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Opinion

Acute Microangiopathy, Key Piece in Covid-19: Acute, Sub-Acute and Chronic

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ISSN: 2578-0379

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Submission: March 16, 2022

Published: March 30, 2022

Volume 4 - Issue 5

How to cite this article: Bárcenas AA. Acute Microangiopathy, Key Piece in Covid-19: Acute, Sub-Acute and Chronic. Surg Med Open Acc J. 4(5). SMOAJ.000598. 2022.
DOI: 10.31031/SMOAJ.2022.04.000598

Opinion

We know that COVID-19 and its causal agent, SARS-CoV-2, have caused unprecedented morbidity and mortality since 2019, not only in its acute form, but also in its subacute and chronic forms. Where the cellular and endothelial damage, caused by the dysregulation of the immune response, with the production of a cytokine storm, and a pro-coagulant state induced by the virus, favor the development of sequelae, within which we can list an endless number: fatigue, precordial pain, cognitive, cardiac, digestive disorders, etc. that reduce the quality of life of patients [1]. We have learned and unlearned a lot during all this time and originally COVID-19 was considered a respiratory disease, today we know that it is a systemic disease, where endothelial damage is a key piece: this endothelium that had been considered as a passive internal lining for many years, today we know that it is an independent and extremely important system, centrally involved in hemostatic balance, in the circulation and interaction of blood cells, in the regulation of vascular tone and fluid exchange, so that endothelial dysfunction, in particular, the rupture of the vascular barrier represents the cornerstone in the development of multi-organ failure. The endothelium is protected by a negatively charged, gel-like mesh called glycocalyx, with various activities, including anticoagulant activity, made up of highly sulfated glycosaminoglycans and proteoglycans, such as keratan sulfate, dermatan sulfate, and heparan sulfate, but the thinning of this glycocalyx, up to 3 microns thick, plays a crucial role in leukocyte recruitment, hyperpermeability, and the development of organ damage, particularly lung, heart, kidney, nervous system, and intestine [2].

This has been evidenced in the histological analysis of the pulmonary vessels of patients with COVID-19, where it has been shown that generalized thrombosis with microangiopathy is nine times more frequent in patients with COVID-19 than in patients with influenza, and the development of angiogenesis is 2.7 times greater in COVID-19 also compared to influenza, and when observing the microvascular alterations in the lungs of patients who died from COVID-19 compared to healthy lungs, endothelial destruction and intussusceptive angiogenesis are observed, which we know today is a dynamic intravascular process capable of modifying easily the structure of the microcirculation, whose distinctive structural characteristic is the growth of a cylindrical microstructure that extends through the lumen of small vessels and capillaries, which may play a role in worsening the pathogenesis [3].

The mechanism of cell invasion carried out by the virus is as follows:

a) First, the virus binds to the cell surface thanks to the presence of heparan sulfate;

b) Subsequently, transmembrane serine protease 2 (TMPRSS2), an enzyme responsible for protein turnover and associated with the host cell surface, binds and cleaves the S_1

subunit from S_2, favoring the binding of S_1 to the ACE_2 receptor (enzyme angiotensin converting 2), through the binding domain; let us remember that the virus is made up of proteins and the spike protein is one of the most important, in turn, it is made up of two subunits, S_1 and S_2.

c) Once again, the serine transmembrane protease 2 (TMPRSS2), releases the virus from the ACE_2 receptor, activating the S_1 subunit and initiating viral entry into the cell;

d) Finally, Cathepsin L (CATL) allows the virus to enter the cell by endocytosis. This is a proteolytic enzyme that is involved in the activation of Vascular Endothelial Growth Factor (VEGF) [4].

And here comes a very important relationship, COVID-19 and FGF (Fibroblast Growth Factor). We know that FGF is a family of critical proteins secreted to control cell proliferation, inflammation, angiogenesis, organ repair and regeneration and is tightly regulated under normal conditions. Under pathological conditions, they are released uncontrollably, participating in the pathophysiology of inflammation and angiogenesis-dependent diseases already documented in the literature and in the dissemination of certain tumors. The uncontrolled production of FGF during COVID-19, to repair the endothelial damage caused by the viral presence and the triggered cytosine storm, plays a crucial role: it favors the activation of TMPRSS2, enhances Cathepsin L, inhibits the ability of the cell to generate an adequate interferon signaling response, which is of most importance, since the innate immune system is altered and all this results in an uncontrolled replication of viral particles, in addition to the activation of the VEGF. Further, the signaling of the VEGF is activated with the possibility of the development of intussusceptive angiogenesis [5]. There are commercial drugs that have been shown to be effective inhibitors of FGF, by stabilizing endothelia and have been used for decades in pathologies with microangiopathy, so they could be applied during COVID-19, since this is also a microangiopathy [6].

