Asymptomatic HBsAg carrier: A Case for Concern

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More than 2 billion people have been exposed to Hepatitis B virus (HBV) infection out of which 360 million persons have chronic HBV infection worldwide. Around 70% of these persons are inactive carriers and may not develop hepatic complications of chronic HBV infection. Estimated 50 million new cases are diagnosed annually.¹ Fifteen to 40% of these patients will develop serious complications like cirrhosis, decompensated disease and hepatocellular carcinoma.² ³ Seventy percent of the patients chronically infected with HBV are found in Asia.⁴ Around 1.2 million deaths occur due to HBV infection and it is 10th leading cause of deaths worldwide.

Various terminologies used in HBV infection are as shown in Table I.

What Is The Natural History Of Hepatitis B Infection?
Natural history of HBV infection is as shown in figure 1 and 2. Infections acquired perinataly or in early childhood are usually asymptomatic. Approximately 30% of infection amongst adults presents as icteric hepatitis of which 0.1-0.5% result in FHF and > 95% resolve.⁵ Risk of developing chronic HBV infection after acute exposure is dependent on age of patient. Risk ranges from 90% in newborns, 25%-30% in infants & children less than 5 years and less than 10% in

Table I

**Definition**

- **HBV Infection**
  - Presence of HBsAg/HBV DNA in serum/liver
- **Acute Hepatitis B**
  - History, raised ALT, HBeAg +ve and IgM antiHBc +ve
- **Chronic Hepatitis B with active liver disease**
  - Chronic necro-inflammation
    - Diagnostic criteria - HBeAg +ve more than 6 months, HBV DNA more than 10⁷ copies/ml elevated ALT/AST and liver biopsy - necroinflammatory score > 4
- **Inactive HBsAg carrier state**
  - Persistent HBV infection without necroinflammation
    - Diagnostic criteria - HBsAg +ve > 6 months, no sign/symptoms, normal AST and ALT, HBeAg -ve,
      Anti HBe +ve, HBVDNA < 10⁵ copies/ml, liver biopsy - necroinflammatory score <= 4
- **Resolved Hepatitis B**
  - Previous HBV infection without active viral infection presently
    - Diagnostic criteria - history of acute or chronic hepatitis B or presence of Anti HBC + Anti HBs, HBsAg -ve, undetectable HBVDNA and normal ALT
- **Occult HBV**
  - Undetectable HBeAg but HBVDNA +ve in serum or liver
adults.\textsuperscript{6-7} Such risk is more in immunocompromised persons. In HIV infected adult’s risk of chronicity increase up to 20% than in HIV negative subjects (6%). Most commonly if HBsAg persists for more than 6 months, it is considered chronic infection, but some individuals may take up to 1 year to clear HBsAg after acute HBV infection.\textsuperscript{6}

**Chronic Hepatitis B infection evolves in 4 different phases**\textsuperscript{7}

Various Stages of chronic HBV infection are as shown in Figure 3. 1. Immune tolerant, 2. Immune clearance, 3. Residual- nonreplicative, 4. Reactivation.

Even though HBV diagnosed at various stages as described above, chronic HBV is a dynamic disease and patients are likely to change from one stage to other stage over a period of time, hence regular follow up is required in these patients.

Clinical presentations of chronic hepatitis B infection can vary from asymptomatic state to complications related to cirrhosis and hepatocellular carcinoma. Using presence and absence of symptom to discriminate between HBsAg carriers without significant disease from those with significant disease is erroneous.\textsuperscript{3} In chronic liver disease, clinical symptoms are an unreliable guide to the severity of chronic liver injury. Majority of the patients with HBV related chronic liver disease have no symptoms or have mild symptoms. Chronic HBV infection is often a silent disease. Absence of symptoms does not accurately distinguish patients with benign, self limited illness from those with

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**Fig.1: Natural history of Acute HBV infection in adults**
Fig. 2: Natural History of Hepatitis B Infection in Infants

4 Phases of Chronic HBV Infection
Current Understanding of HBV Infection

<table>
<thead>
<tr>
<th>Phase</th>
<th>Immune Tolerant</th>
<th>Immune Clearance</th>
<th>Inactive Carrier State</th>
<th>Reactivation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver</td>
<td>Minimal inflammation and fibrosis</td>
<td>Chronic active inflammation</td>
<td>Mild hepatitis and minimal fibrosis</td>
<td>Active inflammation</td>
</tr>
</tbody>
</table>

Optimal treatment times

Fig. 3
significant progressive liver injury. Asymptomatic patients with HBV infection are generally detected at voluntary blood donation, family contacts of patients with HBV related liver disease, immigration and insurance policy requirement, executive health checkups, organ donors, HBV screening camps and health care professionals. Globally 20 to 70% of patients accidentally detected HBsAg +ve are HBeAg+ve and 60 to 70% of them have elevated liver enzymes. Indian data suggests that 5 to 37% patients are HBeAg +ve and 10 to 50% of them have elevated transaminases. When we evaluated 912 consecutive patients with hepatitis B seen at our centre 36% were asymptomatic and accidentally detected. 70% of asymptomatic patients had normal transaminases and they were either inactive carriers or immune tolerant. 30% of them had elevated transaminases with 60% of them had HBeAg -ve disease and 40% of them had HBeAg +ve, 5% of this population had already developed liver cirrhosis and 1 patient had hepatocellular carcinoma.\(^8\)\(^9\)\(^10\) Hence diagnosis and management of patients with chronic hepatitis B infection is not dependent on only clinical presentation but needs to be based on combined serological, virological, biochemical and histological testing. After diagnosis of chronic HBV infection, minimum investigations required are serum ALT, HBeAg, anti HBe & HBV DNA quantitative. These tests are guiding principles in evaluating disease progression to determine the need for liver biopsy and indications for treatment. Algorithm for work up of incidentally detected asymptomatic patients is as shown in Figure 4.

