

Alopecia and Covid-19 Pandemic: A Review Article

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Abstract

Various dermatologic diseases came into notice worldwide after the COVID-19 pandemic. The stress and the anxiety associated with the COVID-19 pandemic have been seen as the causal factor behind many psychosocial dermatologic diseases, such as psoriasis, chronic urticaria, and alopecia areata. It has been seen that there is increasing likelihood in the occurrence of alopecia area after the COVID-19 outbreak which is usually observed after months of contracting the illness. Alopecia areata is described as a non scarring type of autoimmune hair loss, recurrent in nature. As emotional stress burden increases, the incidence of alopecia increases, and after the occurrence of alopecia, psychiatric disorders are often triggered. Given the importance of psychiatric disorders in alopecia, after the COVID-19 pandemic, there are numerous stress factors like travel ban, social distancing, gathering, and conveyance restrictions starting to take place. Henceforth this is clearly suggesting that there is a vicious circle between alopecia and psychiatric disorders. There is a high need to study deeply in order to derive any conclusion establishing the relationship between the Alopecia and COVID-19 pandemic. The transcription of transmembrane protease serine 2 (TMPRSS2) regulated by the AR. This protease is important to cleave SARS-CoV-2 spike glycoprotein, this cleavage, also termed "priming," is essential for the spike protein of virus to bind to human angiotensin-converting enzyme 2 (ACE2), needed for

the cellular entry for infection. Targeting the TMPRSS2, whether directly or indirectly through.

Keywords: Alopecia; Covid-19; Pandemic; Androgenic; Receptor.

Materials and Methods

Various dermatologic diseases came into notice worldwide after the COVID-19 pandemic. The stress and the anxiety associated with the COVID-19 pandemic have been seen as the causal factor behind many psychosocial dermatologic diseases, such as psoriasis, chronic urticaria, and alopecia areata. It has been seen that there is increasing likelihood in the occurrence of alopecia area after the COVID-19 outbreak which is usually observed after months of contracting the illness. Alopecia areata is described as a non-scarring type of autoimmune hair loss, recurrent in nature. As emotional stress burden increases, the incidence of alopecia increases, and after the occurrence of alopecia, psychiatric disorders are often triggered. Given the importance of psychiatric disorders in alopecia, after the COVID-19 pandemic, there are numerous stress factors like travel ban, social distancing, gathering, and conveyance restrictions starting to take place. Henceforth this is clearly suggesting that there is a vicious circle between alopecia and psychiatric disorders.

There is a high need to study deeply in order to derive any conclusion establishing the relationship between the Alopecia and COVID-19 pandemic. As of June 12, 2021, the World Health Organization reported a total of 175 million cases, 3.8 million reported fatalities to date from severe acute respiratory syndrome coronavirus² (SARSCoV)-2 worldwide. Studies have shown various risk factors, such as older age, male gender,¹ ethnicity,² and androgenetic alopecia (AGA).³ depending upon hospital and intensive care unit (ICU) admission rates, and fatalities, Research must be done to know about the increased androgenetic vulnerability to SARS-CoV-2 and possible therapeutic strategies to modify this host-dependent vulnerability factor. Animal research with SARS-CoV have previously showed that males develop increased viral load in the lungs during infections, making them more susceptible to severe disease when compared to females.⁴ X-linked inheritance of genetic polymorphisms include ACE2 gene loci and the androgen receptor (AR), are responsible for it.⁵ The fact that females and children are less susceptible to SARS-CoV-2 due to lower AR activity.⁶ SARS-CoV-2 infection is probably going androgen mediated.⁷ Hyperactivation of the AR causes a decrease in scalp hair, increased facial and chest hair, acne, and oily skin.⁷ Observational studies from prostate cancer patients taking androgen deprivation therapy also support for the role of androgens in COVID-19.¹⁰

Probable Pathogenesis and Related Studies

The transcription of transmembrane protease serine 2 (TMPRSS2) regulated by the AR. This protease is important to cleave SARS-CoV-2 spike glycoprotein, this cleavage, also termed "Priming," is important for the viral spike protein to bind to human angiotensin-converting enzyme 2 (ACE2), needed for the cellular entry for infection.^{11,12} The transcriptional activity of the AR is related to transactivation, and the polymorphisms of the AR modifies its interactions with interleukin-6 (IL-6)—a cytokine responsible for the origin of varied malignant tumors.^{13,14} IL-6 acts as a positive regulator in AR signaling in case of pancreatic cancer.¹⁵

In a study by Bennett et al., it was found that the CAG length of non-Hispanic white men was more when compared to the CAG length of African American men.¹⁸ It was also established that in males, the CAG repeat length is directly linked to testosterone's biological action. A mixture of shorter CAG repeats and shorter GGC repeats was found to be directly associated in case of AGA.¹⁹ Shorter length of CAG in African American men may be

