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Factors related to asymptomatic or severe COVID-19 infection

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ABSTRACT

The factors that may contribute to a COVID-19 patient remaining in the asymptomatic stage, or to the infection evolving into the more serious stages are examined. In particular, we refer to the TMPRSS2 expression profile, balance of androgen and estrogen, blood group-A and/or B, nonsynonymous mutations in ORF3, and proteins NS7b and NS8 in SARS-CoV-2. Also, we review other factors related to the susceptibility and pathogenicity of SARS-CoV-2.

Introduction

Severe acute respiratory syndrome coronavirus-2 (SARS CoV-2) has been spreading around the world. As of September 11, 2020, 28,205,308 infected subjects and 910,157 deaths have been reported worldwide [1]. Thus, researchers are looking for multiple factors that develop efficient antiviral activity in healthy subjects, resulting in asymptomatic infection. Also, attention must be drawn to the asymptomatic presence of COVID-19 in children, adults and even the elderly. Unlike severe pneumonia with hypercoagulopathy and microvascular immunothrombosis [2], COVID-19 is more frequent in older subjects and those with comorbidities, however, it is also presented in young people with and without risk factors [3].

The hypothesis

In the first months of the COVID-19 pandemic, most authors focused their attention on features such as the high expression of ACE2 in the salivary glands in asymptomatic infection [4], and the maturity and binding capacity of ACE2 [5,6]. Nevertheless, there is a possibility that the presumed asymptomatic stage may depend on the virulence of SARS-CoV-2 and the susceptibility of the subject.

Susceptibility may be related, in part, to the nasopharynx, salivary glands and other tissues. Other factors may also be involved, such as the ACE2 gene polymorphisms, which cause variations in the affinity, binding and processing of the SARS-CoV-2 spike protein [7], and lower levels of ACE-2 and its posterior angiotensin II up-regulation [8]. Moreover, the TMPRSS2 variation can influence susceptibility [9] because both are expressed in the salivary glands [10]. Other genes involved in the different responses between the sexes to SARS-CoV-2 are SRY, SOX9 and the TMPRSS2 gene [11,12]. Based on the balance of androgen and estrogen, a low prenatal testosterone/high prenatal estrogen level is indicated by a high mean 2D:4D. This is expressed in females in the index finger (2D), which is generally equal to or longer than the ring finger (4D), while in males, the 2D is usually shorter than the 4D [13]. A higher 2D:4D ratio is associated with COVID-19 severity in men [14], this means that sex hormones play a role in protection, thus, causing women to develop less serious complications or an

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Table 1
Factors related to susceptibility or pathogenicity of SARS-CoV-2.

Factor type	Factor	Research type	Study characteristics	Key findings	Author(s)
Related to susceptibility	Variants and expression of ACE2 and TMPRSS2 genes.	Exome and SNP-array data from a cohort study.	They explored 3,984 exomes from a representative sample of the Italian population to extract the variants in exons and splice junctions of ACE2.	Although there are conflicting data with ACE2, they found sex-related differences in the TMPRSS2 expression.	Asselta et al., 2020 [40]
	TMPRSS2 expression profile.	Genetic variations, expression, functional effects of SNPs, post-translational modifications, and miRNA profiles were studied by *In-silico* analysis.	They explored prostate adenocarcinoma tissues, lung adenocarcinoma and normal tissues in African, Asian, European, South Asian, and American populations	21 SNPs affected the function and structure of TMPRSS2	Kai & Kai, 2020 [6]
	Balance of androgen and estrogen.	Multi-national Internet Study and self-reported cases.	A survey with 255,116 participants from more than 100 countries, with 200 questions on demographic aspects and the self-measurement of the length of the index finger (2D) and the ring finger (4D).	The case fatality rates (CFR) and percentage of male deaths due to COVID-19 correlate positively with a mean of 2D:4D males per nation.	Manning & Fink, 2020 [14]
	Blood group-A and/or B.	Meta-analysis	They compared ABO blood group distribution in a total of 1,775 and patients with COVID-19, 206 deceased cases, in three hospitals, from Wuhan, Hubei and Guangdong provinces, China. 3,694 non-COVID-19 and 23,386 non-COVID-19 from Wuhan and Shenzhen cities respectively,	People in blood group A have a significantly higher risk for COVID-19 infection compared to those in blood group O.	Zhao et al., 2020 [19]
	ABO blood group	Retrospective case-control study	They studied 187 COVID-19 patients and a control group of 1 900 patients from Changsha, Hunan Province, China.	Blood group A has an increased risk for COVID-19 infection, while blood group O is associated with a decreased risk.	Wu et al., 2020 [41]
	Histocompatibility complex (MHC) class I	*In-silico* analysis	They analysed viral peptide-MHC class I binding affinity in 145 HLA-A, -B, and -C genotypes for all SARS-CoV-2 peptides and searched cross-protective immunity conferred by previous exposure to four common human coronaviruses	They report that HLA-B*46:01 has the fewest binding peptides for SARS-CoV-2, proposing that people with this allele have more vulnerability. Furthermore, HLA-B*15:03 has a greater capacity to present conserved peptides, which suggests that it could allow a better T-cell-based immunity.	Nguyen et al., 2020 [21]
	25-Hydroxyvitamin D	A cohort study	A cohort of 107 total patients from Switzerland including 27 SARS-CoV-2 PCR-positive and 80 SARS-CoV-2 PCR-negative.	The authors suggest that vitamin D supplementation may reduce the risk of infection.	D'Avolio et al., 2020 [42]
Related to pathogenicity of SARS-CoV-2	Analysis of variants and mutation in SARS-CoV-2	Isolate of SARS-CoV-2, Vero-E6 cells culture, and Whole-genome sequences of isolates.	They analysed SARS-CoV-2 grown in VeroE6 to identify quasi-species in clinical isolates. They identified a panel of variants (Del-mut) and found that one of the variants attenuates its ability to cause disease in infected hamsters.	Deletion in S1/S2 cleavage site region could attenuate virus pathogenicity.	Lau et al., 2020 [25]
	Functional domains in the 3a protein and ninsynonymous mutations in ORF3a	*In-silico* analysis	2,782 genomes were analysed. Protein domains in 3a protein of SARS-CoV were compared to those of 3a protein in SARS-CoV-2, RaTG13, Pangolin-CoV and SARS-Civets. Alignment, evaluation of Domains, motifs, membrane topology analysis and Phylogenetic analysis were performed.	They found nonsynonymous mutations and identified six functional domains in the SARS-CoV-2 3a protein. These domains were linked to virulence, infectivity, ion channel formation, and virus release.	Issa et al., 2020 [26]
	G614 mutation	Linear regression analysis	Linear regression of average case fatality rate with the percentage of viruses exhibiting mutation of an aspartate (D) at position 614 to glycine (G) in different countries.	SARS-CoV-2 with the G614 mutation is a more pathogenic strain.	Becerra-Flores et al., 2020 [27]

