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Review Article

Hepatitis B and skin: review

Zonunsanga

Department of Dermatology, RNT Medical college, Udaipur, Rajasthan, India

Corresponding author: Dr. Zonunsanga, E-mail: jrkos04@gmail.com

ABSTRACT

Hepatitis B virus (HBV) infection and its complications have become a global health problem. The spectrum of HBV infection ranges from asymptomatic carrier state to chronic hepatitis. It is usually preceded by constitutional symptoms. It has a wide range of dermatological manifestations. This review includes the pathogenesis along with the pathophysiology with their clinical significance and overview of the treatment.

Key words: Hepatitis B; Concomitant infection; Re-infection; steatorrhea

Hepatitis B virus (HBVDNA virus), a double-shelled virion (surface and core), is a member of the hepadnavirus family, classified as hepadnavirus type-1. It is a partially single stranded, partially double-stranded. The spectrum of HBV infection ranges from asymptomatic carrier state to chronic hepatitis, which may progress to cirrhosis and end-stage liver disease. It is estimated that 15-40% of people with chronic HBV will progress to cirrhosis [1,2].

EPIDEMIOLOGY

Hepatitis B virus (HBV)infection and its complications have become a global health problem. Approximately 400 million people are chronic HBV carriers worldwide.

Age

The severity of a hepatitis B virus (HBV)infection seems to be related with age. Fortunately, majority (around 95%)of adults and older children who are infected with HBV clear the virus within four months after they get infected. The rest progress to chronic state. Chronic infection with HBV is more common in infants and children. Around ninety percent of infants who are infected with hepatitis B during delivery are expected to become chronically infected with the virus [1-4].

Serotypes and genotypes

Genotype A is most commonly found in the US, Africa, India and Europe. Genotype B and C are most commonly found in Asia and US. Genotype D is most commonly found in Southern Europe, Turkey, India and US. Type E is most commonly found in West and Southern Africa. Type F is most commonly found in Central and South America. Genotype G is found in France and US. Type H is most commonly found in Central and South America and US [1-6].

TRANSMISSION

Hepatitis B can be transmitted sexually, through injection drug use, during delivery of an infant and through other types of blood exposure, fomites (toothbrushes, razors, etc). HBV can remain infectious outside of the body for up to seven days [2-9].

HIGH RISKS GROUP

High risks group includes people with multiple sex partners, previously infected with STD, homosexual men, people who have a sexual partner with hepatitis, people who are addicted to injection drugs or who have partners who use them, people who share a household with someone chronically infected with hepatitis, Health care workers, Dialysis patients, patients with

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HCV and HIV infections and patient who is taking immunosuppressive or cytotoxic therapy [2-9].

PATHOGENESIS

The mechanism of extrahepatic syndromes seen with chronic viral hepatitis appears to be immune-mediated, including deposition of circulating immune complexes, induction of local immune complex formation by viral antigens, reaction with tissue antigens by viral-induced auto antibodies or direct viral reaction to extrahepatic tissue sites [7-11].

Concomitant infection

Hepatitis D (HDV) can occur only with a concomitant hepatitis B infection, because HDV uses the HBV surface antigen to form a capsid. Co-infection with hepatitis D increases the risk of liver cirrhosis and liver cancer [7-11].

Reactivation

Hepatitis B virus DNA persists in the body after infection and in some people the disease recurs. Reactivation is seen in following alcohol or drug use, people with impaired immunity, Males with baseline ALT of 200 UL/L are three times more likely to develop a reactivation than people with lower levels, people who undergo chemotherapy have a higher risk, Immunosuppressive drugs favor increased HBV replication while inhibiting cytotoxic T cell function. Although those with detectable HBs Ag in their blood are at the greatest risk, those with only antibodies to the core antigen are also at risk [4-11].

CLINICAL FEATURES

The incubation period of Hepatitis B is 30– 180 days (mean 60 – 90 days).

