

Relationship Between Herpesvirus and Covid-19; Literature Review

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Abstract

From the evolution of severe acute respiratory syndrome or COVID-19, which through studies was called SARS-Cov-2. This generated a pandemic that has caused a global crisis in recent years, thus, cases of people with skin manifestations have been reported either before or after the phases of COVID-19 infection. However, most cases with Herpes Virus were evidenced in immunocompromised people, or patients with comorbidities, that is, in patients who presented a critical state where they could manifest through: small papules, vesicles and pustules of different sizes. Therefore, it is important to inform health personal of this condition that increases mortality. This article focused on describing the relationship between Herpes Viruses and Covid-19 in order to facilitate their diagnosis and treatment, thanks to the fact that a search analysis was carried out through scientific bibliographic reviews.

Keywords: Covid 19; Herpes Virus; SARS-CoV-2; immunosuppression; cutaneous manifestations; vesicular rash; Vaccines.

Introduction

In recent years the population has been affected by a health problem and due to the appearance of severe acute respiratory syndrome or COVID-19, by a mutation of SARS-CoV-2 coronavirus causing a health crisis. This highly transmissible virus and pathogen in humans that has caused public health emergencies and global crisis becomes very contagious and spreads massively between people through respiratory secretions such as sneezing, coughing, contact between individuals closeors and thus cause respiratory infections that can range from the common cold to more serious diseases becoming fatal, generating an abnormal immune response of inflammatory type, aggravating the patient's condition thus causing multi-organ damage. (2,3)

Among some of the most frequent symptoms we have fever or chills, cough, shortness of breath (feeling short of breath), fatigue, muscle and body aches, headache, recent loss of smell or taste, sore throat, congestion or runny nose, nausea or vomiting, diarrhea. However, during the pandemic skin manifestations have been witnessed, which show a great relationship with COVID-19, so it could be considered that these conditions at the skin level may be secondary to COVID-19 disease; They range from pharmacodermis to the use of drugs such as vaccines that were used to treat this infection,

dermatoses due to the various protective equipment handled in the fight against the disease, and other dermatoses that have been increased in terms of their incidence such as: acne, rosacea, seborrheic dermatitis, herpes zoster and herpes virus. (3,4)

Since this article is focused on describing the relationship between Herpesvirus and COVID-19, it is necessary to talk about the herpesviridae family, this virus called Herpes Virus (HSV) has been characterized as one of the main causes of numerous infections in the orofacial and genital areas. The herpes simplex virus is the prototype of herpesvirosis, a large family of double-stranded DNA viruses that cause significant morbidity in humans. This is how Herpesviruses are the most important DNA-type viruses in oral pathology and acquire special relevance when they infect subjects with HIV or people with immunosuppression. (1)

Herpesviruses are made up of a well-defined structure, with a strand of DNA surrounded by an icosahedral capsid. This, in turn, is surrounded by a tegument containing between 15 and 20 proteins and which is in direct contact with a vacuum containing numerous glycoproteins. Infection of mucosal epithelial cells causes a variety of clinical manifestations and latent infections at the level of sensory neurons. Several viral proteins are expressed during the proliferative phase of infection, but few of these proteins are expressed during latency. (1.4)

This is how, COVID-19 infection can represent a trigger for the reactivation of the Herpes Virus, since suffering from the COVID-19 disease produces immunosuppression, resulting in people becoming more susceptible to this virus, as well as associated infections.

Methods

A bibliographic review was carried out where the analysis of original articles and systematic reviews obtained during the last years that contribute with information on the relationship between Herpesvirus and COVID-19 was executed. The search was done by consulting the database of PubMed, Scielo, ClinicalKey and Scopus also used in the Google Scholar search engine keywords such as: Herpes Virus, COVID-19 or SARS-CoV-2, immunosuppression, skin rashes, pustules.

