ICU
MANAGEMENT & PRACTICE

COVID-19: Molecular Mechanisms of Gender Differences

The COVID-19 pandemic has resulted in hundreds of thousands of deaths around the globe. An important thing to note is that more men have died from COVID-19 than women. A European study shows that men had a slightly higher incidence of COVID-19 with no respiratory distress compared to women. Still, more males with COVID-19 developed severe respiratory failure compared to females. Other studies also show that men are more likely to die from the SARS-CoV-2 infection than women, and this is true across all age groups under 90 years. The same pattern was observed during the SARS outbreak, where men had a higher case fatality rate than women.

Why is this the case? Is this a biological phenomenon? Or is this the result of gendered behaviours? A number of hypotheses have been proposed to explain this gender difference. Some of these include social and cultural differences between males and females (smoking, underlying disease, sex-specific immune defense factors, etc.).

In this review, the authors discuss the impact of sex on the immune response and explore potential mechanisms to explain gender differences in COVID-19.

ACE2 Activity

Angiotensin-converting enzyme 2 (ACE2) has been linked in the pathogenesis of COVID-19. It catalyses the conversion of angiotensin I and angiotensin II to Ang 1-9 and 1-7. This leads to organ protection. It also serves as the receptor for the entry of the SARS-CoV-2 virus into the cells. The ACE2 gene is located on X chromosomes. Females have two X chromosomes, so they function in a coordinated fashion, but men have a single X chromosome, so they lack the cellular protection that might be needed during COVID-19.

Pattern Recognition Receptors

Toll-like receptors (TLRs) are pattern recognition receptors that recognise pathogen-associated molecular patterns from viruses and initiate immune responses. Several of these TLR singling genes are encoded on the X chromosomes. Women have two X chromosomes hence their TLR-mediated response may be more enhanced compared to males who have only one X chromosome. Also, the X chromosome contains 112 micro-RNAs, while the Y chromosome contains only 2 micro-RNAs. A cytokine storm has been observed in patients with COVID-19. Females have shown a more balanced and adaptive system during this storm compared to men.

Sex Hormone Bias

Another factor that may be going in women's favour is oestrogen, a powerful steroid involved in numerous biological processes. Oestrogen has cardioprotective, anti-inflammatory and anti-oxidative effects. Females have higher levels of oestrogen than males, and the distribution and expression of oestrogen in the local tissue may contribute to lower COVID-19 mortality in women than men.

Immune Response

Immune cells obtained from females have been found to exhibit a stronger response than cells isolated from males. Unlike oestrogen, testosterone has been shown to have a suppressive effect on the immune system.

Conclusion

Several clues could explain the gender difference in COVID-19. Sex differences in genes, chromosomes and hormones may be playing a role, and hence it is important to consider gender as an important parameter when designing and analysing clinical trials. A closer analysis of sex differences could reveal novel therapeutic and interventional approaches to the treatment of COVID-19.

Source: Critical Care

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Published on : Thu, 30 Jul 2020