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LETTER TO THE EDITOR

Racial variations in COVID-19 deaths may be due to androgen receptor genetic variants associated with prostate cancer and androgenetic alopecia. Are anti-androgens a potential treatment for COVID-19?

Dear Editor,

As the SARS-CoV-2 (COVID-19) pandemic continues to infect many more Americans, a racial disparity in the number of deaths from infection has emerged. On April 7, 2020, the Washington Post reported that counties with census demographics indicating a majority black population had almost six times the rate of death from COVID-19 as counties where the majority of residents were white.[1] In the report, the deaths per hundred thousand residences for counties consisting of a majority white, Asian, black, and Hispanic populations was 1.1, 0.4, 6.3, and 0.6, respectively. There is undoubtedly a multifactorial etiology to this racial disparity that can include socioeconomic as well as other factors. However, a similar racial bifurcation is evident in conditions influenced by sensitivity to androgens, for example, prostate cancer and androgenetic alopecia.[2,3] Further, gender and age differences in the severity of COVID-19 disease and mortality rates have also been reported[4] and might also be explained by an androgen-mediated mechanism.

We have recently published two communications offering an explanation for a gender disparity in COVID-19 disease severity.[5,6] SARS-CoV-2 enters type II pneumocytes by binding to angiotensin-converting enzyme 2 (ACE2). Binding of SARS-CoV-2 to ACE2 is mediated by proteolytic cleavage of a viral surface protein by transmembrane protease, serine 2 (TMPRSS2).[7-9] As such, concentrations and activity of both ACE2 and TMPRSS2 in host pneumocytes are crucial to SARS-CoV-2 ability to infect a host. Both ACE2 and TMPRSS2 are regulated by the androgen receptor; in fact, the 15-base-pair androgen response element is the only known transcription promoter for the TMPRSS2 gene.[10-13] Androgen-mediated expression of ACE2 and TMPRSS2 may explain the gender difference in COVID-19 disease severity and mortality.

Racial variations in other androgen-mediated conditions have been noted. For example, it has been reported that African American men are at higher risk for aggressive prostate cancer.[2] Polymorphisms in the length of CAG repeat in exon 1 of the androgen receptor have been shown to correlate with incidence of prostate cancer.[14] In a study of men without prostate cancer, Sator et al reported that the average CAG repeat length for non-Hispanic white men (n = 130) was 21.0, while the average CAG repeat length for African American men (n = 65) was 19.0. [15] In a study of men with prostate cancer, Bennett et al reported a CAG length of 21.9 in non-Hispanic white men (n = 168) and 19.8 in African American men (n = 151). Additionally, it was found that the occurrence of stage D prostate cancer (currently classified as High Risk) was highest in men with shorter CAG repeats.[16] Racial variations in androgenetic alopecia (AGA) have also been reported to correlate with CAG length polymorphisms in the androgen receptor.[3] Finally, while no direct association between CAG repeat length in the AR gene and SARS-CoV-2 viral infectivity has been reported, studies in animal models demonstrated the effect of androgens (testosterone) on influenza disease severity.[17] In males, testosterone's biological action is dependent on the length of the CAG repeat of the AR gene.

Currently, our group is planning a clinical study to measure CAG length polymorphisms in patients hospitalized with COVID-19 infection. While a direct link between polymorphisms in the androgen receptor and COVID-19 disease severity has not been established, we believe that the similarities in racial and gender bias to other androgen-mediated conditions are noteworthy. If androgen sensitivity can be confirmed as a predisposition to SARS-CoV-2 disease severity, it could suggest the use of anti-androgens or androgen-modulating drugs as a means of treatment, either alone or combined with TMPRSS2 inhibitors. For example, anti-androgens like bicalutamide and enzalutamide or androgen modulators like finasteride and dutasteride may be beneficial.

CONFLICT OF INTEREST

There is no conflict of interest.

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