Inactive Carriers of Hepatitis B Virus: A Never Ending Story

Portadores Inativos do Vírus da Hepatite B: Uma História Interminável

Guilherme Macedo

Gastroenterology Department, Centro Hospitalar de São João, Porto, Portugal

The so-called inactive carriers are regularly revisited in hepatologist's literature, but many pending issues are yet unsolved. Magalhães et al. looked back into a cohort of patients carefully followed with serial assessment of some blood parameters, trying to indirectly validate their own strategy of monitoring.

Patients infected with hepatitis B virus (HBV) present several patterns of serological markers and viral activity. When adopting viremia as an indicator of HBV replication, subsets of patients may be defined: HBs Ag positive patients with persistent and on-going viral replication; Hbs Ag positive patients with permanent or temporary inhibition of viral replication: this is a highly heterogeneous group and included coinfected patients with HDV, HCV, inactive carriers and patients with fluctuating viral load levels detectable with more sensitive HBV DNA assays.

It is also known that although HBV is not cytopathogenic, patients with chronic HBV infection have a significant risk of developing severe liver diseases. During the natural course of chronic hepatitis B virus (CHB) infection, different immune phases have identified as immune tolerant phase, immune clearance (or immuneactive, phase, low replicative phase and asymptomatic chronic carrier state).

The low replication phase, being referred as the inactive HBsAg carrier state, occurs after HBeAg seroconversion and is usually characterized with a marked reduction or undetectable level of serum HBV DNA, ALT normalization and resolution of liver necroinflammation. The inactive carrier state may last a lifetime, but proportion of patients may undergo subsequent spontaneous or immunosuppression-induced of HBV replication generally referred as relapse. The CHB patients with a relapse often exhibit reappearance of high levels of serum HBV, ALT abnormalization and reversal of HBeAg seroreversion. It is important to distinguish between inactive carriers and individuals with HBeAg-negative CHB, because the form has been carried to have a favourable long-term outcome, whilst the latter is less responsive treatment and associated with progressive liver disease.

Another very important issue is that if inactive carriers are not followed, they might be engaged in any sort of immunosuppressive therapy, not easily recognized by other specialists, which may introduce a significant risk factor for reactivation. Reactivation of hepatitis B is a rare but distinctive syndrome defined by an abrupt, marked increase in HBV replication usually accompanied by elevations in serum aminotransferase levels and sometimes by jaundice. Reactivation of HBV can occur spontaneously but is more common in the setting of immune suppression or cancer chemotherapy.

Even with these risks to follow up strategy for inactive carriers have been very disputed reflecting the need of a precise knowledge of the replicative phase and the baseline histology of the liver. We and others have looked in to the histology of inactive carriers and found out that cirrhosis featured in 12% of these patients; and that the overall burden of inactive carriers within the chronic

E-mail address: guilhermemacedo59@gmail.com
hepatitis B population was not higher than 23% stressing the fact that many of these “quiet” individuals were indeed chronic HBeAg negative hepatitis patients.

The paper from Magalhães et al has an interesting mean follow up period (4.6 years), in which transient elevation of ALT was surprisingly rare and liver biopsies were available only in a minority of patients. These facts of course preclude any definitive assumption of a favourable progression of the patients, but acknowledged the need of regular assessment with biochemical and with virological activity. Concerning the recent data on the role of HBsAg quantification for monitoring natural history, including the recognized issue that in patients with chronic HBV infections, a high HBsAg level was associated with an increased risk of HCC and was an independent risk factor for HCC in those with a low HBV viral load this could stand as an additional strategy to be implemented. The rational for its implementation relies on the fact that viral proteins of clinical importance include the envelope protein (HBsAg) whose synthesis during the HBV viral life cycle is complex. HBsAg production exceeds that required for virion assembly, and excess surface envelope proteins are covalently linked secreted as empty non-infections filamentous or spherical sub-viral particles.

These empty particles may co-exist with anti HBs as part of circulating immune complexes.

Serum HBsAg is a result of the combination of these proteins (complete virion, filamentous or spherical sub-viral particles). HBsAg quantification measures all three forms of systemic HBsAg.

The combination of a single measurement of HBsAg less than 1000 IU/ml and HBV DNA less than 2000 IU/ml identifies “inactive carries” with a PPV of 86%. More recently, the authors in this French study reported that the combination of single measurement of HBsAg above 1000 IU/ml and HBV DNA above 200 IU/ml identifies patients with a “high risk of reactivation” with a negative predictive value (NPV) of 96%, and sensitivity 92%. The authors conclude that combination of HBsAg and HBV DNA levels at a single time point may accurately identify HBeAg (−) CHB patients, during remission with a high probability of reactivation and who are good candidates for treatment.

In conclusion, no final word has yet to be proclaimed. It is reasonable to follow up these patients, thoroughly, with regular ALT and DNA assessment, eventually also profiling HBsAg levels, so that prompt recognition of trouble is warranted in a presumed benign and stable condition.