Results

Epidemiology

When analyzing the studies and articles in which there is evidence of an increase in cases in patients with Herpes virus after the presence of COVID-19 or SARS-CoV-2, the prevalence of herpesvirus in patients with COVID-19 is estimated. HSV spreads in the world, being highly transmissible, is highly contagious and affects the whole society. Cases and studies show that in both men and women it occurs, however, the highest risk of appearance of Herpes virus is in immunosuppressed people, the population that is affected is approximately 67% ranging from 0 to 49 years, but usually occurs between the ages of 10 and 40 years. Minor and major canker sores are seen in both sexes equally; with onset between 5 and 19 years, and herpetiformes from 20 to 29 years, predominate in women. (4,7)

Physiopathology

SARS-CoV-2 has caused a pandemic with a global crisis in recent years, causing a large number of deaths, with a large number of production systems, but even more, with skin manifestations by herpes virus.

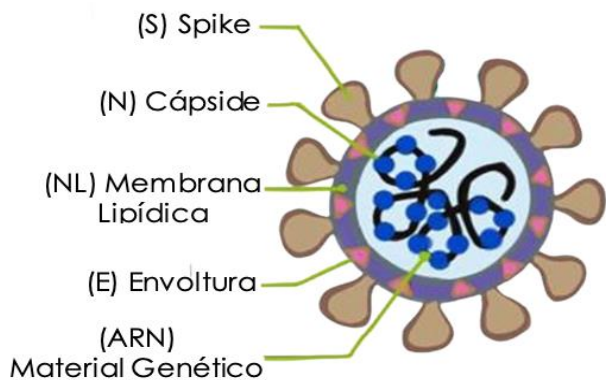


Figure 1. It is the structure of the SARS-CoV-2 virus. Source: Own preparation, 2022

This is how the Herpes Virus also known as herpes simplex, is characterized by an infection caused by

herpes simplex virus (HSV) type 1 and type 2, affects the skin and mucosa or oral or genital and is characterized by groups of vesicles that live on an erythematous base and disappear on their own without leaving the immune system, so they can be repeated. There is no specific treatment. The nine human viruses are herpes simplex virus 1 (HSV-1), HSV-2, varicella zoster virus, human cytomegalovirus (CMV), human herpes virus (HHV) 6A, HHV-6B, Epstein-Barr virus, HHV-7 and Kaposi's herpes sarcoma virus. (1,3,4)

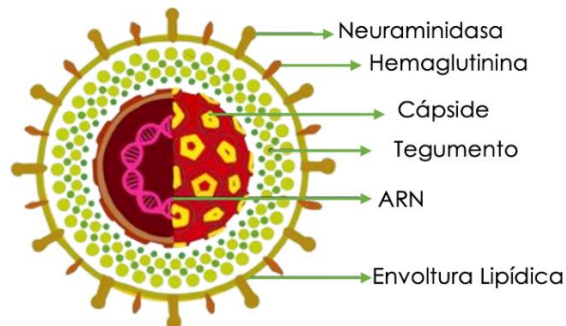


Figure 2. Herpes simplex virus. Source: Own confection, 2022.

Several recent publications show a warning of skin manifestations of covid-19 being associated with human herpesviruses. Among the most common risk factors for this disease are advanced age and immunosuppression. Therefore, the aforementioned increase in herpes zoster during the COVID-19 pandemic can be attributed to patients on invasive mechanical ventilation and recently acute respiratory distress syndrome, lymphopenia and even neurological disorders. (4)

Similarly, four mechanisms have been proposed to explain the resurgence of herpes virus during SARS-CoV-2:

- Immune dysregulation causes herpes viruses to leave latency and travel anterograde to epithelial surfaces, where the virus performs the replication and lytic stages. Interestingly, a possible relationship has been proposed between IL-6, which is overrepresented in COVID-19 patients, and herpes virus reactivation.
- Direct effect of SARS-CoV-2 on neurons: it has a potential neurotropic mechanism that explains neurological manifestations, such as loss of taste and smell, headache, dizziness, meningitis, cerebrovascular disease and acute Guillain-Barré syndrome.
- SARS-CoV-2-related stress is thought to affect the detection of cytotoxic T cells in infected neurons, thereby initiating the activation and replication of hidden viruses. Other theories include the stress-related activity of catecholamines and glucocorticoids and the direct and indirect effects on herpes virus activity.
- Fever associated with SARS-CoV-2 being an environmental factor associated with recovery from human herpes virus infection through direct effects on virus infection in neurons and the release of pyrogenic cytokines, including IL-6. (8)