Differential progression rate with HBV infection may be

![Algorithm For Managing Accidently Detected HBsAg +ve Individual](image-url)
related to various clinical serological and histological markers.11,12 Recognized risk factors for progression are presence of hepatitis B e-antigen, advanced age, increased transaminases levels (ALT), co-infection with other hepatitis viruses and diabetes mellitus. Hence ALT levels have been routinely used in assessment of patients with chronic HBV infection and making the treatment decisions.

Epidemiology and natural history of inactive HBV carriers
Inactive carriers form the largest group in chronic HBV infected patients. Around 300 million people are inactive carriers. Inactive HBsAg carrier is currently defined as a persistent HBV infection of liver without significant ongoing necroinflammatory disease. Diagnosis is based on demonstration of HBsAg positive > than 6 months, no sign/symptoms of liver disease, HBeAg negative, antiHBe Positive, HBVDNA < 105 copies/ml (optional), persistently normal ALT/AST levels and liver biopsy (optional) confirming absence of significant hepatitis (necroinflammatory score<4).13 Differentiation of chronic HBeAg negative disease from carrier state requires serial testing of ALT and HBVDNA for 1 year before designating as inactive carrier state. Natural history of such patients is generally but not invariably benign. It depends on duration and severity of preceding chronic hepatitis and presence of cirrhosis. These subjects can have normal histology in 7.5-32%, mild inflammation in 50%, and significant liver histology in 18-25% of which CPH in 14-19%, CAH in 3-6%, cirrhosis in 1.6% and HCC in 0-0.2%. This remains unchanged in 73.2%, improves in 5.4% and worsens in 21.4% on long-term follow up.14,15 Reactivation of hepatitis B is defined as reappearance of active necroinflammatory disease of liver in a person known to have inactive carrier state or have resolved hepatitis B. Up to 20% of inactive carriers develop exacerbations in hepatitis as evidenced by elevated ALT up to 5-10 times ULN with or without seroreversion to HBeAg and such repeated episodes can lead to progression to fibrosis.16 These flares can be due to super-infection with other hepatotropic viruses like HCV, HDV, HAV, HEV or other causes of acute liver diseases such as drugs, alcohol, etc. Some patients even non-cirrhotic may develop HCC. HBsAg clearance rate is around 0.5%/year overall,3,17 1-2% per year in developed countries and 0.05-0.8% in endemic areas.1 However, very low levels of HBVDNA may persist in almost 50%.4

Based on the definition of inactive carrier state there are some controversial areas differentiating it from HBeAg negative chronic HBV infection, a French study revealed when HBV DNA levels were less than 2,000 IU/ml, 98% patients were inactive carriers and remained so in follow up period of 6 years.18 Chu et al19 from Hongkong showed cut off limit of 2,000 IU/ml excludes all inactive carriers but only one time testing is inadequate. Serial testing's are required. Similar cut off limits of HBV DNA in a Greek study found 13% misclassification of HBeAg negative disease for inactive carriers.20 Similar data from Japan shows the 20% of the HBeAg negative CHB are misclassified as inactive carriers.21 A data from India shows that around 21% of patients who are classified as inactive carriers have significant histological abnormalities.22 Another study from Taiwan shows that patients with mildly elevated serum aminotransferase with HBe negative disease have significant histological disease and predictors for significant disease are age more than 35, male gender and elevated ALT.23 Natural history data shows that cumulative incidence of cirrhosis in inactive carriers is around 10% after 20 to 25 years of follow up. In conclusion patients with asymptomatic chronic HBV infection cannot be considered as an innocuous long lasting condition and needs persistent follow up.

Current Recommendation for Management of inactive HBV carriers13,24-26
1. No treatment is required.
2. Reassurance should be given to the patients.
3. Family screening with HBsAg and antiHBs, if negative vaccinate them and success of vaccination should be confirmed with antiHBs testing.
4. Protected intercourse is advised until partner has developed protective antibodies. Eventual offspring needs active and passive vaccination. If unrecognized, the baby is at risk of fulminant hepatitis.
5. Alcohol should be avoided.
6. The patients should be made aware of the possibility of reactivation or super infection by other viruses and advised to consult their physician if there is jaundice, malaise or increased fatigue.
7. They should regularly follow up at every 6-12 monthly intervals with ALT. If ALT is raised by > 2 times ULN, check HBV DNA levels and if negative look for other causes of liver disease should be ruled out.
8. If more than 50 years of age or family history of HCC-AFP and USG every 6-12 monthly should be done.
9. They should not be denied employment or hospital treatment. Universal precautions should be taken while treating such patients in the hospital.
10. For health care worker, they should be allowed to
do routine designated duties and there is no need for changing the duty. They must follow universal precautions carefully.

11. They should not be allowed to donate blood or organ or tissue or semen.

12. For pregnant women- the newborn is vaccinated at birth with active and passive immunization within 12 hours of the birth.

REFERENCES

8. Puri A S, Agarwal SR. Incidentally detected asymptomatic HBsAg positive subjects. In Hepatitis B In India Prevention and management Eds Sarin SK and Singh AK CBS publishers New Delhi 2004 pp 93-98.
22. Kumar M, Sarin SK, Hissar Syed et all Virologic and histologic features of chronic hepatitis B virus infected asymptomatic patients with persistently normal ALT. Gastroenterol 2008;134:1370-1384