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A PRELIMINARY OBSERVATION: MALE PATTERN HAIR LOSS AMONG HOSPITALIZED COVID-19 PATIENTS IN SPAIN – A POTENTIAL CLUE TO THE ROLE OF ANDROGENS IN COVID-19 SEVERITY

RUNNING TITLE:
MALE PATTERN HAIR LOSS IN HOSPITALIZED COVID19 PATIENTS

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Abstract/summary:
A preliminary observation of high frequency of male pattern hair loss among admitted COVID-19 patients, and suggest that androgen expression might be a clue to COVID-19 severity.

During the continuing SARS-CoV-2 (COVID-19) pandemic, several studies have reported a significant difference in the rate of severe cases between adult females and adult males (42% vs 58%).[1] Among children under the age of 14, the rate of severe cases was reported to be extremely low.[1] To explain this difference, several theories have been proposed including cigarette smoking and lifestyle habits. However, no theory fits both the gender difference in severe cases as well as reduced risk in pre-pubescent children. Our past research on male androgenetic alopecia (AGA) has led us to investigate an association between androgens and COVID-19 pathogenesis.[2] In normal subjects, androgen expression demonstrates significant variation between men and women as well as between adults and pre-pubescent children.

SARS-CoV-2 primarily infects type II pneumocytes in the human lung. SARS-CoV-2 enters pneumocytes, by anchoring to the ACE2 cell surface receptor. Prior to receptor binding, viral spike proteins undergo proteolytic priming by the transmembrane protease, serine 2 (TMPRSS2).[3–5] TMPRSS2 inhibition or knock down reduces ability of SARS-CoV-1 (a related virus to SARS-CoV-2) to infect cells *in vitro*.[6] Additionally, TMPRSS2 also facilitates entry of influenza A and influenza B into primary human airway cells and type II pneumocytes.[7]

The human TMPRSS2 gene has a 15 bp androgen response element and in humans, androgens are the only known transcription promoters for the TMPRSS2 gene.[8-10] In a study of androgen-stimulated prostate cancer cells (LNCaP), TMPRSS2 mRNA expression increase was mediated by the androgen receptor.[10] Further, the ACE2 receptor, also critical for SARS-CoV-2 viral infectivity, is affected by male sex hormones with higher activity found in males.[11]

Androgenetic alopecia (AGA), often referred to as male pattern hair loss, is the most common form of hair loss among men.[12] The development of androgenetic alopecia is androgen mediated and is dependent on genetic variants found in the androgen receptor gene located on the X chromosome. We hypothesized that males with AGA are more likely to be hospitalized for COVID-19 complications compared to controls. To explore this potential association, we conducted a preliminary observational study of the prevalence of AGA patients among hospitalized COVID-19 patients at two Spanish tertiary hospitals between March 23-April 6, 2020, the diagnosis of AGA was performed clinically by a dermatologist.

In total, 41 Caucasian males admitted to the hospitals with a diagnosis of bilateral SARS-CoV-2 pneumonia were analyzed. The mean age of patients was 58 years (range 23-79). Among them, 29 (71%) were diagnosed with clinically significant AGA (Hamilton–Norwood scale higher than 2) and 12 (29%) had clinically irrelevant relevant signs of AGA (Hamilton–Norwood scale 1 or 2). 16 (39%), were classified as severe AGA (Hamilton–Norwood scale 4 to 7).

The precise prevalence of AGA among otherwise healthy Spanish Caucasian males is unknown; however, based on published literature,[13, 14] the expected prevalence of a similar age-matched Caucasian population is approximately 31-53%. Due to the burden exerted on the emergency departments participating in this study, the study was limited to visual diagnosis only; therefore, no information was available as to the use of anti-androgens, prostate cancer or benign prostatic hyperplasia; thus if a later study demonstrates that a significant portion of this population was already treated with androgen modulators it would alter the conclusion of this communication. Following this preliminary observation, we plan to conduct a controlled study to determine whether a correlation between androgens and COVID-19 disease severity exists.

If AGA is confirmed as a risk factor for increased severity of COVID-19 infection, then we could hypothesize that anti-androgen therapy may reduce the risk of developing severe symptoms following COVID-19 infection. While no anti-androgen therapy for COVID-19 has been studied to-date, recent attention to the anti-malarial drug hydroxychloroquine is of interest. Chloroquine phosphate, an analogue of hydroxychloroquine, has been demonstrated to reduce testosterone in rodents.[15] Further, a combination of hydroxychloroquine and Itraconazole is being studied for the treatment of prostate cancer (NCT03513211).[16] Although the data supporting the use of hydroxychloroquine for treatment of COVID-19 is limited and the potential negative side effects in COVID-19 patients are

unknown, the connection to androgens may prove important. Finally, the US FDA has recently granted expanded emergency use access for nitric oxide as a treatment for COVID-19. The use of nitric oxide was demonstrated to inhibit androgen receptor activity in prostate cancer.[17] If our theory proves correct, anti-androgen drugs could be employed, such as finasteride, dutasteride, spironolactone, enzalutamide,[19] and possibly cannabidiol.[18]

In conclusion, based on the scientific rationale combined with this preliminary observation, we believe investigating the potential association between androgens and COVID-19 disease severity warrants further merit. If such an association is confirmed, anti-androgens could be evaluated as a potential treatment for COVID-19 infection.

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