Dermatological signs and symptoms [12-22]

1. **Jaundice**
   This is yellow discolouration of sclera ad/or skin due to deposition of bilirubin. Jaundice is usually visible in the sclera or skin when the serum bilirubin value is >43 mol/L (2.5 mg/dL).
2. **Pruritus**
   This is due to deposition of bile salts and toxins which are not metabolized due to impaired liver function. It tends to be generalized, but worse on the hands and feet. Although the severity of pruritus is not directly associated with the level of bile salts and toxic substances, lowering bile salt levels can mitigate symptoms.
3. **Spider angiomas**
   Spider angiomas or spider nevi, are collections of dilated blood vessels near the surface of the skin. They appear as slightly raised, small, reddish spots from which fine lines radiate outward, giving them a spider-like appearance.
4. **Bier spots**
   Bier spots are small, irregularly shaped, hypopigmented patches on the arms and legs. They are likely due to venous stasis associated with functional damage to the small vessels of the skin.
5. **Paper-money skin**
   Paper-money skin (or "dollar-paper" markings) describes the condition in which the upper trunk is covered with many randomly scattered, needle-thin superficial capillaries. It often occurs in association with spider angiomas.
6. **Palmer erythema**
   It occur anywhere on the palm and fingers but is most common on the hypothenar eminence. It can occur in a number of liver conditions but most often with cirrhosis.
7. **Xanthelasma**
   It is a localized cholesterol deposit beneath the skin, often presents as a painless, yellowish, soft plaque with well-defined borders, which may enlarge over the course of weeks. Several liver diseases can lead to various forms of secondary dyslipoproteinemia leading to this condition.
8. **Bleeding, petechiae and bruising**
   Liver disease can cause hypersplenism and thrombocytopenia and decrease in clotting factors. These may present purpura, bleeding gums and easy bruising and bleeding, even with minor trauma.
9. **Hyperpigmentation of the skin**
   It may accompany cirrhosis.
10. **Dupuytren contracture**
    Dupuytren contracture is characterized by progressive fibrosis and thickening of tendons in the palmar fascia, the connective tissue that lies beneath the skin of the palms. It is seen in cirrhosis. The reason behind this is still to explore.
11. **Disseminated superficial porokeratosis**
    Both humoral and cell-mediated immune responses are impaired in liver disease which favors development of porokeratosis. These lesions can

transform into squamous cell carcinoma.

12. **Granuloma annulare**
    It is not only associated with hepatitis B infection, is also reported with hepatitis B vaccination [17,18].
13. **Lichenoid eruption**
    Although this is not directly associated with Hepatitis B infection, it is reported to be associated with hepatitis B vaccination [19,20].
14. **Alopecia**
    Alopecia is also reported to be associated with both HBV and HCV infections [21].
15. Other reported associated skin diseases are Giannoti-crosti syndrome, serum sickness, urticaria and angioedema, EM-Like lesions and Polyarteritis Nodosa.
16. **Hair changes**
    Patients with hepatocellular dysfunction may develop hair-thinning or hair loss.
17. **Nail changes**
    Nail changes are seen such as clubbing, leukonychia (whitening), or onycholysis, Terry's nail, affecting the nails of the hands and feet.

Extra hepatic sites

Hepatitis B may affects extra hepatic sites, including lymph nodes, bone marrow, circulating lymphocytes, spleen, and pancreas [23-26].

Constitutional symptoms

Approximately 70% of people who become infected with hepatitis B will show some symptoms, usually within three months of infection and may include jaundice (yellowing of the skin/whites of the eyes), fatigue, abdominal pain, loss of appetite, nausea, vomiting, joint pain, low grade fever and flu-like symptoms. In general, children are less likely to experience symptoms than adults [3-7,12-17,23-26].

INVESTIGATIONS

Blood

Neutropenia and lymphopenia are transient and are followed by a relative lymphocytosis. Atypical lymphocytes (varying between 2 and 20%)are common during the acute phase. Blood sugar should be checked as prolonged nausea and vomiting, inadequate carbohydrate intake and poor hepatic glycogen reserves may contribute to hypoglycaemia. The serum aminotransferases aspartate aminotransferase (AST) and ALT (previously designated SGOT and SGPT) show a variable increase during the prodromal phase of acute viral hepatitis and precede the rise in bilirubin level. The acute level of these enzymes, however, does not correlate well with the degree of liver cell damage. Mild elevation of the gamma globulin is common during acute viral hepatitis. Serum alkaline phosphatase may be normal or only mildly elevated, while a fall in serum albumin is uncommon. Measurement of the prothrombin time (PT)is important in patients with acute viral hepatitis, for a prolonged value may reflect a severe hepatic synthetic defect, signify extensive hepatocellular necrosis, and indicate a worse prognosis [14-16,23].

