REVIEW ARTICLE

The Extrahepatic Manifestations of Hepatitis B Virus

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ABSTRACT

Hepatitis B Virus (HBV) leads to a number of hepatic complications, from acute to chronic hepatitis, cirrhosis and hepatocellular carcinoma, is a well-established fact. Upcoming clinical research, over the years, associates numerous extrahepatic manifestations during the acute and chronic episodes of hepatitis B with significant morbidity and mortality. A causal relationship between HBV and serious autoimmune disorders has also been observed among certain susceptible vaccine recipients in a defined temporal period following immunization. The cause of these extrahepatic manifestations is generally believed to be immune mediated. The most commonly described include skin rash, arthritis, arthralgia, glomerulonephritis, polyarteritis nodosa, and papular acrodermatitis etc. The serum-sickness like "arthritis-dermatitis" prodrome has also been observed in approximately one-third of patients acquiring HBV infections. Skin manifestations of HBV infection typically present as palpable purpura reported to be caused by chronic HBV, although this association remains controversial. To consider the relationship between HBV and other clinically significant disorders as well as serious autoimmune disorders among certain vaccine recipients is the topic of this review. Variable factors that influence extrahepatic manifestation are discussed, including possible synergy between hepatitis B virus and the immune system.

Key words: *Hepatitis B virus. Acute. Chronic. Autoimmunity. Immunization. Extrahepatic.*

INTRODUCTION

Hepatitis B Virus (HBV) is ubiquitous in attaching liver but it also has been seen to establish persistent infections on many other human organs. However, the evidence of a putative HBV association with other organs needs to be investigated. Liver has been the sole target for research on hepatitis B virus for the past 40 years. Scientists and clinicians had been more interested in knowing the genotypes, their differences in biological properties, the prevalence of hepatitis B virus mutants in various geographic regions, the clinical outcome and response to antiviral treatment in different population groups.[1,2] There are scattered reports of hepatitis B virus association with other organs and as such no comprehensive study or review is available to study the manifestations expansively. Now, acknowledging its association with a spectrum of extra-hepatic manifestations,[3] there is a need to assess the molecular systems in depth. The intracellular mechanisms and the involvement of immune system need to be evaluated to discern the exact mechanism of these manifestations.

The objective of this review was to highlight the relationship between HBV and other clinically significant disorders as well as serious autoimmune disorders among certain vaccine recipients also the variable factors that influence extrahepatic manifestation during HBV infection are discussed, including possible synergy between hepatitis B virus and the immune system.

Hepatitis B Virus (HBV) is a noncytopathic, hepatotropic virus with a 3.2-kb circular DNA genome that encodes four overlapping 3.5-, 2.4-, 2.1-, and 0.7-kb unspliced messages that terminate at a common polyadenylation site.[4] The host-virus interactions involved in viral clearance and disease pathogenesis has been extensively studied in HBV transgenic mouse model,[5-8] and will be discussed here, briefly.

Immune Complexes

Surface antigen-antibody complexes, created during hepatitis B infection, are found in the sera of all patients with fulminant hepatitis but are seen only in some patients during acute phase of the illness. These immune complexes have been detected by electron microscopy and have been identified in variable proportions of patients with virtually all the recognized chronic sequelae of acute hepatitis. Immune complexes also are important in the pathogenesis of other disease syndromes characterized by severe damage of blood vessels (for example, polyarteritis nodosa, some forms of chronic glomerulonephritits, and infantile papular acrodermatitis). The deposits of such immune complexes have been demonstrated in the cytoplasm and plasma membrane of hepatocytes and on or in the nuclei, whereas, a small proportion of patients with circulating complexes develop other conditions such as vasculitis or polyarteritis etc.[9]