Therefore, it is important to assess the incidence, risk, and prognosis of herpes virus reactivation in severe cases of COVID-19 and in immunocompromised patients. (6) In addition, another reason why herpesvirus has been modified for the SARS-CoV-2 vaccine is the T-cell-mediated response caused by mimicking the epitope of the viral molecule. Due to the global spread of COVID-19 with mRNA vaccines, it is important for doctors and patients to be aware of potential side effects.

Clinical Manifestations

The most frequent clinical sign is the vesicular rash, which appears in different phases of COVID-19 infection, that is, there are cases that report that this clinical manifestation appears before the respiratory symptoms of the SARS-COV-2 virus and others arise after the diagnosis of the COVID-19 disease, however, a median latency time of 14 days is maintained, with a range of 4 to 30 days. This rash has two different morphological patterns: first, there is the one that has a diffuse pattern with paporsmall, vesicles and pustules of different sizes, invading a specific body area such as the palms of the hands and the soles of the feet. The following is a localized pattern itself characterized by monomorphic lesions, colonizing a single area of the body. (9,10)

Patients who reported these cutaneous manifestations were subjected to a PCR of microarrays of the herpesvirus family using vesicular fluid from skin rashes, the examination showed that the viruses that were infecting the patients were HSV-1, HSV-6, Epstein Barr virus (EBV), HSV-7 and Varicella Zoster virus (VZV). These results show that there is a probability of coinfection by herpes virus, which gives rise to these clinical manifestations, but at the same time the etiopathogenic role of SARS-COV-2 must be taken into account. On the other hand, subjects who have gone to health institutions after the COVID-19 pandemic show a particular picture of lesions at the skin level, produced by the HHV-6 virus, skin diseases caused by this virus include infantile roseola, pityriasis rosea, Gianotti-Crosti syndrome, among other systemic symptoms that include vesicular eruptions, erythema multiforme lesions and pityriasis rosea. (9,10)

Giacobbe et al. (11) have reported that pulmonary reactivations of HSV-1 have occurred in patients with COVID-19, patients who possess risk factors are immunosuppressed, critically ill subjects on mechanical ventilation, and severe pneumonia due to SARS-CoV-2 virus infection. The symptoms of these patients manifested with systemic skin reactions, hepatitis or encephalitis, worsening of the respiratory tract and lung lesions to highlight the most serious.

Within the herpes virus family, we find Epstein-Barr (EBV), cytomegalovirus (CMV) and human herpes-6 (HHV-6), similar to other viruses of the same family herpesviridae have caused signs of clinical

importance in infected patients of SARS-COV-2. La reactivation of pre-existing herpes viruses in the absence of immunodeficiency, in patients with the use of anti-inflammatory drugs and those who have remained in the intensive care unit (ICU) for a while prolonged. The median age of patients diagnosed was 58 years, and overall the results reveal that critically ill patients with SARS-COV-2 infection are more likely to coexist with a reactivation of EBV, CMV, and HHV-6 while in the ICU. (12)

The Epstein-Barr virus belonging to the herpes virus family, appears within 1 or 2 weeks of COVID-19 infection with common symptoms such as fever, insomnia, headaches, myalgia and confusion, the reactivation of this virus and the appearance of these signs and symptoms are associated with the treatment used against the SARS-COV-2 virus since it gives rise to a Alteration of immune responses by regulating intracellular signaling pathways. Similarly, the prolonged use of corticosteroids and the use of medications such as remdesivir affects the appearance of diseases caused by herpes viruses. (13)



Figure 3 A 68 year old male patient diagnosed with *Gibberella ptyriasis rosea* a month after SARS-CoV-2 infection