a reported as one of the underlying genetic cause within the literature for the development of AGA. 2 AR polymorphisms may also be correlated to the vulnerability of and therefore, the higher death rate within the African American population² as shorter CAG repeats within the AR gene has been shown to correlate to a rise of SARS-CoV-2 mortality.²⁰⁻²² However, studies have shown that there is increased protein synthesis in other tissues having androgen receptor which was directly associated with CAG repeat length in vitro.²³ Though the studies have demonstrated that AR CAG repeat polymorphisms influence TMPRSS2 expression in the lung tissues or endothelial cells but the reason behind the fact is still unknown. Activation of the AR is also affected by the longer glutamine residues in some tissues, while in other, it can affect the interactions with specific repressing protein.¹⁷ Males with longer CAG repeats are at higher risk for thrombosis and metabolic syndrome which may be a result of AR-independent testosterone-induced thromboembolic events, thereby leading to a serious risk factor for COVID-19.^{24,25} However the claim that longer CAG would cause a decreased risk in COVID-19 can be refuted by the fact that the lower AR activity secondary to the longer CAG repeats can be compensated by increased testosterone levels.²⁶ The studies had also found out that the epigenetic protein "Protein arginine methyltransferase 6" (PMRMT6)²⁷ in lung tissue may have a protective effect that lowers the incidence of emphysema from cigarette smoke which can also confer some protection against COVID-19.²⁸ There are evidences derived from studies that anti-androgens may improve the immunity against intracellular pathogens and improve vaccine efficacy by enhancing the cell mediated immunity.²⁹

"Gabrin sign"³⁰ was described in order to classify the patients with severe AGA and who are at greater risk for severe COVID-19 outcomes. The term was coined after Dr. Gabrin who was the first physician to die from the virus.³¹ A preliminary observational study conducted in March-April 2020 had showed that caucasian males with AGA, Hamilton-Norwood scale (HNS) higher than 2 were admitted with severe SARS-COV-2 related pneumonia. Birch study had showed a frequency of 67%, and the Norwood study had showed a frequency of 58% at the same age range.^{32,33} Classification of patients with severe AGA can be done using the Gabrin sign. Lee et al.³⁴ also reported a greater proportion of COVID-19 among those having pattern 4 frontal and vertex baldness, or NHS 3-7.4 Studies had shown very severe baldness as having a higher

odds-ratio in comparison to other comorbidities for contracting COVID-19. As Lee et al. conducted the self-reported baldness survey a few years ago, those that initially self-reported a pattern 2 or 3 baldness, ultimately developed very severe baldness.³⁵ A web survey showed that AGA was related to increased COVID-19 diagnosis and hospitalizations.⁹ In a pilot study done in India in 2020,⁴ it was shown that the patients with severe AGA with HNS > 2 had most severe outcomes of COVID-19 in terms of ICU admission and mortality.³ In a cross-sectional study, hyperandrogenic women group had showed more severe COVID-19 disease course with more pronounced signs and symptoms, $p < 0.05$.³⁵ A prospective cohort study that involved 77 males hospitalized had showed that those who were using 5-alpha-reductase inhibitors or other antiandrogen drugs were admitted less to the ICU, in comparison to those not taking the antiandrogens.³⁶ Similarly, the previous study showed the use of 5ARi resulted in lower COVID-19 symptoms in males with AGA.³⁷ An antiandrogenic drug, spironolactone, was also proved to provide protection against the novel coronavirus (SARS-CoV-2) induced acute respiratory distress syndrome (ARDS) in COVID-19.³⁸ Vicenzi M et al. in a retrospective study of 69 patients had proved the efficacy of the mineralcorticoid receptor antagonist canrenone, a diuretic similar to spironolactone in COVID-19 patients.³⁹ McCoy J, et al. had shown in a prospective longitudinal study of hospitalized COVID-19 male patients that AR gene polymorphisms was strongly correlated with disease severity with longer duration of hospitalization and more ICU admission with longer CAG repeat polymorphism.⁴⁰ Similar results were obtained by another group from Italy that again demonstrated that longer CAG repeats (>22) were associated with severe outcomes in COVID-19.⁴¹ Cadegiani FA, McCoy et al. had demonstrated in the results of a randomized double blind placebo controlled interventional trial (the DUTA AndroCoV-trial/biochemical) that Dutasteride, an ARi had reduced viral shedding, inflammatory responses and accelerated remission in COVID-19.⁴²

Bromhexine hydrochloride (BRH), commonly used as anticough medication, was the first reported drug as a TMPRSS2 inhibitor.⁴³ A recent study was conducted for COVID-19, where a randomized controlled trial was conducted involving 78 patients of COVID-19 pneumonia.⁴⁴ It was found that use of BRH is associated with decreased number of ICU admissions and fatality rate.⁴⁴ Li T et al. had conducted an open label randomized controlled pilot study where high dose of Bromhexine

hydrochloride was used for the treatment of moderate COVID-19.⁴⁵ demonstrated that the BRH resulted in improvement in chest X-raying, lower liver injury, and a quicker rate of discharge. Ambroxol, a substance of BRH was shown to prevent the binding of SARS-COV-2 to ACE2, whereas BRH showed an equivalent inhibition solely at lower concentrations.⁴⁶ Ambroxol may have similar activity in TMPRSS2 inhibition of BRH. Combination therapies of BRH with anti-androgens are projected and would possibly give any profit than monotherapy by block antecedently expressed TMPRSS2 and speed AR promoted transcription.

Abbreviations: COVID-19, coronavirus disease 2019; SARS-COV-2, severe acute respiratory syndrome coronavirus 2; HNS, Hamilton-Norwood scale; ICU, intensive care unit; AGA, androgenetic alopecia; AR, androgen receptor.

Conclusion

Targeting the TMPRSS2 directly or indirectly through androgen pathway with various therapeutic antiviral agents clearly shows the correlation between the androgenic alopecia and COVID-19 virus.

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