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This is because of the fact that, as more and more antigen-antibody complexes are formed, some of them are deposited in vascular beds. Antibodies in these complexes have been implicated to activate complement. Complement activation promotes inflammation mainly by production of chemotactic factors, mainly C5a, which direct the migration of polymorphonuclear leukocytes and monocytes and by release of anaphylatoxins (C3a and C5a), which increase vascular permeability. The leukocytes that are drawn in by the chemotactic factors are activated by the engagement of their C3b and Fc receptors by the immune complexes.[10] This results in the release or generation of a variety of pro-inflammatory substances, including prostaglandins, vasodilator peptides, chemotactic substances, oxygen free radicals and several lysosomal enzymes. Immune complexes also cause aggregation of platelets and activation of Hageman factor. Both of these reactions augment the inflammatory process and initiate the formation of microthrombi. Because the complexes are deposited mainly in small arteries, renal glomerul, and the synovia of joints, the clinical manifestations are vasculitis, nephritis, and arthritis (Figure 1).[11]

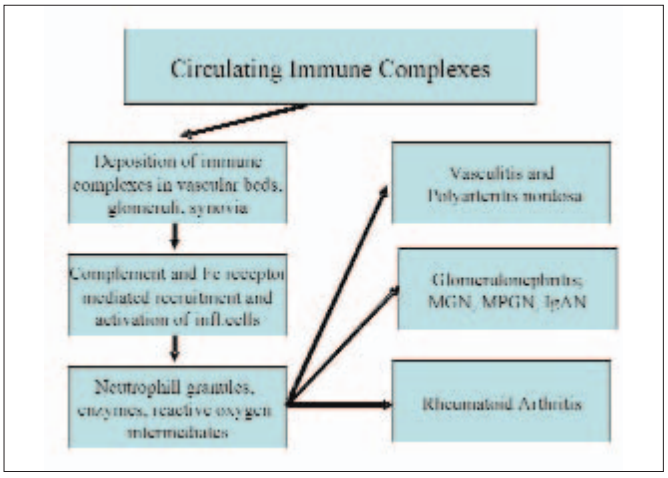

Figure 1: Pathogenesis of immune complex-mediated diseases in HBV infections.

Cell Mediated Immunity Against HbsAg

The vigor and kinetics of the cellular immune response to HBV, especially the cytotoxic T-lymphocyte (CTL) response, determines the outcome of HBV infection.[12] These HBV-specific CTLs can downregulate hepato-cellular HBV gene expression and replication by a noncytopathic, cytokine-induced process that is mediated by inflammatory cytokines such as gamma interferon (IFN-γ) and tumor necrosis factor alpha (TNF-α) secreted by the CTLs following antigen recognition in the liver.[13] These cytokines downregulate HBV gene expression posttranscriptionally.[14] Thus, evidence suggests that the pathogenesis of liver damage in the course of hepatitis B infection is related to the immune response by the host. Cellular immune responses are known to be particularly important in determining the clinical features and course of viral infections. The occurrence of cell-mediated immunity to hepatitis B antigens has been demonstrated in most patients during the acute phase of hepatitis B and in a significant proportion of patients with surface-antigen-positive chronic active hepatitis, but not in asymptomatic persistent hepatitis B carriers. These observations suggest that cell-mediated immunity may be important in terminating the infection and, under certain circumstances, in promoting immune-mediated liver damage and in the genesis of autoimmunity. Also, evidence suggests that progressive liver damage may result from an autoimmune reaction directed against hepatocyte membrane antigens, initiated in many cases by infection with hepatitis B virus.[9]

Genotype and Subtype-related Clinical Differences

Remarkable clinical and pathogenic differences do exist among HBV genotypes; however, the clinical picture, the response to treatment and the long-term prognosis may differ depending on which genotype/subtype has infected the patient. There is increasing evidence of clinical differences between subtypes and genotypes at various levels regarding extra hepatic expressions. Early studies demonstrating subtype-related clinical differences include the association of Gianotti's disease with subtype ayw in Japan and a higher frequency of liver dysfunction in adr-infected patients compared to those infected with adw.[15-18] Taking into account that genotype C strains are most often of subtype adr, the latter results have been confirmed by several studies of Southeast Asian chronic carriers.[19-21]