1. Marte Colina IJ, Vivas-Toro SC. Patients with SARS-CoV-2 and herpes virus. [Internet]. 2022 [cited 24 October 2022]. Available in: <http://revisionporpares.com/index.php/Derma/artic/e/view/7935>

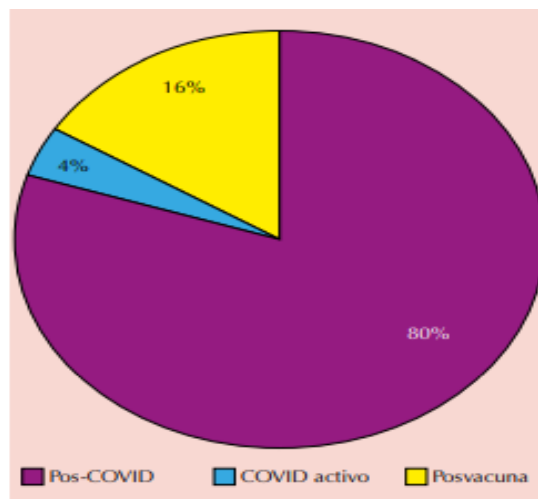


Figure 4 Patients with SARS-CoV-2 and herpes viruses

Marte Colina IJ, Vivas-Toro SC. A 48-year-old male patient diagnosed with Gibert's pityriasis rosea, one month after SARS-CoV-2 infection [Internet]. 2022 [cited 24 October 2022]. Available in: <http://revisionporpares.com/index.php/Derma/article/view/7935>

Complications

The most common complications usually occur in patients with comorbidities, causing systemic infections and confined to an organ, for example, HSV infection that causes pneumonia and another virus commonly found in PCR studies is CMV. Pityriasis rosea caused by HHV-6 or HHV-7 reactivation has been found in two cases, with clinical manifestations such as erythematous plaques with well-defined regular borders around the chest, abdomen and flanks with a typical cleavage distribution, these signs appeared weeks after COVID-19 was diagnosed.

The use of remdesivir produces and reactivation of oncogenic herpes viruses, its adverse effects are counterproductive in the health of patients, this drug is usually used in the treatment of COVID-19, however, studies show that its use leads to the appearance of Kaposi's sarcoma-associated herpes virus (KSHV) and Epstein-Barr virus (EBV) that produce human tumors from their interaction by regulating several intracellular signaling pathways. Patients with factors are subjects who, after acquiring the infection, may have neoplasms associated with KSHV/EBV. (14,15,16)

Treatment

Within the prophylaxis until antiviral treatment in patients with HSV-1 reactivation, there have been great discordances due to the poor clinical results in the use of antiviral therapy in HSV-1 reactivation, the mortality of this reactivation in critically ill patients with SARS-CoV-2 infection and without it, and other setbacks that leave a great bias for a possible effective treatment, Within clinical studies, adequate management has been shown with a range of effectiveness between 70 and 92% from therapy with acyclovir or valacyclovir in critically ill patients. However, in immunosuppressed patients cases of resistance to acyclovir have been described, it is for this reason that it has been chosen to use foscarnet as a supplementary treatment, adjusting the dose according to renal function. The use of cidofovir has also been described, but is limited.

Among the serious patients admitted to the ICU, the most used pharmacological management is the use of ganciclovir for CMV infection, however, in the case of drug resistance or even its lack of response, the administration of foscarnet is necessary. (11)

Discussion

There are different positions regarding the appearance of dermatological lesions associated

with the herpesviridae family in times of COVID-19 pandemic, however, many of these are more accepted than others. Within them, the relevance of the risk factors can be highlighted, only on this population group who has shown clinical manifestations on the skin such as vesicular eruptions around the first or second week after infection by the SARS-CoV-2 virus, many of the cases usually appear during COVID-19 infection, weeks after diagnosis and even later, when the respiratory infection culminated its contagious process.

