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HYPOTHESIS

COVID-19 pandemic: is a gender-defined dosage effect responsible for the high mortality rate among males?

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Humankind is currently confronting a new type of coronavirus, and it may take considerable time before the human population and the virus arrive at a mutual equilibrium. The first patients with coronavirus disease 2019 (COVID-19) were recorded in December 2019 in China (Zhu et al. 2020), and since then the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has spread globally. Other reputed members of the coronavirus family are SARS-CoV-1 and MERS-CoV, which caused zoonotic events that resulted in epidemics in 2002 and 2012, respectively (Peiris et al. 2003; Zaki et al. 2012). According to the WHO (22/4/2020), more than 2,400,000 individuals have been infected by SARS-CoV-2, and at least 165,000 have succumbed to the disease (https://covid19.who.int). Most patients with COVID-19 suffer from severe respiratory problems, and elderly people in particular or persons with comorbidities seem to be at greatest risk (Wang et al. 2020). The fatality rates for males are two to three times higher than for females (Porcheddu et al. 2020), but seem to fluctuate depending on the territory and demography of the population. Gender-related social factors, immunological differences, hormonal disparaties, and lifestyle habits such as smoking and alcohol consumption are considered to play a role (Wenham et al. 2020). The vulnerability of the male population with regard to the COVID-19 pandemic may to some extent be a result of gender-defined genetic polymorphisms.

At least two coronaviruses use Angiotensin Converting Enzyme 2 as port of entry (ACE-2) to infect the host (Hoffmann et al. 2020; Kuba et al. 2005). ACE2 plays an important role in controlling blood pressure and regulating cardiac function, and is abundantly present on the epithelial cells of the lung, heart, blood vessels, kidneys, and intestines. Although the gene for ACE2 is located on the female sex chromosome, its location and polymorphisms do not seem to have had a bearing on the poor prognosis for male patients during the SARS-CoV-1 epidemic (Chiu et al. 2004).

Another group of promising candidates could be genes involved in immunity. One of the prominent families that senses infection, and that is essential to the innate immune system, comprises the Toll-like receptors (TLR) (Akira and Takeda 2004). In humans, there are 10 different members, and each of them can be activated by different types of ligands stemming from disparate pathogens. TLR often act in the form of homo- or heterodimers, and play a role in clearing infections. Some TLR types are expressed on the cell surface, but the ones present on intracellular membranes of endosomes (TLR3, 7, 8, and 9) are intended to register, though not exclusively, viral infections by detecting foreign types of nucleic acids (Fitzgerald and Kagan 2020). The nuclear material of coronaviruses is single-stranded RNA (ssRNA). TLR3 and 9 interact with double-stranded viral RNA and unmethylated CpG DNA from bacteria and viruses, respectively (Parker et al. 2007). TLR3 may respond to infections by the West Nile virus – also an ssRNA virus – in a rodent model (Wang et al. 2004). In contrast to TLR3 and 9, the structurally related TLR7 and 8 tandem is encoded by the female X chromosome (Armant and Fenton 2002). Therefore, these latter two genes may represent gender-related risk factors. The prominent ligand for TLR7 and 8 is viral ssRNA (Diebold et al. 2004; Heil et al. 2004) and, more specifically for TLR8, its RNAse T2 degredation products (Greulich et al. 2019). In humans, TLR7 is constitutively expressed on the membranes of endosomes in plasmacytoid dendritic cells (DC) and B lymphocytes, whereas TLR8 is more prominently present in cells of the myeloid lineage such as monocytes and neutrophils (Hornung et al. 2002). TLR7-positive plamacytoid cells are copiously present in lung tissue (Plantinga et al. 2010). Upon activation of the TLR7 pathway, for instance by the influenza virus, plasmacytoid DC have the capacity to produce significant amounts of type I interferon (Di Domizio et al. 2009).

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Moreover, TLR8 is present in the lung, and is known to act upon infection by various viruses (Beignon et al. 2005; Heil et al. 2004). An immune response activated via the TLR7 and/or 8 pathway may also induce unwanted side effects. SARS-Cov-1, for instance, may induce a cytokine storm (Tang et al. 2016), and the viral activation of neutrophils in the case of asthma may result in lung pathology (Li et al. 2013). One of the two female sex chromosomes is generally inactivated in females (Lyon 1992; Schurz et al. 2019). In female immune cells, however, TLR7 genes – and probably TLR8 – escape such silencing. As a consequence, the genetic information on both chromosomes is expressed, whereas male individuals possess only a single copy of the X chromosome (Souyris et al. 2018). Gender-related expression profiles may result in a prominent dosage effect in which females are more prone to activate an immune response to single-stranded viruses such as SARS-CoV-2. Furthermore, the induction of cytokine profiles seems also to be dose dependent on the amount of genetic material delivered by the virus (Tang et al. 2016).

This gender-determined dosage effect, however, is probably not the whole story. The TLR7 and 8 genes display copy number variation (CNV) in the population (Wang et al. 2014). In addition, TLR genes display allelic polymorphisms (Menendez et al. 2019; Wang et al. 2014) that may influence the strength of the interaction with their respective ligands or the quality of the ensuing signal that is transduced to the nucleus. There is ample proof that gender-based CNV of TLR7 has medical implications. The best-documented example is provided by systemic lupus erythematosus (SLE), a disorder in which the immune system attacks healthy tissue. This disease is far more prominent in females than in males, and the risk of developing SLE is associated with a higher copy number load of TLR7 (Deane et al. 2007; Wang et al. 2014). As a result, TLR7-related CNV may act as a two-edged sword. A high copy number load of TLR7 may guarantee a better protective response to ssRNA viruses, but it may also suggest a poor prognosis for individuals who are at risk of developing SLE. One has to realize, however, that CNV of TLR genes was not selected in nature to foster autoimmune-related disease – its biological role in controlling virus irradication is likely to be more relevant. Therefore, it seems worthwhile to start documenting the types of TLR7 and 8 polymorphisms in different well-defined populations/cohorts that have been affected by COVID-19. Knowledge regarding the mechanisms of disease pathology may be applicable not only in future vaccine development (the constitution and dosage of vaccine components for males versus females) but also with respect to the route by which such a vaccine should be administered (local versus systemic).

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