Stool and urine examination

May be done as mild and transient steatorrhea as well as slight microscopic hematuria and minimal proteinuria are seen in some patients[14,15].

Serology

1. **Serum IgG and IgM levels**
   They are elevated in viral hepatitis. IgM reflects acute infection. During the acute phase of viral hepatitis, antibodies to smooth muscle and other cell constituents may be present and low titers of rheumatoid factor, nuclear antibody and heterophil antibody can also be foundoccasionally [14,23-27].
2. **Antibodies to LKM**
   They may be positive in case of Hepatitis D.
3. **HBsAg**
   A diagnosis of HBV infection may be made by detection of HBs Ag in serum. The titer of HBsAg bears an inverse with the degree of liver cell damage [14,15,23-27].
4. **IgM anti-HBc**
   The levels of HBs Ag may be too low to be detected during acute HBV infection, even with contemporary, highly sensitive immunoassays. In such cases, the diagnosis can be made by detection of IgM anti-HBc [14,15,23-27].
5. **HbeAg**
   It is an indicator of relative infectivity. HBeAg testing is indicated primarily during follow-up of chronic infection because HBeAg is invariably present during early acute hepatitis B [14,15,23-27].
6. **Anti-HBs**
   This is rarely detectable in the presence of HBsAg in patients with acute hepatitis B, but 10–20% of persons with chronic HBV infection may harbor

low-level anti-HBs. It has no recognized clinical significance. After immunization with hepatitis B vaccine, which consists of HBsAg alone, anti-HBs is the only serologic marker to appear [14,15,23-27].

7. **PCR assay**
   PCR assay can detect as few as 10 or 100 virions/mL. The commercially available PCR assay is the most useful, with highest sensitivity (5–10 IU/mL)and the largest dynamic range (10^0–10^9 IU/mL). With increased sensitivity, amplification assays remain reactive well below the threshold for infectivity and liver injury [14,15,23-27].

TREATMENT

Most cases of typical acute viral hepatitis do not require specific treatment.

Pruritus

It is very resistant to therapy. Cholestyramine at a starting dose of 4 g/day, gradually increased to 24 g/day in two doses at mealtimes. If the pruritus does not respond adequately to cholestyramine or the patient cannot tolerate the drug, then the antituberculosis drug rifampin can be tried. Rifampin promotes metabolism of endogenous pruritogens and has been effective against cholestatic pruritus when started at 150 mg/day and increased up to 600 mg/day, depending on the clinical response. Third-line drug therapies include opioid antagonists such as naltrex one and nalmefene. Plasmapheresis can be considered if drug therapy fails. The other options include antioxidant treatment, light therapy and even Liver transplantation for intractable pruritis when all other options failed [27-32].

Fulminant hepatitis

The goal of therapy is to support the patient by maintenance of fluid balance, support of circulation and respiration, control of bleeding, correction of hypoglycemia and treatment of other complications. Protein intake should be restricted. Oral lactulose or neomycin may be administered. Glucocorticoid, exchange transfusion, plasmapheresis, human cross-circulation, porcine liver cross-perfusion, hemoperfusion and extracorporeal liver-assist devices have not been proven to enhance survival. The prophylactic antibiotic coverage improves survival. Orthotopic liver transplantation shows excellent results in patients with fulminant hepatitis [27-32].

Pharmacological therapy

The drugs which have been approved for treatment of chronic hepatitis includes injectable interferon (IFN) and oral agents such as lamivudine, adefovir dipivoxil, entecavir, telbivudine and tenofovir [27-32].

Lamivudine

The nucleoside analogues approved, the dideoxynucleoside lamivudine, inhibits reverse transcriptase activity of both HIV and HBV and is a potent and effective agent for patients with chronic hepatitis B. The daily doses of 100 mg for 48–52 weeks suppressed HBV DNA by a median of approximately 5.5 log10 copies/mL and to undetectable levels, as measured by PCR amplification assays [27-32].

Interferon

IFN- was the first approved therapy for chronic hepatitis B. It is no longer used to treat hepatitis B. For immunocompetent adults with HBeAg-reactive chronic hepatitis, a 16-week course of IFN given subcutaneously at a daily dose of 5 million units, or three times a week at a dose of 10 million units, results in a loss of HBeAg and hybridization-detectable HBV DNA (i.e. a reduction to levels below 105 –106 virions/mL)in 30% of patients, with a concomitant improvement in liver histology. Seroconversion from HBeAg to anti-HBe occurs in approximately 20 [27-32].