However, there are hypotheses that are not yet well founded about the close relationship that exists of the reactivation of herpes virus after vaccination with the Comirnaty vaccine and COVID-19 Vaccine Modern, about 29 patients presented symptoms after the first dose, and others after the second dose, the number of cases are insufficient therefore it has been taken into consideration to the relevant authorities for a possible exacerbation of the data. (17)

In relation to the aforementioned, statements and postulations were also given against, under the premise that, as we well know, there are viruses, especially viruses of the herpesviridae family, which produce persistent infections with symptoms that go unnoticed and remain in people's lives without realizing it for years, as in countries where cases of persistent infection by the Epstein-Barr virus (EBV) oscillates in 90% of the population, in the same way Human Herpesvirus 6 (HHV-6) is found in certain sectors of the world infecting 60% of the inhabitants. It is this comparison which allows us to analyze that many of the patients who come to hospitals in times of pandemic with skin manifestations similar to those produced by herpes viruses, are not always a consequence of SARS-CoV2 infection. (18)

In the same way, it is incongruous to associate a skin lesion with herpes virus infection in all cases, just as it is unnecessary to relate a respiratory picture to the contagion of the SARS-CoV-2 virus, simultaneously as a consequence are these actions which lead us to erroneous diagnoses and therefore to the inadequate management of patients. This is how Lovati et al. (19) report a clinical case where a 73-year-old female patient who went to the emergency room with symptoms of fever and unconsciousness during the morning hours, after having analyzed the patient's clinic and under the condition that she was with a reduced oxygen saturation, was diagnosed with a cerebral ischemic stroke in a patient possibly positive for COVID-19, however, after an exhaustive medical evaluation it is deduced that the real diagnosis of the patient was a status epilepticus caused by HSV-1 encephalitis, days later an MRI was performed that showed the extent of brain damage and confirmed a typical distribution of herpetic encephalitis. They are cases like these that happen daily that show us the clear example that after the pandemic we have associated any disease with the SARS-CoV-2 virus without stopping to think about other scenarios, in this case it was a herpes virus that

caused the pathology of the patient but not exclusively after a COVID-19 infection since the woman did not suffer from this pathology, The differential diagnosis is essential and if it had been taken into account during that particular case the consequences could have been minimal and the disease treated in time to avoid it. (19)

Herpesviruses and COVID-19 are two distinct viral infections that have been studied extensively in recent years. While there is currently no direct evidence to suggest that herpesviruses play a role in the severity or progression of COVID-19, several studies have examined the relationship between these viruses. For example, Jami Carrera et al. (21) used a neutrosophic analytical hierarchy process to evaluate skin manifestations associated with the use of COVID-19 protective equipment, while Manuel Antonio Calderón Ramírez et al. (22) employed a PESTEL-based analysis to explore factors influencing neo-constitutionalism in Ecuador. In another study, María Fernanda Latorre Barragán et al. (23) utilized a neutrosophic analysis to select treatments for COVID-19, and Ricardo et al. (24) applied compensatory fuzzy logic with single-valued neutrosophic numbers to analyze university strategic management. These studies provide insight into the broad range of applications for neutrosophic computing and machine learning in various fields, including COVID-19 research

Concludediones

Through the bibliographic review on the relationship between herpesvirus and Covid-19, taking into account the points treated such as its complications, pathophysiology and possible treatments, based on the evidence, the presence of herpesvirus in patients with Covid-19 is thus shown, being a clinical manifestation during the pandemic. It is important to take into account the different interpretations of the studies carried out, in order to reach an adequate diagnosis and determine the relationship between Covid-19 and Herpes Virus, in this way it is possible to reduce complications in different groups of patients with comorbidities.

It is of utmost importance to make differential diagnoses that are useful to solve the conditions of patients, since when crossing through a pandemic period many of the clinical cases that are referred to health units are usually presumed in the first instance to be an infection by COVID-19, it is this literature review which shows us that this disease can coexist with other pathologies, that are not only cutaneous, rather manifestations are shown at the level of various organs and systems, which after a fortuitous diagnosis are easy to solve.

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