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Editorial

Gender Disparity in Hepatitis: A New Task in the Challenge Against Viral Infection

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Abbreviations

HCV: Hepatitis C Virus; HBV: Hepatitis B Virus; HBsAg: HBV Surface Antigen; HCC: Hepatocellular Carcinoma; AR: Androgen Receptor; ARE: Androgen Response Elements; SVR: Sustained Virological Response

Editorial

Gender/sex-specific medicine is still a neglected field of investigation, which is devoted to the analysis of the disparity between men and women in disease pathogenesis and prevention, in the detection of clinical signs or symptoms, in the prognosis and response to therapy as well as in psychological and social determinants of morbidity. For instance, it is well documented that incidence and outcome of several human diseases, such as cardiovascular diseases, tumors, degenerative diseases, or some respiratory and neurological disorders display a significant disparity between males and females [1-4]. In addition, it is now emerging that men and women also experience a different susceptibility to some virus infections, often with a different outcome. In addition, even the prevention or the response to antiviral treatments can display significant differences between male and female patients [5].

Hepatitis B (HBV) and C viruses (HCV) are responsible of chronic liver disease and are the major risk factors for development of hepatocellular carcinoma (HCC) [6]. It is estimated that 240 million people worldwide are chronically infected with HBV and at risk of serious illness, like cirrhosis and HCC. One hundred seventy million people are estimated to be chronically infected with HCV, whose infection prevalence is about 3% in the developed countries whereas, only in Europe, about 4 million people are HCV carriers [7,8]. Beside these epidemiological data, sex disparity in the natural history of HBV and HCV infections and in the evolution and progression of the associated liver disease in different geographic areas of the world [9] have been reported since many [10]

A number of studies are available regarding gender differences in HBV infection, whereas HCV infection appears studied in less detail. After the initial knowledge that men are more likely than women to become chronic carriers for HBV [11], it has been recognized that the serum prevalence of HBV surface antigen (HBsAg) and the DNA virus titers are higher in serum of men than women [12,13]. Both these viral factors probably contribute to the increased risk to develop HCC in male with respect to female. In fact, the male/female ratio for HCC prevalence has been reported to be from 2:1 to 4:1 [14]. Due to the close interaction between virus and host, both host and viral mechanisms could be responsible of this gender disparity in HBV infection and disease progression. One of these mechanisms seems to be ascribable to hormonal milieu [15]. For instance, steroid hormones have been suggested to mediate sex differences in susceptibility to liver cancer upon HBV infection: elevated testosterone levels and expression of Androgen Receptor (AR) genes were found strictly related with the increased risk of HCC in men [16]. One mechanism by which androgens affect HBV replication has been identified in their direct binding to Androgen Response Elements (ARE) in the enhancer I of HBV thus causing modulation of virus transcription and increasing virus titer in serum of males [17]. In turn, HBV directly increases AR level through the enhancing transcriptional activity of AR, mediated by the HBV encoded X protein [18]. In addition, hormones can affect host immune response. With regard to this, 17-beta estradiol (E2), a major naturally occurring estrogen in women, reduces the synthesis of Interleukin-6 by Kupffer cells, a cytokine known to play a crucial role in fibrosis and HCC. This apparently occurs in the livers of male mice through the inhibition of the transcription factor NFkB (nuclear factor kappa-light-chain- enhancer of activated B cells) via the universal adapter protein Mydd88 [19]. Recently, an HCC-related mutation in the large surface antigen of HBV genotype C has been found only in male patients [20]. All these mechanisms can at least partially explain the gender disparity in the progression of HBV infection towards HCC. Furthermore, given the hormone modulation exerted by HBV, this virus has recently been considered as a sex-hormone responsive. One more facet of disparity is the sex difference in response to HBV vaccine: anti-HBV antibodies titers have been found higher in vaccinated females than in males so that male sex has been suggested to represent a sort of predictor of unresponsiveness to HBV vaccination [5].

In the case of HCV infection, the progression from chronic hepatitis C to cirrhosis is slower in females than males and the risk to develop HCC in female chronic carriers is significantly lower than in chronically infected male patients [10,21]. Moreover, females have been suggested to experience a higher rate of spontaneous HCV clearance than males [22]. As for HBV, also in the case of HCV the steroid hormones have been suggested to be possible players of the reported sex differences. It has been shown that treatment with E2 of HCV infected cell cultures reduced the production of HCV virions, probably inhibiting virus assembly /secretion, whereas E2 did not affect HCV RNA replication nor virus protein synthesis [23]. However, in the post-menopausal women, when estrogen levels decrease, these sex differences are mitigated and partially reversed.

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In fact, in post-menopausal women fibrosis, liver inflammation and pro-inflammatory cytokine concentrations are more elevated than in women in reproductive age.

Sex is variably associated also with higher and lower Sustained Virological Response (SVR) to anti- HCV therapy based on pegylated interferon and ribavirin [24] and to the efficacy of standard therapy. In fact, pre-menopausal women have shown a higher rate of SVR to the standard therapy compared to men and experience more adverse reactions to therapy [25]. According to the above, in postmenopausal women therapy is less effective [26]. Investigations on the mechanisms responsible for the disparity in response to HCV treatment highlighted the possibility that interferon signaling pathway could be more active in pre-menopausal patients than in post-menopausal patients as well as in males. Furthermore, MxA expression (a marker for JAK/STAT pathway activation) was found up-regulated in pre-menopausal women compared to males and post-menopausal women This is probably related to the reported different production of interferon upon toll-like receptor 7 agonists, greater in pre-menopausal women [27].

Although sex differences in hepatitis B and C virus infection are becoming evident, investigation of the host and viral mechanisms involved are often neglected and only partially clarified. From the revised literature it appears that HBV and HCV infection have worse outcome and faster progression in men than in women. Women also display a better response to therapy and to anti- HBV vaccination. In addition, sex hormones not only directly affect viral replication but, also, exert potent immunomodulating effects. Estrogens potentiate immune response, both humoral and innate, whereas androgens are mainly immunosuppressive [28,29]. Improving our knowledge on gender differences as concern hepatitis virus pathogenesis and progression will improve treatments and vaccination schedules, leading to point out more adequate doses and quality of vaccines and drugs, also in post-menopausal women. This will probably represent a pre-requisite for a mandatory objective of the modern medicine: the appropriateness and the personalization of the cures.

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