asymptomatic COVID-19 Infection [12].

Following SARS-CoV-2 translation and RNA replication, a complex group of glycans is expressed and added to new viruses [15]. These glycans are formed in cells that co-express ACE2 [16]. Among these new virus glycans, the ABO (H), blood group-A and/or B-specific mucin-types [17] may play an important role, i.e., if the subject is blood group "O" and has anti-A and anti-B antibodies, these antibodies may block the attachment and entry of the virus, similar to SARS-CoV spike protein [18]. This could mean that individuals with blood group O would have a much lower risk of becoming infected, depending on the type of anti-αGal, anti-A or, Anti-B antibodies, as reported in an earlier study [19]. Although there are still no complete studies related to histo-blood group antigens and susceptibility of low or non-secreting fucosyltransferase 2 salivary status, fucosyltransferase 2 is known to be related to viral infections or complications [20].

Alleles of the major histocompatibility complex (MHC) class I may cause vulnerability to a more severe infection, such as HLA-B*46:01 and, subsequently, to COVID-19, although, HLA-B*15:03 may present a better response of T lymphocytes [21]. Furthermore, a mineralocorticoid receptor that controls blood pressure may explain cardiac injury in severe cases of COVID-19, due to an aberrant CD8 + T cell activation [22].

A case report based on viral kinetics monitoring, shows that clinical evolution could depend on the viral load in the nasopharynx, despite its limitations due to the number of cases studied [23,24].

On the other hand, the 15–30-bp deletions in the S1/S2 cleavage site region attenuate the ability to cause severe lung disease, as seen in the hamster model [25]. Nonsynonymous mutations in ORF3a could be related to the pathogenicity of SARS-CoV-2 [26]. In addition, the mutation of an aspartate (D) at position 614 in the D614G viral spike has a significant correlation with case fatality rates [27]. Thus, the deletion of the accessory proteins in NS7b and NS8 could be related to the virus infectivity [28]. Other important factors considered useful in keeping a subject at the asymptomatic stage are vitamin D levels in addition to 'essential' amino acids (I, L, K, M, F, T, W, V, H) [29], zinc, and vitamin E status [30].

Evaluation of the hypothesis

The world faces a new disease, named COVID-19 [31]. It begins with a lung infection, which we now know is a significant basis in endothelial inflammation and micro thrombosis [32]. It affects numerous systems and organs such as the cardiovascular, central and peripheral nervous, gastrointestinal, reproductive, and vascular, as well as the haematological, renal, and skin [33]. The elderly are known to have a higher death rate from COVID-19, moreover, more than 30% of infected subjects have comorbidity, men having a 1.5 times greater probability of dying [34].

The ACE2 receptor and the TMPRSS2 protease facilitate entry of SARS-CoV-2 are highly expressed in the nasal goblet and ciliated cells [35]. The coexpression of these receptors in these cells suggests that they could be the sites of the original infection and possible reservoirs of dissemination [35]. The coexpression of both cells in specific tissues may explain different phenotypes such as gastrointestinal [36], neurological [37], cutaneous [38] and ocular [39], among others.

Mechanistically, it is possible that the interaction of factors related to susceptibility or pathogenicity makes a subject asymptomatic or not. An in-depth study of the factors associated with asymptomatic subjects can provide information to limit severe COVID-19 as much as possible. The evidence reported to date is shown in Table 1.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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