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Extrapulmonary complications of COVID-19 disease

Complicaciones extrapulmonares de la enfermedad por COVID-19

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Abstract

SARS-CoV-2 infection is the most important emerging disease of this century. Since its inception to the present, it has caused almost a million deaths worldwide, becoming a real threat to public health. For this reason, new reviews and scientific studies in this regard are extremely important. In the same way, it is known that the main disease caused by this virus is confined to the respiratory system. However, there are still unknown aspects of the disease and within them are extrapulmonary complications. This review attempts to summarize all that is known at the time regarding the disease and its neurological, hematological, cardiological, kidney and liver complications.

Keywords: COVID-19, SARS-CoV-2, complications, neurologic manifestations.

Resumen

La infección por SARS-CoV-2 es la enfermedad emergente más importante del presente siglo. Desde su aparición hasta la actualidad ha ocasionado casi un millón de muertes en todo el mundo, convirtiéndose en una verdadera amenaza para la salud pública. Por tal motivo las nuevas revisiones y estudios científicos al respecto resultan sumamente importantes. De igual manera se sabe que la afección principal por este virus está confinado al sistema respiratorio. Sin embargo, aún existen aspectos desconocidos de la enfermedad y dentro de ellas se encuentran las complicaciones extrapulmonares. La presente revisión intenta resumir todo lo conocido al momento respecto a la enfermedad y sus complicaciones neurológicas, hematológicas. cardiológicas, renales y hepáticas.

Palabras clave: COVID-19, SARS-CoV-2, complicaciones, manifestaciones neurológicas.

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Introduction

Extrapulmonary Complications of COVID-19 Disease

SARS-CoV-2 infection is the most important emerging disease of this century, at the moment there are approximately one million deaths worldwide. The respiratory system is mainly affected by this disease; However, it is also important to know the complications outside of it, since they have a very significant statistical and clinical impact (1).

Within the following review, the search engines were used: PUBMED, COCHRANE and UPTODATE. The NICE guide for cardiac complications was taken as a reference, likewise all the rest of the content was extracted from systematic reviews together with their disaggregated articles in order to provide the closest possible approach to the scientific evidence available to date (2,3).

Among these complications, the following were observed: Cardiovascular, Hepatic, Neurological, Hematological, and Renal Complications and inflammatory response syndromes in adults and children (1-5).

Neurological complications

Neurological symptoms are divided into 3 categories: Central, peripheral and musculoskeletal (6-12). In a study of 43 patients in the UK, neurological symptoms were divided into 4 subgroups: Stroke (8), Encephalopathy (10), Peripheral Nervous System (12) and Inflammatory Syndromes (7.9).

Similarly, in Brescia until April 5, 9,340 cases compatible with Covid-19 were documented and many of them presented hyposmia, anosmia, dysgeusia, dysarthria, allodynia or acroparesthesia. An atypical debut was reported in few patients where delirium precedes respiratory pathology. Within a cohort with 2,660 patients hospitalized for Covid-19, 6 patients reported encephalitis as the only symptom, 2 of them died and 4 had non-febrile seizures. All patients in the study had a respiratory condition afterwards (5).

The incidence of ischemic stroke associated with COVID-19 in hospitalized patients has varied from 0.4 to 2.7 percent, while the incidence of intracranial hemorrhage has

varied from 0.3 to 0.9 percent (8,10 -17). Ischemic brain lesions were more frequent in 20% of those who died from a severe picture of covid-19, showing signs of hypoxic encephalopathy (18).

Neuroimaging shows microhemorrhages and thrombosis in atypical locations such as the corpus callosum or juxtacotical, as well as cerebral venous thrombosis (19-24).

It was reported that 22% of patients who died from Covid-19 experienced delirium (25), the brain MRI after contrast showed a sign of leptomeningeal inflammation and in another French study 27% had an electroencephalogram and magnetic resonance imaging suggestive of encephalopathy (23). Case reports have also reported acute necrotizing encephalopathy or posterior reversible encephalopathy syndrome (26,27).