Clinical Implications of the Above Immune Responses

All disorders associated with hepatitis B virus infection have been reported with some peculiar symptoms. The prevalence of such clinically important manifestations is relatively low, but it can be associated with significant morbidity and even mortality. An awareness and recognition of these manifestations is of paramount importance in facilitating early diagnosis and in offering treatment.[22] As in liver disease of non-viral etiology, these HBV related extra hepatic manifestations are non-specific for HBV infection. Table I highlights some of the distinct clinical conditions in which the underlying disease is specifically due to HBV. The variety of disorders is mainly based on immune complex reaction that includes skin rash, arthritis, arthralgia, glomerulonephritis, polyarteritis nodosa, and papular acrodermatitis etc. The precise pathogenesis of these extrahepatic complications has not been fully determined, although the majority represents the clinical

expression of autoimmune phenomena. The concept is that lesions could result from the deposition of viral Antigen/Antibody complexes soluble in Ag excess, possibly involving HBe Ag.[23] Extrahepatic manifestations of hepatitis B infection can occur and are commonly limited to the gastrointestinal system. Acute glomerulonephritis can occur along with acute tubular necrosis, commonly seen in hepatic failure (Table I).[9]

Table I: Diseases associated with Ag-Ab complexes.

Syndrome	Symptoms
Serum sickness syndrome	Fever (<39°C), skin rash erythematous, macular, macopapular, urticarial, nodular or petechial lesions.
Polyarthralgia, polyarthritis	Acute articular symmetrical inflammation, painful, fusiform swelling of joints of hand and knee, morning stiffness.
Dermatologic manifestations	Pitted keratolysis, urticaria, purpura, oral lichen planus.
Gianotti-Crosti syndrome	A distinctive disease of childhood, with skin lesions, lentil-sized, flat, erythematous, and papular eruptions appear which are localized to the face and extremities-- have HBsAg and an IgM type anti-HB core as causative agent

The IgG concentration of immune complexes have been found greater in patients with acute hepatitis B compared to other conditions.[24] More importantly, the presence, composition, and concentration of these circulating immune complexes correlates with the clinical findings of rash, arthritis, and angioedema, which strongly suggests an etiological relationship. Although circulating immune complexes are present in both acute hepatitis with and without arthritis, their composition differs significantly in several important respects. First, complement components C3, C4, and C5 and IgA were detected only in cryoproteins isolated from patients with arthritis complicating hepatitis, and the IgG subtypes in these immune complexes were predominantly the complement-fixing IgG1 and IgG3.[25] Chronic HBV infection presents as one of three potentially successive phases-immunotolerant, immunoactive, and low- or non-replicative (grade A). In the immunotolerant phase, serum HBsAg and HBeAg are detectable and serum HBV-DNA levels are high.[26] The extrahepatic syndromes associated with chronic HBV infection are again immune-mediated and contribute significantly to morbidity and mortality.[27] Immunologic manifestations include circulating autoantibodies and concurrent autoimmune disorders.[28] The possible mechanisms, include deposition of circulating immune complexes (IC's), induction of local IC formation by viral antigens, reaction with tissue antigens by viral-induced autoantibodies or a direct viral reaction to extrahepatic tissue sites.[27]

Transient Serum Sickness-like Syndrome: In 10-20% of hepatitis B patients as extrahepatic manifestations are seen as transient serum-sickness like syndrome.[29] Pathogenesis in the serum sickness association is with circulating immune complexes composed of HBsAg in antigen excess and anti-HBR with subsequent consumption of complement components.[24] Symptoms usually precede the onset of jaundice by a few days to 4 weeks and subside after onset of jaundice and may persist throughout the course of the disease. Usually manifest with fever (<39°C), skin rash (erythematous, macular, maculopapular, urticarial, nodular, or petechial lesions), polyarthritis (acute articular symmetrical inflammation, painful, fusiform swelling of joints of hand and knee, morning stiffness. No recurrent or chronic arthritis occurs after recovery.[29-32]