Adefovir Dipivoxil

The oral dose of 10 mg per day of Acyclic nucleotide analogue Adefovir dipivoxil, the prodrug of adefovir, reduces HBV DNA by approximately 3.5–4 log10 copies/mL, with resulted in histologic improvement in 2/3rd, normalization of ALT in 3/4th and suppression of HBV DNA to PCR-undetectable levels in ½ to 2/3rd of the patients [27-32].

Pegylated Interferon

In HBeAg-reactive chronic hepatitis B, comparative studies were done, one with PEG IFN- 2b, 100 g weekly for 32 weeks, then 50 g weekly for another 20 weeks for a total of 52 weeks; compared with combination PEG IFN with oral lamivudine; and the other was on PEG IFN- 2a, 180 g weekly for 48, compared with lamivudine monotherapy and combination PEG IFN plus lamivudine. Although the combination of PEG

IFN and lamivudine was superior at the end of therapy in one or more serologic, virologic or biochemical outcomes, neither the combination arm (in both studies) nor the lamivudine monotherapy arm (in the PEG IFN- 2a trial) demonstrated any benefit compared to the PEG IFN monotherapy arms 6 months after therapy [27-32].

Entecavir

Entecavir, an oral cyclopentyl guanosine analogue polymerase inhibitor, (the most potent of the HBV antivirals so far according to most of the studies), is not only just as well tolerated as lamivudine, with a dose of 0.5 mg daily orally, also effective against lamivudine-resistant HBV infection. It has had an excellent safety profile; doses need not be reduced in patients with reduced creatinine clearance. Entecavir has low-level antiviral activity against HIV and should not be used as monotherapy to treat HBV infection in HIVHBV co-infected persons [27-32].

Telbivudine

Telbivudine, a cytosine analogue with oral daily dose of 600 mg, appears to be similar in efficacy to entecavir; however it is slightly less potent in suppressing HBV DNA. Although it is well tolerated, it is associated with a low frequency of asymptomatic creatine kinase elevations and with a very low frequency of peripheral neuropathy; frequency of administration should be reduced for patients with impaired creatinine clearance [27-32].

Tenofovir

Tenofovir disoproxil fumarate, an acyclic nucleotide analogue and potent antiretroviral agent used to treat HIV infection, with an oral once-daily dose of 300 mg for 48 weeks, is similar to adefovir but more potent in suppressing HBV DNA and inducing HBeAg responses (according to most of the studies). It seems to be highly active against both wild-type and lamivudine-resistant HBV and active in patients whose response to adefovir is slow and/or limited [27-32].

PREVENTION

Passive immunoprophylaxis

This is done either with standard Immunoglobulins, containing modest levels of anti-HBs or hepatitis B immunoglobulin (HBIG), containing high-titer anti-HBs [27-32].

Active immunization

These includes

1. Purified, noninfectious 22-nm spherical forms of HBsAg derived from the plasma of healthy HBsAg carriers
2. Plasma-derived vaccine, supplanted by a genetically engineered vaccine derived from recombinant yeast, consisting of HBsAg particles that are nonglycosylated but are otherwise indistinguishable from natural HbsAg.

Pre-exposure prophylaxis

It is indicated for health workers exposed to blood; hemodialysis patients and staff; residents and staff of custodial institutions for the developmentally handicapped; injection drug users; inmates of long-term correctional facilities; persons with multiple sexual partners; persons such as hemophiliacs who require long-term, high-volume therapy with blood derivatives; household and sexual contacts of HBsAg carriers; persons living in or travelling extensively in endemic areas; unvaccinated children under the age of 18; unvaccinated children who are immigrants from endemic countries [27-32].

Dose

Three IM (deltoid, not gluteal)injections of hepatitis B vaccine are recommended at 0, 1 and 6 months. Pregnancy is not a contraindication to vaccination.

Precautions

To reduce the risk of sexual transmission, it is important to use condoms every time you have sex. Avoiding sharing personal items that may have become contaminated with blood, such as toothbrushes or razor blades, is also essential. HBV can remain infectious outside of the body for up to seven days, so it is important always wear gloves when cleaning up blood - even if it has dried. A 1:10 solution of bleach and water can be used to kill the virus on most surfaces [27-32].

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