Within neuropsychiatric disorders in the UK, new-onset psychosis, neurocognitive syndrome and affective disorders have been prominent in a sample of 23 patients (28).

In Parkinson's disease, 51 patients diagnosed with covid-19 experienced a clinical worsening, mainly those who already had the first long-term diagnosis. These were: New or worsened motor symptoms (63%) and non-motor symptoms (75%) (27). In Wuhan, 10.7% myalgias and muscle injuries were found and a case report of rhabdomyolysis (8,16).

Finally, manifestations of Guillian Barre are being presented, even without ending the infection by covid-19, with Guillian Barre being a classically post-infectious picture (17). Other inflammatory syndromes found were: acute disseminated encephalomyelitis (ADEM), Miller Fisher and facial nerve palsy (9,19,24).

Hematologic Complications

Laboratory tests are a fundamental point in decision-making in medicine and current evidence suggests the following findings: lymphopenia as a cardinal prognostic result, a value of less than 1.5x109 L can predict serious clinical results (4.29). The ratio of neutrophils / lymphocytes and platelets / lymphocytes can give us a prognosis for severe cases (4).

Older adults and people with comorbidities have a higher risk of mortality, but young people without risk factors can present fatal complications such as fulminant myocarditis and disseminated intravascular coagulation (30,31).

Note that in the 1 to14 day incubation period and the onset of symptoms, lymphopenia levels are still normal or slightly decreased. It is in the 7 to 14 days of the onset of symptoms that clinical manifestations arise due to the increase in inflammatory mediators and that is where this peripheral lymphopenia becomes evident. Let us also remember that lymphocytes have ACE2 receptors that mediate the entry of the virus, thus causing lysis and alteration in the hemogram (4,33).

In a study with 1099 patients in China, patients had 83.2% lymphopenia, 36.2% thrombocytopenia, and 33.7% leukopenia (34). The association between lymphopenia and the development of ARDS has been demonstrated (35). In addition, 2 studies were conducted in China which mentioned an association between lymphopenia and the need for admission to the ICU (36,37). In Washington, lymphopenia was also prominent in critically ill patients (38,39).

Lymphopenia was also subjected to systematic reviews where the almost 3 times higher risk of unfavorable outcomes compared to better outcomes was mentioned (combined OR: 3.33), thrombocytopenia also significantly higher probability of poor outcomes (combined OR: 2, 36) (40).

The platelet / lymphocyte and neutrophil / lymphocyte index showed a greater increase in severe than non-severe patients (41,42). Platelet count (<150,000) was associated with poor outcomes (40).

The finding of elevated CRP (> 10mg / l) in a meta-analysis that included 4843 patients with covid-19 showed that there is a 4 times greater risk of poor results (combined OR: 3.97%) (40). CRP has been associated with the appearance of ARDS (35).

A systematic review found a significant difference in mean ferritin levels of 606.37 ng / ml (95% CI 461.86, 750.88) between survivors and non-survivors (43). D-dimer and prothrombin time are higher on admission in patients requiring ICU support (37,44-46).

Patients with a cardiac lesion due to covid-19 are more prone to a coagulation disorder, being

those who have troponin-T levels more frequently in the alteration of PT, aPTT and D-dimer (47,48). In 201 patients with COVID-19 pneumonia, increased PT was associated with a higher risk of ARDS and D-dimer was associated with a higher risk of ARDS and death. Complications from DIC can occur in a subset of patients who die independently of ARDS (4,35).

Cardiological Complications

In Italy, in 11% of those who died from covid-19, myocardial injury was found independent of the stage of the disease until July 4, 2020 (49). The NICE guideline on the spectrum of acute myocardial injuries by covid-19 patients found: Acute coronary syndromes, arrhythmias, cardiac arrest, cardiogenic shock, cardiomyopathy, heart failure, myocarditis, pericarditis, and pericardial effusion. In addition to this, the guide emphasizes taking into account the following signs and symptoms: angina, palpitation, severe fatigue, dyspnea.