Lichen Planus: The prevalence of oral lichen planus and pitted keratolysis in HBsAg carrier group was significantly higher than that of controls. HBsAg positivity may induce or cause proneness to oral lichen planus and pitted keratolysis with some mechanism that needs to be elucidated.[23]

Gianotti-Crosti Syndrome: Papular acrodermatitis of childhood or Gianotti-Crosti syndrome is a distinctive disease of childhood. Skin lesions, lentil-sized, flat, erythematous, and papular eruptions appear which are localized to the face and extremities.[29] The association of Gianotti-Crosti syndrome was reported as ealy as 1976 by Ishimaru *et al.*[14] More reported cases of Gianotti-Crosti syndrome caused by hepatitis B virus (HBV) infection, were evaluated to have HBsAg and an IgM type anti-HB core as causative agent.[33] Analysis of the virus revealed it to be genotype D with the HBsAg serotype *ayw3*. There is possibly a relationship between Gianotti-Crosti syndrome and the D genotype of HBV.

Arthritis Associated with Acute HbsAg+ve Hepatitis: Anti-HB was detected in the cryoprotein complex in all patients with arthritis. Hepatitis-B antigen titers were highest during joint symptoms consistent with the presence of soluble circulating immune complexes in antigen excess.[34,35] Anti-HB has been detected in the cryoprotein complex in patients with arthritis. Anti-HB8 appear before detectable serum levels and is concentrated several-fold when compared to serum titers. A sequential study demonstrated the appearance of anti-HB in the cryoprotein complex was found associated with detectable IgM, suggesting the primary immune response to HbsAg.[36, 37]

HBV-Associated Glomerulonephritis (GN)

The association between chronic HBV and renal disease dates back to the mid 1970s. Brazosko *et al.* in 1974 were the first to suggest that HBV might be involved in the pathogenesis of high percentage of GN and found the incidence 34.6% with various types of glomerular diseases.[38] Subsequently incidences reported were by Nagy et al as 34.6%.[39] Over the last few years, various morphologic patterns of HBV-related glomerulonephritis have been reported, with Membranous Glomerulonephritis (MGN) being the most

commonly described.[40,41] This extrahepatic syndrome occurs mainly in children, predominantly males, in HBV endemic areas of the world. In these children, liver tests are frequently normal and 60% show spontaneous complete remission in follow-up.[44] In adults, spontaneous remission of HBV-related MGN rarely occurs and a slow progression to chronic renal failure is reported in about 50% of patients.[42] The three main GN associated with HBV infection are Membranous Glomerulonephritis (MGN), Membrano Prolipherative Glomerulonephritis (MPGN) and IgA Nephropathy (IgAN) (Table II).[43]

Table II: Diseases of renal and other organs associated with hepatitis B infection.

Syndrome	Manifestations
Glomerulonephritis	1. Membranous Glomerulonephritis (MGN). 2. Membrano Prolipherative Glomerulonephritis (MPGN). 3. IgA Nephropathy (IgAN).
Polyarteritis nodosa	Occurs at any time in patients who are HBsAg+. Circulating immune complexes containing viral proteins have been implicated in the pathogenesis of hepatitis B virus (HBV) related PAN.
Putative associations	RA, polymyalgia rheumatica, dermatomyositis,uveitis, myocarditis, neurological diseases.

Membranous Glomerulonephritis: MGN has been more frequently reported in Asian populations and in pediatric cases.[44] The diagnosis of HBV-associated MGN is based on the presence of persistent HBV antigenemia, detection of at least one HBV antigen in renal tissue and no other causes of Glomerulonephritis. Lai *et al.* studied a large series of patients with HBV-associated GN, detecting HBV antigen in renal tissue by a monoclonal F(ab) antibody method.[47] The disease is usually self-limited in several months to years (85% by 2 years, 95% by 5-7 years), especially in children with membranous glomerulonephropathy (MGN). This resolution is often associated with HBeAg seroconversion and there is only rare progression to renal failure.[45]

