B virus with various types of autoimmune phenomena – from the generation of autoantibodies to the development of autoimmune diseases [6]. Distribution of the hepatitis B vaccine indeed led to a dramatic reduction in HBV complications in countries that implemented large-scale vaccination programs [7], but large series of autoimmune adverse events were reported following this vaccine [8,9]. In this review we will summarize the relevant data regarding HBV and hepatitis B vaccination and their association with autoimmunity.

Hepatitis B infection

Hepatitis B is a hepatotropic virus that has infected two billion people worldwide. It is a major cause of liver disease and varies greatly in severity from person to person [10-12]. The intact infectious particle is composed of an inner core termed the nucleocapsid, which is covered with an envelope. The nucleocapsid contains hepatitis B core antigen (HBcAg), a major structural component of the nuclear capsid, hepatitis B e antigen (HBeAg) that is a secreted form of the viral core antigen, an incomplete double-stranded DNA molecule, and DNA polymerase with reverse transcriptase activity. The envelope is composed mainly of lipids and hepatitis B surface antigen (HBsAg), which is found both on the surface of the virus and as self-assembling, non-infectious spherical or tubular particles [10,13,14].

Hepatitis B vaccine

The first licensed hepatitis B vaccines were plasma derived and composed of purified HBsAg. Most currently available hepatitis B vaccines are produced by recombinant DNA technology [10]. These genetically engineered hepatitis B vaccines were first licensed in the United States in the 1980s. The current vaccine is most commonly produced by inserting the gene for the HBsAg into the yeast *Saccharomyces cerevisiae*. Following growth of the yeast, vaccine is prepared by lysing the yeast to free HBsAg particles that are separated from yeast components by biochemical and biophysical methods [8].

HBV infection, vaccination and autoimmunity

Many cases regarding the association of HBV, HB vaccination and autoimmunity were described in the literature. We have summarized the important data in Table 1. Hepatitis B surface antigen and antibody are seromarkers of both HBV infection and vaccination. Therefore, in some studies that presented an association between HBsAg or HBsAb and autoimmune disease, it was unclear whether it was the infecting agent or the vaccine that caused these phenomena. These cases appear in the Table under the column "Other associations."

Mechanism of autoimmunity induction

Autoimmune diseases develop in genetically susceptible individuals who encounter an environmental trigger such as viruses or vaccines. Once this condition is met, there is a break in self-tolerance and one or more of the following mechanisms occur:

Molecular mimicry is when the antigenic determinant of the infectious agent or the vaccine contain a sequence of amino acids sufficiently similar to a self-antigen to produce cross-reactivity [4,15].

Epitope spreading is defined as the process in which specific antiviral responses in the early stages of infection become less sharply defined and extend to self-antigens [16].

Bystander effect is a process whereby the continued immune response to infection and attendant inflammation allows exposure

* Incumbent of the Laura Schwarz-Kip Chair for Research of Autoimmune Diseases, Tel Aviv University.

HBV = hepatitis B virus
HBsAg = hepatitis B surface antigen

Table 1. Description of known association linking HBV infection, vaccination and different autoimmune diseases

AID	Association with HBV	Association with hepatitis B vaccine	Other associations*
MS	• Molecular mimicry between HBV-DNA polymerase and MBP that leads to EAE in animals [17,19].	• MS-like syndromes following hepatitis B vaccination using plasma-derived HBsAg [19]. • Several case reports in the literature on the onset or recurrence of demyelination symptoms shortly after HBV vaccination [2,4]. • Neurological symptoms and signs, as well as magnetic resonance imaging documenting central nervous system demyelinization appearing days to weeks after HBV vaccination [3]. • A nested case-control study conducted within the General Practice Research Database in Britain showed that HBV immunization was associated with a threefold increase in the incidence of MS for 3 years following vaccination [20]. • Several studies did not find an association between HBV vaccine and risk of MS [2,4]. • Other studies provide evidence against such an association [2].	• In one case a high titer of HBsAg correlated with acute demyelinating attacks [19].
APS	• Prolonged damage to hepatic tissue may stimulate the synthesis of aCL antibodies [21]. • Cell receptors for the lipid components of the HBV envelope include both annexin V and β2GPI, which may act as a trigger mechanism for a possible aCL response [22]. • Elevation of aCL antibodies in HBV-infected patients compared to controls [22]. • Harada et al. [21] showed that aCL antibodies were rarely positive in patients with chronic HBV infection.	• Healthy young population that was vaccinated for HBV showed elevated levels of aCL and one individual had anti-β2GPI [23].	
RA	• Patients with chronic HBV may have arthralgia or arthritis similar to RA [24]. • RF was present in 20–75% of patients with chronic HBV while anti-CCP was rarely found [24].	• Evidence for this association is limited to case reports or case series where most of the patients shared HLA types associated with RA [2,3,25]. • General Practice Research Database in the UK did not find an elevated risk of RA following HBV vaccination [2].	
SLE	• Lai et al. [26] did not find a high incidence of HBsAg or HBcAg in the glomerular immune complex deposits of patients with SLE.	• Some authors have described exacerbation and development of SLE following HBV vaccination [2,3,27]. • Vaccinating female lupus-prone (NZB x NZW) F1 mice with HBV vaccine led to increase in serum immunoglobulin G levels and a slight increase in ANA levels [5].	• Ziegenfuss et al. [28] found HBsAg in serum of SLE patients only after breaking down RF, which had previously been shown to be capable of masking HBsAg. • Looi and Prathap [29] found a high prevalence of HBsAg in glomerular immune complexes in lupus nephritis.
GN	• Lai et al. [30] showed glomerular deposits of immune complexes containing HBsAg and/or HBcAg in 41%, 61% and 60% of mesangial nephritis • IgA nephropathy and mesangial proliferative glomerulonephritis respectively.		• Maggiore et al. [31] found 8% of GN patients had HBsAg compared with 2.7% in the general hospitalized population of southern Italy.
PAN	• Guillevin et al. [32] showed that the cause in 33.7% of observed patients was HBV.		• Circulating immune complexes composed of HBsAg and Igimmunoglobulin have been detected in patients with PAN [33].
AIH	• Few case reports have linked HBV infection to AIH, particularly to type 1 [34]. • Czaja et al. [35] found that patients with severe autoimmune hepatitis typically lack serological markers of viral infection.		