Troponin is the fundamental auxiliary test in cardiac complications, reflecting cardiac inflammatory injury rather than an acute coronary syndrome. In patients with suspected or confirmed acute myocardial injury, the following should be taken into account: Refer to an environment where cardiac or respiratory deterioration can be recorded. Continuously monitor the EEG. Monitor blood pressure, heart rate, and fluid balance. In patients with a proven diagnosis of myocardial injury, evaluation and management by the cardiology service should be considered.

In patients with high clinical suspicion of myocardial injury, but without a clear diagnosis, it is recommended: a) Repeat high-sensitivity troponin (hs-cTnI or hs-cTnT) and EKG, b) Transthoracic echocardiography evaluation by cardiology department, c) When the clinical condition improves, re-evaluate the treatment goals and adjust, d) Stop the treatment in intensive care when it is not able to achieve the desired general goals.

As has been studied, there is a link between cerebrovascular disease and COVID-19. Let us remember that one of the favorite sites for the expression of ACE2 (angiotensin converting enzyme 2) is the heart. The coronavirus alters the ACE2 signaling pathway, resulting in neuro-humoral imbalance and injury (50). Biochemically, it is ACE2 that stops the activation of the renin-angiotensin-aldosterone system because it converts angiotensin II into angiotensin I, a vasodilator. Then the covid-19 causes its negative regulation by increasing the levels of angiotensin II and the number of ACE2 receptors will increase the viral load (51).

However, a systematic review found no convincing evidence to justify the initiation or discontinuation of currently prescribed medications to influence COVID-19 disease outcomes (52). The AHA (American Heart Association) also mentions this suggestion (53).

Another finding in the alteration of the ACE2 pathway is a decrease in fibrinogen and redox alteration, causing a plaque rupture associated with a stent. This concept presents us with a pathophysiological origin in IMA due to covid-19 and at the same time answers us to: Why does a cerebrovascular disease occur in patients diagnosed with covid-19? (54).

Another pathophysiological mechanism observed in COVID-19 AMI is that of patients who did not have any plaque, presenting a type 2 AMI according to the Killip classification; Remember that in all fever or inflammation our metabolic demand increases and the oxidative stress of the lung also alters gas exchange (55-58). Fulminant myocarditis can also occur in covid-19 due to the great compromise of inflammation in the heart (58).

Within laboratory tests, troponin I is an important predictor even in patients without CVD. The highest mortality occurs in those patients with CVD and elevated troponins, after patients without CVD with elevated troponins; Among those with the lowest mortality we have patients with CVD without elevated troponins and finally without CVD or elevated troponins (59,60).

Supraventricular arrhythmias were found in 393 hospitalized ICU patients with COVID-19 in New York (61). The most common arrhythmia is sinus tachycardia and the most pathological are: atrial fibrillation, atrial flutter, monomorphic or polymorphic VT. Another finding in a Chinese cohort was 11 patients with ventricular tachyarrhythmias in hospitalized patients (59).

Kidney complications

As observed in the review for cardiac complications, the increase in angiotensin II generates vasoconstriction, and the heart is not the only organ affected by it.

A meta-analysis found an association of acute kidney injury (AKI) with severe disease due to covid-1 and an increase in mortality. Being the incidence of AKI by Covid -19 in 10%, revealed by increased levels of BUN and serum creatinine; The fatality rate of 20.3% (62).

Liver complications

In a study investigating the characteristics and prognostic factors in 339 elderly COVID-19 patients, 28.7% of the patients were found to have developed liver enzyme abnormalities (63).

A meta-analysis found a combined OR of elevated ALT (OR = 2.5), AST (OR = 3.4, hyperbilirubinemia (OR = 1.7) and hypoalbuminemia (OR = 7.1) were higher subjects in the Critical COVID-19 - COVID-19-associated liver injury is more common in severe COVID-19 than in non-severe COVID-19 (64).

Conclusion

The COVID-19 disease is new, and although it has affected the whole world, there are still many mechanisms of its pathophysiology and extrapulmonary complications that we have yet to know, so continuing to investigate and generate scientific knowledge in the correct way will help us to close this gap in knowledge of this disease that has become the most important pandemic of this century.

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Contribution of the authors

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Interest conflict

We declare that we have no conflict of interest

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