The pathophysiology of the post-COVID-19 syndrome is multifactorial and has been proposed to involve mainly microvascular ischemia, which predisposes to subsequent metabolic alterations [6]. There are different molecular pathways involved in the phases of COVID-19, which produce histopathological alterations in different organs such as endotheliitis, thrombosis and hypercoagulability, among many others, and importantly, we must mention netosis by neutrophils, this concept, relatively new, extends the phagocytic activity and production of chemotactic substances of neutrophils, as was initially thought for a long time, being recognized today, the ability to form a DNA mesh with enzymes and molecules with toxic potential released into the extracellular space, such as initial antimicrobial defense mechanism, but which can also contribute to the pathophysiology, since there is an increase in the deposition of interstitial collagen and fibrosis [6]. We know the usefulness of PCR (Polymerase Chain Reaction) in the acute phase of the disease to make a diagnosis, when taking the swab of the nasopharynx and after the fourth week, its negativity in most patients, but we also know that the virus is present in other organs, as Eastern scientists demonstrated by performing anal PCR, so endothelial dysfunction continues [1]. Some of the many symptoms reported by patients in different organs and systems, 12 weeks after the onset of the condition, what we call Long COVID-19, are: hyposmia, chronic fatigue, anxiety, cardiovascular disease, coagulopathies, kidney failure, alterations cognition, muscle weakness, diarrhoea, etc [7]. An the central nervous system, sequelae are frequently reported, and the aforementioned molecular pathways are triggered by angiotensin-converting enzyme 2 receptors that can facilitate direct invasion of neurons, microglia, and endothelial cells, causing apoptosis and necrosis of the cells same [8]. The presence of dispersed viral particles, such as nucleocapsid proteins, have been identified in many organs, including the colon, appendix, hemorrhoids, and liver [9].

The endothelial dysfunction produced by COVID can affect any organ, as has been published in relation to erectile dysfunction, where histopathological, immunohistochemical and ultrastructural studies of the human penis have shown the presence of SARS-CoV-2 after the initial infection, viral particles have been visualized in perivascular tissue by transmission electron microscopy in patients with severe erectile dysfunction undergoing penile prosthesis surgery [10]. Today we already have a clear nomenclature and we call acute COVID-19 the manifestations during the first 4 weeks of the disease, subacute COVID-19 the set of symptoms and abnormalities present from 4 to 12 weeks after the onset of the disease and chronic, post-COVID-19 or LONG-COVID-19 syndrome to symptoms that persist or present beyond 12 weeks from the onset of COVID-19 and are not attributable to an alternative diagnosis [1]. In such a way, that we are facing a disease that not only causes morbidity and mortality in the acute phase, but also the long-term evolution and clinical picture with the presence of symptoms that are a consequence of multiple organ damage are documented. Therefore, today the management of these patients is multidisciplinary and involves cardiologists, pulmonologists, otorhinolaryngologists, intensivists, nephrologists, psychiatrists, physiotherapists, psychologists, etc. and within the long-COVID-19 category, the so-called multisystem inflammatory syndrome is also included, which we know is a late inflammatory response to SARS-CoV-2 infection, being one of the most serious forms of infection in children and recently in adults, which usually presents with high fever and digestive symptoms (especially intense abdominal pain) [11]. Several North American and European studies report an incidence of long-COVID-19 of 30 to 90% of patients at 6 months, where fatigue occurs in up to 60% and hair loss in 22%, even reaching the alopecia, more frequent in females [6].

Conclusion

For all of the above, we are facing a large area of opportunity with COVID-19 by focusing its management on the endothelial damage caused by the virus and thus reduce the exaggerated signaling of the Fibroblast Growth Factor (FGF) and the Growth Factor Vascular Endothelial (VEGF) that perpetuate the pathophysiology of the disease.

References

1. Nalbandian A, Sehgal K, Gupta A, Madhavan MV, McGroder C, et al. (2021) Post-acute COVID-19 syndrome. Nature Medicine 27(4): 601-615.
2. Smadja MD, Mentzer SJ, Fontenay M, Laffan MA, Ackermann M, et al. (2021) COVID19 is a systemic vascular hemopathy: Insight for mechanistic and clinical aspects. Angiogenesis 24(4): 755-788.
3. Ackermann M, Verleden SE, Kuehnel M, Haverich A, Welte T, et al. (2020) Pulmonary vascular endothelialitis, thrombosis, and angiogenesis in Covid-19. N Engl J Med 383(2): 120-128.
4. Rabi FA, Zoubi M, Kasasbeh GA, Salameh DM, Al-Nasser A (2020) SARS-CoV-2 and coronavirus disease 2019: What we know so far. Pathogens 9(3): 231-235.
5. Hoffmann M, Kleine-Weber H, Schroeder S, Krüger N, Herrler T, et al. (2020) SARS-CoV-2 cell entry depends on ACE_2 and $TMPRSS_2$ and is blocked by a clinically proven protease inhibitor. Cell 181(2): 271-280.
6. Cuevas P, Manquillo A, Angulo J, Giménez-Gallego G (2021) Dobesilate: A potential therapy for long-covid? Int J Med Rev Case Rep 5(14): 5-10.
7. Higgins V, Sohaei D, Diamandis EP, Prassas I (2021) COVID-19: From an acute to chronic disease? Potential long-term health consequences. Critical Reviews Clinical Laboratory Sciences 58(5): 297-310.
8. Ghazal A, Marin BG, Katchur NJ, Chaves-Sell F, Asaad WF, et al. (2020) Neurological involvement in COVID-19 and potential mechanisms: A review. Neurocritical Care Society 34(3): 1062-1071.
9. Cheung CCL, Goh D, Lim X, Tien TZ, Lim JCT, et al. (2022) Residual SARS-CoV-2 viral antigens detected in GI and hepatic tissues from five recovered patients with COVID-19. Gut 71(1):226-229.
10. Kresch E, Achua J, Saltzman R, Khodamoradi K, Arora H, et al. (2021) COVID-19 endothelial dysfunction can cause erectile dysfunction: Histopathological, immunohistochemical, and ultrastructural study of the human penis. The World Journal of Men's Health 39(3): 466-469.
11. Carod-Artal FJ (2021) Post-COVID-19 syndrome: Epidemiology, diagnostic criteria and pathogenic mechanisms involved. Rev Neurol 72(11): 384-396.