Membrano-Proliferative Glomerulonephritis: HBsAg has been detected with MPGN and IgAN patients. Histologically, MPGN is associated with mesangial and capillary wall deposits of HBsAg. The pathogenesis most likely involves glomerular deposition of circulating IC containing HBV antigens. With persistent viral infection, the heightened immune response favors formation of circulating IC's, with ultimate deposition into extrahepatic sites.[45] Dense deposits bearing HBsAg immunoreactivity in a thickened glomerular basement membrane has been found in these patients.[46]

IgA **Nephropathy**: Sometimes with mesangial IgA deposition at immunofluorescence, in association with IgG sub epithelial deposits, giving a combination of MGN and IgAN.[47] Electron microscopy, besides the typical sub epithelial deposits, frequently shows tubulo-reticular inclusions, made of branched microtubules, located within dilated cisternae of the endoplasmic reticulum belonging to the endothelial cell cytoplasm of glomerular and peritubular capillaries. They are the expression of endogenous virus-induced interferon production.[48] The clinical presentation of HBV-related MGN was in most cases a nephrotic syndrome, in the asymptomatic cases proteinuria, chronic renal failure, impairment of renal function and hypertension.[40] Because of high frequency of HBV asymptomatic carriers in the general population, it is difficult to establish and asses the relation between HBV and GNs. HBV and MGN need not be causally related, there may be an interaction between virus and vulnerable individuals due to biosocial or genetic background.[48] Secondly, the reduction of clinical and laboratory signs of nephropathy, spontaneously after successful treatment of the HBV infection, favors an etiopathogenic link between HBV and GN.[49,50]

Polyarteritis Nodosa: PAN is a primary systemic necrotizing vasculitis. HBV infection, characterized by hepatitis B surface antigen positivity (HBsAg+), can cause a vasculitis that almost always takes the form of PAN. Polyarteritis may occur at any time in patients who are HBsAg+. Circulating immune complexes containing viral proteins have been implicated in the pathogenesis of hepatitis B virus (HBV) related PAN. Only 1% or less of the total population of patients who are HBsAg positive develops PAN, Clinical symptoms of non–HBV related and HBV related PAN are the same except for orchitis, which appears to be more frequent in groups with HBsAg positive.[51] Janssen *et al.* reported in 2004 acute HBV positive patients with a confirmed diagnosis of PAN. HBV-DNA was isolated and amplified before and after Interferon treatment.[52] Clinical remission of PAN was observed in treated patients, but in none of the patients who were not receiving antiviral medication. Analysis of the HBV genome revealed no mutations that could be associated with PAN. In one patient a stop codon in the pre-core region and a double mutation A1762T-G1764A were found during antiviral therapy. The pathogenesis of hepatitis B virus-associated polyarteritis nodosa has therefore been attributed to immune-complex deposition with antigen excess. Importantly, the frequency of HBV-PAN has decreased in relation to improved blood safety and vaccination campaigns.[53]

Syndromes Following Hepatitis B Vaccination

HBV vaccination may induce hypersensitivity and autoimmune reactions in susceptible individuals and healthy Subjects. Vaccine Adverse Event Reporting System (VAERS) and PubMed (1966-2003) were searched for autoimmune conditions following

