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Contents

Quarterly Volume 12 Number 3 June 25, 2023

REVIEW

- 136 Gastrointestinal tract and viral pathogens
Jagirdhar GSK, Pulakurthi YS, Chigurupati HD, Surani S
- 151 Impacts of SARS-CoV-2 on diabetes mellitus: A pre and post pandemic evaluation
Nabi AHMN, Ebihara A, Shekhar HU
- 172 Viruses and autism: A Bi-mutual cause and effect
Al-Beltagi M, Saeed NK, Elbeltagi R, Bediwy AS, Aftab SAS, Alhawamdeh R

MINIREVIEWS

- 193 Pediatric multisystem inflammatory syndrome associated with COVID-19: Insights in pathogenesis and clinical management
Silva Luz M, Lemos FFB, Rocha Pinheiro SL, Marques HS, de Oliveira Silva LG, Calmon MS, da Costa Evangelista K, Freire de Melo F
- 204 Etiopathogenic theories about long COVID
Del Carpio-Orantes L

ORIGINAL ARTICLE

Basic Study

- 209 Re-analysis of hepatitis B virus integration sites reveals potential new loci associated with oncogenesis in hepatocellular carcinoma
Kojima R, Nakamoto S, Kogure T, Ma Y, Ogawa K, Iwanaga T, Qiang N, Ao J, Nakagawa R, Muroyama R, Nakamura M, Chiba T, Kato J, Kato N

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Etiopathogenic theories about long COVID

Luis Del Carpio-Orantes

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Abstract

The main etiopathogenic theories of long coronavirus disease (COVID) are listed and a conjunction of them is carried out with the objective of deciphering the pathophysiology of the entity, finally the main lines of treatment existing in real life are discussed (Paxlovid, use of antibiotics in dysbiosis, triple anticoagulant therapy, temelimab).

Key Words: Long COVID; Viral persistence; Amyloid microthrombosis; Dysbiosis; Weakened immune system; Paxlovid; Triple therapy

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Core Tip: List the main etiopathogenic theories of long coronavirus disease (COVID) and evaluate their interrelation as pathophysiological agents of long COVID syndrome.

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INTRODUCTION

Long coronavirus disease (COVID) is broadly defined as signs, symptoms, and conditions that continue or develop after initial COVID-19 or severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. The signs, symptoms, and conditions are present four weeks or more after the initial phase of infection; may be multi-systemic; and may present with a relapsing-remitting pattern and progression or worsening over time, with the possibility of severe and life-threatening events even

months or years after infection; this being the definition adjusted by the Centers for Disease Control and Prevention's, since the previous definition of the World Health Organization mentioned persistent symptoms after 12 wk[1].

However, for all these etiopathogenic processes that define long COVID to occur, there is still no specific evidence on it and various theories have been created that try to decipher the pathophysiology of said entity, some are independent, but others have strong ties between them. And depend on each other, the main etiopathogenic theories of long COVID are mentioned below:

Theory of viral persistence or viral particles: There is evidence that after an acute episode of COVID-19, there is persistence of viral particles in various organs up to one year after the episode and the organs mainly affected are: Brain, Gastrointestinal and Hemolymphatic; Similarly, they have been detected in blood, feces and urine[2,3].

Theory of endothelial dysfunction: This theory deals with the damage to the vascular endothelium that leads to endothelitis which, in turn, will favor platelet increase and activation, increased risk of thrombus formation with subsequent damage to organs and tissues by a mechanism of tissue ischemia that can affect the main organs and systems of the human body[4,5].

Theory of platelet hyperactivity: Which is related to the previous theory and mentions that this hyperactivity favors the formation of microthrombi which have the characteristic of being amyloid and in this area, is linked to the theory of viral persistence which mentions that protein S has amyloidogenesis potential, which makes these amyloid thrombi more resistant to degradation and more hard, which ensures occlusion of the microvasculature with subsequent diverse organic damage (highlights tissue destruction and damage to central and peripheral nerves)[6-8].

Crucial nerve damage theory: This theory ties in with the previous one and refers to damage to nerves crucial to the functioning of the autonomic nervous system, such as damage to the vagus nerve, which controls various functions of the cardiovascular systems, gastrointestinal and pulmonary, so damage to it can cause many symptoms in these systems[9].

Theory of immune abnormalities: After an acute COVID-19 case, there is evidence of persistent inflammation that feeds the inflammasome of each person, in addition to the presence of autoimmunity that adds various comorbidities to the patients and even the *de novo* appearance of rheumatological diseases such as lupus, dermatomyositis, rheumatoid arthritis, *etc.* In addition, the production of antibodies against the angiotensin converting enzyme-2 (ACE2) receptor has been demonstrated that could decrease the activity of ACE2, both in the soluble part and in the membrane-bound part, which would finally activate the immune system, which can act as immunological priming by molecular mimicry. In the same way, an "exhaustion of the immune system after an acute COVID-19 condition has been demonstrated, which conditions a decrease in lymphocyte subpopulations and the subsequent risk of opportunistic diseases[10-14].

Theory of interaction with subclinical viruses: This theory mentions that after the maladjustment of the immune system produced by acute COVID-19, some viruses that tend to remain in a subclinical form (mainly those of the herpesviridae family), can be activated again by adding morbidity to the long COVID picture, with various symptoms according to the viral type[15-17].

