



Commentary

The evolving scenario of HBV infection and disease: A never-ending story

Martina Milana, Mario Angelico*

Hepatology and Liver Transplant Unit, Tor Vergata University, Fondazione Policlinico Tor Vergata, Rome, Italy



ARTICLE INFO

Article history:

Received 11 October 2018

Received in revised form 21 October 2018

Accepted 24 October 2018

In the last 30 years or so there has been a substantial reduction of HBV endemicity in Italy, largely as a consequence of the universal vaccination program introduced in 1991 in newborns and adolescents and the improved socio-economic and hygienic conditions, but also favoured by the introduction and wide availability of potent antivirals. This gradually led to a significant change in the profile of HBV-infected individuals, who turned to be mostly represented by adults over 50 years of age, often with an advanced liver disease, being infected in more than 90% of cases by HBeAg negative viral strains [1]. Brancaccio et al. in the current issue of *Digestive and Liver Disease* [2], report the results of a large multicenter prospective observational study promoted by the Italian Association for the Study of the Liver (AISF) which recruited slightly less than 3000 HBsAg positive subjects across the country. The key finding of the study is that more than one quarter of HBsAg positive subjects consecutively observed in the period 2012–2015 at liver-specialized centers were found to be non Italian natives (NINs). This figure is remarkably higher than the proportion of HBsAg positive NINs found in similar surveys performed 10–20 years earlier [1]. This finding is clearly the consequence of demographic changes caused by immigration from several areas of the developing world, which has steadily increased over the last decades.

The study by Brancaccio et al., unfortunately, does not provide true prevalence rates of HBV infection in the country, which would be very helpful to know from a public health point of view, given that HBV-infected individuals were recruited only through admission at out-patients clinics and/or hospital centers, hence being likely predominantly represented by those with overt or more advanced disease. Indeed, only 28% of subjects were categorized as having HBV infection without evidence of disease, since

they had normal laboratory, sonographic, or endoscopic findings in the absence of antiviral therapy. Despite this limitation, these data indirectly suggest that, while the prevalence of HBV infection is continuing to decrease in the Italian native population, the overall prevalence in the country might have increased in recent years due to immigration-related demographic changes and perhaps might be currently underestimated. Notably, the AISF survey shows that immigrants with HBV infection are considerably younger compared to infected native Italians, likely due to prevalent vertical transmission and/or absence of vaccination programs in their countries of origin. Moreover, NINs are more often highly viremic, HBeAg positive (especially those of Asian origin) and HDV-coinfected (especially those from Eastern Europe). This changing spectrum of HBV infection entails a higher potential for viral transmission in the unprotected population, which in Italy is mostly represented by unvaccinated native Italians aged >36 years [3]. It also underlines the need to facilitate linkage-to-care, as well as HBV screening programs, among immigrants, who should have full access to current vaccination and treatment options, as needed. It is disturbing to see that cirrhosis was already present 15.7% of HBsAg positive immigrants, despite they had a median age of only 35 years and even more that, conceivably, hepatocellular carcinoma was detected at a much lower age among immigrants compared to native Italians. Why cirrhosis and hepatocellular carcinoma develop at a younger age in immigrants remains currently unknown, yet it could be due to a number of factors, including younger age at time of infection, differences in HBV genotypes and/or levels of viral replication, presence of coinfections and exposure to other liver toxins.

The study by Brancaccio et al. [2] highlighted also that there is still not enough attention, even in specialized units, to test for HDV infection all HBsAg positive individuals, which is bad news, given that this infection is coming back as a consequence of immigration from endemic areas, particularly from Eastern Europe [4]. Treatment of HDV infection remains a major unmet need in clinical hepatology, being still limited to the long-term interferon-alfa

DOI of original article: <https://doi.org/10.1016/j.dld.2018.09.008>.

* Corresponding author.

E-mail address: angelico@med.uniroma2.it (M. Angelico).

administration, which is poorly effective and associated with several adverse effects. Prompt recognition of HDV infection is indeed very easy and should be mandatory in all HBsAg positive subjects, not only to allow earlier treatment, but also to avoid further viral spread.

Interestingly, the AISF survey showed that HCV coinfection, although being not investigated in as much as 25% of HBV-infected individuals, was a relatively uncommon event, yet it was higher among native Italians than among NINs, especially in patients with more advanced liver disease. This likely reflects the greater endemicity of HCV among older Italians, and given that HCV, as HBV, is a blood-borne infection sharing the same risk factors, underlines the need to always recommend to investigate for the presence of a coinfection, which may enhance the likelihood of disease progression.

A surprising and perhaps unexpected finding of the AISF survey was that only a limited number of HBsAg positive individuals was being treated with oral antivirals at time of recruitment, even among those who were already cirrhotics, especially among NINs. Although this might be due to the fact that many of them were first entries as outpatients, and conceivably to the difficulty to treat irregular immigrants (this crucial information however is not provided in the study), the data clearly suggest that there might be a large underestimation of the spread of HBV disease in the territory, and/or a significant underreferral of patients to specialized centers. The data also indicate that there might be a lack of attention/knowledge even among specialists of the correct use of antivirals, which, if timely used, may markedly improve the natural history of HBV-related cirrhosis. Indeed, international guidelines recommend since already many years that all HBsAg positive and viremic cirrhotic patients must be treated with oral nucleos(t)ide analogs with high genetic barrier, regardless of the level of viremia and transaminases [5,6]. It would be interesting to know which

is the real-life adherence to this recommendation among Italian doctors.

In conclusion, the evolving scenario of HBV infection and disease again proves to be a “never-ending story”, which should always be kept in mind and requires even greater attention in the current and the forthcoming era of demographic changes potentially associated with enhanced risk of viral spread. The example of the continuously growing Chinese community in Western societies is perhaps the clearest example of this, also showing that many efforts to control HBV infection in this population are feasible, given the greater level of linkage to care of Chinese individuals compared to immigrants from many other areas. This reminds us that a lot can still be done to control HBV-related infection and disease, both from a public health as from a clinical perspective.

Conflict of interest

None declared.

References

- [1] Stroffolini T, Almasio PL, Sagnelli E, Mele A, Gaeta GB, Italian Hospitals' Collaborating Group. Evolving landscape of chronic hepatitis: a multicenter Italian study. *J Med Virol* 2009;8:1999–2006.
- [2] Brancaccio G, Nardi A, Madonia S, Fasano M, Verucchi G, Massari M, et al. The present profile of chronic hepatitis B virus infection highlights future challenges. An analysis of the multicenter MASTER-B cohort. *Dig Liver Dis* 2018, in press.
- [3] Morisco F, Coppola N, Smedile A, Pisaturo M, Colloredo G, Babudieri S, et al. Influence of universal HBV vaccination on chronic HBV infection in Italy: results of a cross-sectional multi center study. *J Med Virol* 2017;89:2138–43.
- [4] Gaeta GB, Stroffolini T, Smedile A, Niro G, Mele A. Hepatitis delta in Europe: vanishing or refreshing. *Hepatology* 2007;46:1312–3.
- [5] EASL 2012 Clinical Practice Guidelines on the management of hepatitis B virus infection. *J Hepatol* 2012;57:167–85.
- [6] EASL 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection. *J Hepatol* 2017;67:370–98.