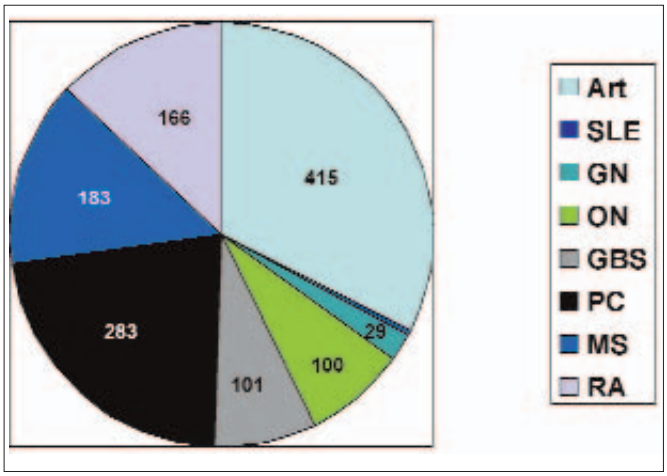

Figure 2: Distribution of cases caused by hepatitis B vaccination.[54] Art= Arthritis, RA= Rheumatoid arthritis, MS= Myelitis, SLE= Systemic lupus eryt, ON= Optic neuritis, GBS= Guillain-Barre syndrome, GN= Glomerulonephritis, PC= Pancytopenia / thrombocytopenia, and MS= Multiple sclerosis

hepatitis B vaccination (HBV). There were 415 arthritis, 166 rheumatoid arthritis, 130 myelitis, 4 SLE, 100 optic neuritis, 101 GBS, 29 glomerulonephritis, 283 pancytopenia/thrombocytopenia, and 183 MS events reported following HBV vaccination.[54]

HBV-related Dermatological Manifestations: Various cutaneous disorders associated with hepatitis B virus infection, reported so far, almost all had some peculiar eruptions or some disorders mainly based on immune complex reaction. Skin rashes in chronic HBV are more likely to have palpable purpura, which histologically is a neutrophilic necrotizing vasculitis involving small vessels.[55]

Bullous Pemphigoid: Bullous pemphigoid (BP) an acquired autoimmune bullous disorder of the elderly, transpire following various vaccines and tetanus toxoid booster is well documented, especially in children where BP is rare and the cause is unknown.[56] This lesion developed following one week after hepatitis B immunization in a Turkish Caucasian child. This case suggests that the hepatitis B surface antigen can function as the triggering factor for bullous pemphigoid lesion by inducing a nonspecific immune reactivation which unmasks sub clinical Bullous pemphigoid or by stimulating a specific antibody production that may cross-react with Bullous pemphigoid antigens.[57]

HBV-Associated Polymyalgia Rheumatica: Serious reactions like arthritic, neurologic, immunologic, and gastrointestinal following, adult hepatitis B vaccination (HBV) have been observed. Some reactions may be acute and self-limiting that does not lead to chronic problems, but chronic conditions may occur similarly following adult HBV adult vaccine.[58]

HBV-overlaping with TB and HIV: Hepatitis B and C has been found overlapping with TB and HIV in the newly independent states of Eastern Europe and Central Asia. Viral hepatitis is highly prevalent among prisoners HBV 24.1%, injection drug users HBV 55%, the homeless HBV 4.8%, and people in tuberculosis treatment programs HBV or HCV: 22.4%.[59]

HBV-associated Psychological Problems: A high prevalence of HBV infection with mental illnesses has been reported.[60-62] The prevalence of serological markers for the human hepatitis B virus in a psychiatric patients was first observed by Prats et al in 1990.[63] Both hepatitis B surface antigen (HBsAg) and HBV-DNA have been detected in cerebrospinal fluid (CSF), A markedly elevated level of CSF adenylate kinase (AK), suggests an organic brain disorder. Demonstration of intra-blood-brain barrier production of IgG supports the possibility of local infection by HBV within the central nervous system.[64]

Neurologic Manifestations: Peripheral neuropathy was described in a patient with chronic HBV.[65] Guillain-Barre syndrome has been reported to be associated with chronic HBV, but this is unconfirmed.[66]

CONCLUSION

A spectrum of extrahepatic manifestations are associated with HBV infection, some with devastating consequences, though the hepatic manifestations are often mild. There is causal relationship between HBV and serious autoimmune disorders among certain susceptible vaccine recipients in a defined temporal period following immunization. Immune complexes (e.g. surface antigen-antibody) are important in the pathogenesis of other disease syndromes characterized by severe damage of blood vessel. The physician while treating hepatitis B infection should also evaluate the patient for any extra hepatic manifestation. Similarly, while immunizing adults should also weigh the small risks of the adverse effects of HBV, with the risk of exposure to deadly hepatitis B virus.

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