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AID	Association with HBV	Association with hepatitis B vaccine	Other associations*
T1D	• Khuri et al. [36] demonstrated a significantly higher prevalence of HBV markers in diabetic subjects compared with controls. • Halota et al. [37] demonstrated HBcAb in the sera of 40% of patients with T1D.	• Accumulating human data from various epidemiological studies do not support a causal association between vaccination and an increased risk of T1D [4].	
Uveitis	• HBV infection may sensitize mononuclear cells to cross-react with self proteins such as retinal S-Ag through a molecular mimicry mechanism [38].		
Graves' disease		• Slightly elevated risk of Graves' disease following HBV vaccination [2].	
Pemphigus		• Case report describing the onset of pemphigus 3 months from HBV vaccination [9].	
Lichen planus		• Few case reports depicting the occurrence of Lichen planus following HBV vaccination [39].	
GBS		• This complication is very rare and statistically, apart from one study, there is no significant evidence of increased rate of GBS after HBV vaccine [40].	

* Refers to those cases that could have been the result of the infection or the vaccination.
AID = autoimmune disease, MS = multiple sclerosis, MBP = myelin basic protein, APS = antiphospohlipid syndrome, EAE = experimental autoimmune encephalomyelitis, aCL = anticardiolipin, β2GPI = beta-2 glycoprotein-I, RA = rheumatoid arthritis, RF = rheumatoid factor, anti-CCP = anti-cyclic citrullinated peptide antibody, HBcAg = HB core antigen, SLE = systemic lupus erythematosus, GN = glomerulonephritis, MN = membranous nephropathy, PAN = polyarteritis nodosa, AIH = autoimmune hepatitis, T1D = type 1 diabetes, GBS = Guillain-Barré syndrome.

of normally sequestered autoantigens to the immune response [16].

Microbial superantigens possess the ability to bind and activate a wide variety of T cells including those specific for a self-antigen [17].

Formation of immune complexes by viral antigens and antibodies generated against them. As a result, an immune response will develop to clear the complexes. A continuous presence of antigen in antibody complexes could result in the development of autoimmunity [18].

Expression of major histocompatibility complex class II molecules on non-immune cells could occur when viral infection or vaccination may produce interferon-gamma or other inflammatory cytokines in the target organ, which in turn induce human leukocyte antigen class II expression, for the first time, in non-immune cells. This can lead to presentation of autoantigens and activation of autoreactive T cells [5,18].

Direct inflammatory damage is another important mechanism caused by the inflammatory response to the microbial agent, resulting in cell destruction and the subsequent release of different cell ingredients. These cellular ingredients present to the immune system at the inflammation site, where they induce an immune response that may result in an autoimmune disease [17].

High levels of INFγ that follow vaccination could probably lead to the development of autoimmune diseases [4].

Vaccine components such as adjuvant (e.g., aluminum) stabilizers (e.g., gelatin), preservatives (e.g., thiomersal) and residual yeast proteins from cell cultures (e.g., fibronectin) might trigger the induction of autoimmunity [3,4,8].

Conclusions

Although the role of HBV infection and vaccination in the development of autoimmunity has been extensively discussed in the literature, it remains vague. Whether there is a causal relationship between them and the mechanisms leading to the autoimmune phenomena has yet to be discovered. As mentioned above, we know that the virus and vaccine share only the HBsAg and differ in other components, and that the autoimmune response could be the consequence of different mechanisms. For example, the virus contains the DNA polymerase that was found to share a amino acid sequence with myelin basic protein [17,19] although it might trigger autoimmunity via a molecular mimicry mechanism. The vaccine, for instance, is composed of an adjuvant that might lead to the development of autoimmunity [3,4,8].

We believe this topic warrants further research, since better understanding of the pattern leading to the autoimmune phenomena following infection or vaccination would generate great progress in the field of autoimmunity.

IFNγ = interferon-gamma

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Correspondence: Dr. Y. Shoenfeld, Head, Dept. of Medicine B, Sheba Medical Center, Tel Hashomer 52621, Israel.
Phone: (972-3) 530-2652
Fax: (972-3) 535-2855
email: shoenfel@post.tau.ac.il

The only way to have a friend is to be one

Ralph Waldo Emerson (1803-1882), American essayist and poet.