COVID-19 revolution: a new challenge for the internist

COVID-19 and gender differences: lights and shadows

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ABSTRACT

As the main title '*COVID-19 revolution: a new challenge for the internist*' states, the global coronavirus infection disease 2019 (COVID-19) pandemic represented a new challenge for the internists. This paper is part of a series of articles written during the difficult period of the ongoing global pandemic and published all together in this fourth issue of the *Italian Journal of Medicine*, with the aim of sharing the direct experiences of those who were the first to face this severe emergency, expressing each point of view in the management of COVID-19 in relation to other diseases. Each article is therefore the result of many efforts and a joint collaboration between many colleagues from the Departments of Internal Medicine or Emergency Medicine of several Italian hospitals, engaged in the front line during the pandemic. These preliminary studies therefore cover diagnostic tools available to health care personnel, epidemiological reflections, possible new therapeutic approaches, discharge and reintegration procedures to daily life, the involvement of the disease not only in the lung, aspects related to various comorbidities, such as: coagulopathies, vasculitis, vitamin D deficiency, gender differences, *etc*.. The goal is to offer a perspective, as broad as possible, of everything that has been done to initially face the pandemic in its first phase and provide the tools for an increasingly better approach, in the hope of not arriving unprepared to a possible second wave.

This paper in particular deals with COVID-19 and gender differences.

Introduction

It has been described that both severe acute respiratory syndrome- and Middle East respiratory syndrome-coronavirus infected more males than females.[1] To this regard, number of deaths for coronavirus infection disease 2019 (COVID-19) is unequally distributed between genders, with males having a less favorable profile.[2-4] In particular, it has been reported that the male:female death ratio in confirmed cases of COVID-19 goes from 1.8 to 2.8.[1] To this regard Xie *et al*. reported that 75% of deaths due to COVID-19 occurred in male.[3] Several factors may contribute for these epidemiologic results. In particular, we report risk factors in gender differences that may contribute to COVID-19 infection.

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COVID-19 and gender differences

Comorbidities, alcohol abuse and smoking

These factors play a relevant role in disease evolution. In particular, pre-existing diseases, such as cardiovascular or respiratory impairment, hypertension or diabetes may unfavorably impact the course of the COVID-19. However, higher risk behaviors, such as alcohol abuse and smoking, more common in males than in females, may play a role in the pathophysiological process of COVID-19.[2,3]

Hormones and immune regulation

It has been reported that hormones such as estrogens, androgens and progesterone exert different effects

on immune regulation. Sex dependent hormones, as well as the difference in immune response X-linked genes, may play a role in the immune response to virus.[4] As reported in Figure 1, females exhibit more vigorous innate, cell-mediated, and humoral immune responses to antigenic challenges than males. These factors can reduce pathogen load and accelerate pathogen clearance, but can lead to a consequent increase in immune-related pathology, such as autoimmune or inflammatory diseases. The crucial differences in the immune systems of males and females are attributed not only to differences in sex hormones, but are related to X chromosome gene contributions and the effects of environmental factors.[5,6] It is well known that estrogen suppresses T and B cell lymphopoiesis, activates B cell function and influences T cell development. Moreover, estrogen regulates a number of cytokines [such as interleukin (IL)-1, IL-10, and interferon γ (INFγ)] that modulate the immune response. While estrogen has immune-stimulatory roles, progesterone and androgens are immune-suppressive and counteract the pathways affected by estrogen.[7] In particular, progesterone increases IL-4, reduces IFN-γ T helper cell type 1 (Th1)7 responses and reduces T cell proliferation and T cell dependent antibody responses. However, in CD8 T cells, progesterone reduces IFN-γ and cytotoxicity.[8] The androgens also have immune-suppressive effects on the immune response.

X chromosome

X chromosome contains several immune-related genes. In particular, females are mosaics for X-linked genes, and this contribute to generate a stronger immune response (both innate and adaptive) and more frequent autoimmune and inflammatory diseases in female subjects.[9]

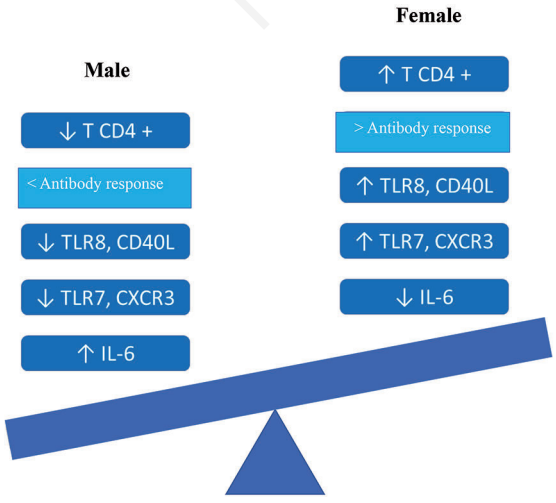

Figure 1. Immune regulation by gender differences.

