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Image Article

Gender Preponderance Might be Associated with the Severity of COVID-19 Infection

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CLINICAL IMAGE

The outbreak of coronavirus disease (COVID-19) has raised many concerns around the world. At first glance, it was expected that the primary victims of coronavirus are a vulnerable group, children due to having immature immune system; but, the epidemiological data have shown that the virus has mostly spared this group and instead posed a particular threat to middle-aged and older adults, predominantly men. In a study conducted by the Chinese Centre for Disease Control and Prevention [1], it was reported that although both genders are literally infected in equal numbers, the mortality rate among men is nearly two folds higher than women (2.8%vs.1.7%, respectively). In affected individuals with the age of less than 50, the death rate was 0.5%, while the death rate among patients with the age of above 80 was 8%. Interestingly, no death reported in children under the age of 10 years old since 26 February 2020.

Another study performed in Hong Kong in 2003 [2] showed that the mortality rate of male patients with Severe Acute Respiratory Syndrome (SARS) caused by coronaviruses was 50% higher than that of female patients. Correspondingly, the death rate of men was significantly higher in epidemic infection of influenza that occurred in 1918 [3].

The above evidence casts doubt on the contribution of androgens to the severity of covid-19, due to the higher incidence of infection in males and the absence of mortality in children that may stem from the lack of maturity and sex hormones. The sex-based difference in immune responses is well established, and the interaction between sex hormones and the immune function is a well-known event [4]. It has been confirmed that females are more prone to develop autoimmune diseases and respond better to pathogenic infections and vaccination both in murine models and clinical practice [5-7]. It has been reported that castration raises the immune response and enhances the efficacy of vaccination in a mouse model of prostate cancer [8]. Besides, the susceptibility of human newborns to infectious diseases is significantly higher in males as compared with females that might be due to an early androgen surge experienced by male infants at birth [9]. It is apparent that the immune-suppression of testosterone is not confined to specific species but can be extrapolated as a broadly distributed phenomenon across species, and It is suggested that it is a part of the evolutionary program. There are also intrinsic/genetic attributes of the immune system, but evidence shows the significance of sex hormones in the modulation of the immune response to both induced (immunization) and spontaneous (autoimmune) reactions. The studies, as mentioned earlier, demonstrate that androgens play an immunosuppressive role in natural immune responses against pathogens and after vaccination; however, the cellular and molecular mechanisms underlying the effect of testosterone on the immune system are not very well understood [4].

This premise is further supported by a cutting-edge study [10] that revealed that the spike protein of SARS-CoV-2 is primed by TMPRSS2, which is a cellular serine protease. In this study published in the journal of "Cell," it was indicated that the presence of TMPRSS2 would be indispensable for the infection of the cells. On the other hand, it has been shown that androgens can pave the way for the expression of TMPRSS2 [11]. When androgens bind to their cognate receptors, which are located in the nucleus of the cells, they trigger the expression of various proteins such as TMPRSS2. Therefore, it would be plausible that the androgen signaling pathways inadvertently make the cells prone to be infected by the virus, as schematically represented in Figure 1. It seems that the blockade of the DHT receptor may halt the progression of coronavirus; however, it is still premature to blame testosterone or its active metabolite dihydrotestosterone (DHT) for the severity of covid-19, and further studies are warranted to delicately elucidate the precise mechanism underlying the gender preponderance of coronavirus infection.

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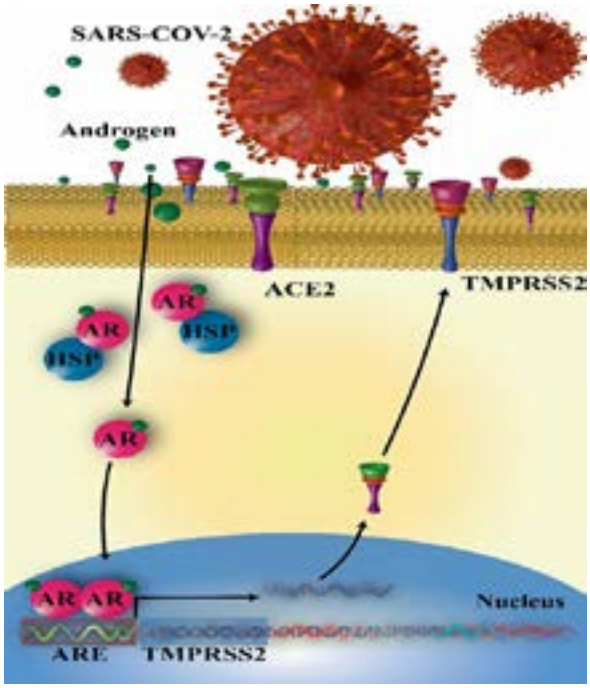

Figure 1: A proposed mechanism of androgens in facilitating the cell entry of coronavirus. Upon the binding DTH to androgen receptors, TMPRSS2 is produced and transferred into the cytoplasm priming the S protein and thus paving the way for the entry of SARS-COV-2 into the lung cells.

TRANSPARENCY

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Declaration of competing interest

The authors declare that they have no competing interests.

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