ACE-2 enzyme expression

Angiotensin-converting enzyme 2 (ACE-2) represents the primary route of infection of COVID-19. It is located on X chromosome, and female may have higher levels of this enzyme. It is expressed in lungs, kidneys, myocardium, gastrointestinal system and reproductive organs. Although it remains unclear how a greater expression of ACE-2 in female patients seems not linked to worst rates of infection and worst outcomes in COVID-19 pandemic, it is clear that ACE-2, that represents the route of infection, also exerts several immunomodulating effects that may explain less severe clinical outcomes. Actions exerted by this enzyme consist not only in the conversion of angiotensin I, but also in immunomodulation and prevention of lung injury, with a protective effect in female subjects.[10]

Vitamin D

The protective effect of vitamin D has been reported in many conditions associated with pneumonia, cytokine hyper-production and acute respiratory distress syndrome.[11] Some studies suggest the effectiveness of vitamin D as an adjuvant therapy with antiretroviral agents in HIV-infected patients.[12] Vitamin D also enhances cellular immunity, reducing the cytokine storm induced by the innate immune system[13] and reduces the production of pro-inflammatory Th1 cytokines, such as tumor necrosis factor α and INFγ.[14] Vitamin D is a modulator of adaptive immunity.15 In fact, it suppresses responses mediated by the Th1, repressing production of inflammatory cytokines as IL-2 and INFγ.[16] Furthermore, 1,25(OH)2D3 promotes induction of the T regulatory cells inhibiting inflammatory processes.[17] Unfortunately, serum 25(OH)D concentrations decrease with age and in male subjects,[18] and it may be crucial for COVID-19 infection and for case-fatality rates.[19] To reduce the risk of infection, it is recommended that people at risk of influenza and/or COVID-19 consider taking 10,000 IU/d of vitamin D3 for a few weeks to rapidly raise 25(OH)D concentrations, followed by 5000 IU/d.[20]

Gender-based pandemic violence

Stress, the disruption of social and protective networks, loss of income and decreased access to services can all exacerbate the risk of violence for women in the pandemic period, as reported in Figure 2. The problem of gender violence has been addressed in literature. In particular, it has been reported that females have a demonstrated higher prevalence of posttraumatic stress symptoms than males, as negative alterations in cognition or mood and hyper-arousal.[21] The COVID-19 infection is new to humans, and only limited scientific evidences are available to identify the impact of these infection on mental and sexual health.[22] Therefore, there is an urgent

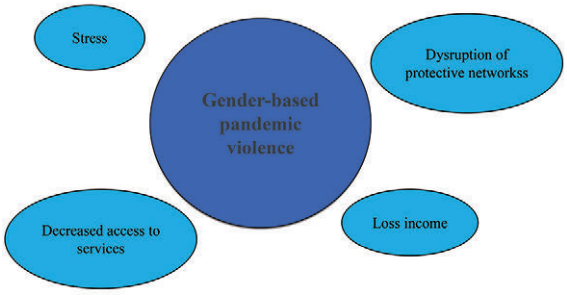

Figure 2. Risk factors and gender-based pandemic violence.

need for the scientific community to generate sound clinical, epidemiological, and psycho-social behavioral links between COVID-19 and rights outcomes.

Key messages

- Comorbidity and higher risk behaviors may unfavorably impact the course of the COVID-19.
- Females exhibit more vigorous innate, cell-mediated, and humoral immune responses.
- ACE-2, more expressed in female patients than in males, seems to exert a protective effect.
- Vitamin D also enhances cellular immunity, reducing the cytokine storm induced by the innate immune system. It is reduced in male and older subjects.
- Stress, the disruption of social and protective networks, loss of income and decreased access to services all can exacerbate the risk of violence for women in the pandemic period.

Conclusions

Future studies are needed to evaluate the gender differences on the death rate, outcome, susceptibility and risk factors in COVID-19 disease.

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