Dysbiosis theory: This theory mentions that patients with Long COVID present a dysbiosis which would hinder the relationships between the microbiota and the virome, favoring symptoms of the main organ systems and systems, highlighting the involvement of the respiratory system and the gastrointestinal system (Which have a large number of ACE2 and transmembrane serine protease 2 receptors that favor viral entry into cells), which are the main ones that harbor the microbiota, conditioning dysbiosis[18,19].

Theory of aggravation of chronic diseases or de novo appearance of chronic diseases: in this etiopathogenic theory it is mentioned that diseases previously diagnosed with an acute picture of COVID-19 can get out of control or worsen concomitantly, which adds greater comorbidity to the patient both in the acute stage as in long COVID; It has also been seen that after the acute picture, many patients develop chronic degenerative diseases such as: Diabetes, Hypertension, various Cardiopathies, Dementias, Thyroid diseases, *etc*[20-26].

Once the main theories have been described, we will try to put them together in order to be able to describe pathophysiology.

In recent times, viral persistence has stood out, mainly of the S and N proteins that greatly affect the central and autonomic nervous system, coupled with the neurotropism of SARS-CoV-2 that causes damage to the nervous system and the vagus nerve, hence the main manifestations are neuropsychiatric; protein S has the particularity of conditioning amyloidogenesis together with the presence of amyloid peptide A product of inflammation in the acute stage, which could lead to the presence of amyloid microthrombi, perpetuating both inflammation and thrombotic risk; in aggregate form, these characteristics can condition both positive and negative immune deregulation; positive deregulation would increase the activity of the immune system conditioning autoimmunity while negative deregulation is associated with completeness of the system with disorder of B, T and NK cell lines, the latter reveals the reactivation of latent viruses that increase morbidity as well as the virome, causing an imbalance between it and the intestinal microbiota, giving way to the theory of dysbiosis, which is associated, in addition to gastrointestinal symptoms, to neuropsychiatric and cardiovascular disorders, even leading to dysautonomia and hormonal changes, leading to a vicious circle.

Table 1 Diagnosis and treatment based on the theories of long coronavirus disease

Pathological condition to study	Clinic	Basic diagnostic method	Extension studies	Treatments
Neuropsychiatric manifestations	Anxiety depression headache; brain fog; early dementia fatigue/weakness/myasthenia mitochondriopathy suspected	Psychological tests; clinical questioning neurological examination	Cranial CT head MRI brain PET scan CSF analysis; electroencephalogram EMG/CNV; serum lactate-pyruvate/CSF	Psychological therapy psychiatric treatment pacing; brain electrostimulation; speech therapy; behavioral therapy
Viral persistence	Leukopenia, lymphopenia virus reactivation (herpes, EBV); persistently positive COVID tests	Nasal COVID antigen (or PCR-RT); IgM-IgG serology for herpes, CMV, EBV	Total body PET to viral reservoirs, RT-PCR for Sars Cov2: Serum; urinary; stool	Antivirals: Paxlovid (Yale trial); oral remdesivir; acyclovir, ganciclovir
Immunothrombosis	Clinical data of inflammation or thrombosis: Arthralgias/arthritis; myalgias; arterial/venous thrombosis	D-dimer ferritin; C reactive protein reactive thrombocytosis DHL; creatine phosphokinase myoglobin	Intentional search for amyloid microthrombi: Immunofluorescence microscopy; flow cytometry; alpha 2 antiplasmin; serum amyloid A platelet hyperactivation; platelet aggregometry	Triple therapy: Oral anticoagulants; dual antiplatelet; gastric protection. Fibrinolytics chelators vitamins
Immune dysregulation	Frequent infections; de novo appearance of autoimmune diseases	Leukopenia, lymphopenia reactive lymphocytosis	Lymphocyte subpopulation; CD4/CD8/natural killers; miscellaneous and specific antibodies	Immunomodulators immunostimulants biological therapy; monoclonal antibodies (temelimab)
Vagus nerve injury	Brain fog dysautonomias	Electrocardiogram holter; ambulatory blood pressure monitoring	Vagus nerve ultrasound tilted table test	
Dysbiosis	Brain fog depression/ anxiety irritable colon chronic diarrhea	Coprological stool culture	Intestinal dysbiosis test stool calprotectin dysbiosis specific kits: Gastrotest; GI effects; healthy gut	
Miscellany	Hepatic steatosis chronic kidney failure dysthyroidisms; chronic lung disease		Kidney, liver, thyroid function female hormonal profile spirometry, chest X-ray, chest CT	Specific treatments
Commercial kits for persistent COVID diagnosis			CheqUp; IncellKINE	

CT: Computed tomography; CMV: Cytomegalovirus; EMG: Electromyography; EBV: Epstein-Barr virus; GI: Gastrointestinal; MRI: Magnetic resonance imaging; PET: Positron emission tomography; PCR-RT: polymerase chain reaction reverse transcriptase; IgM: Immunoglobulin M; IgG: Immunoglobulin G; COVID: Coronavirus disease.

There are currently many researcher-led treatment efforts and initiatives, notably the following:

Dr. Iwasaki from Yale University, leads a clinical study using Paxlovid in these patients affected by Long COVID, based on the theory of viral persistence, who receive the antiviral for 15 days waiting for symptomatic improvement, the study is still recruiting participants and promising results are expected (ClinicalTrials.gov Identifier: NCT05668091)[27].

Other researchers led by Dr. Ethersia Pretorius, are addressing the theory of immunothrombosis, in which they have demonstrated the presence of amyloid microthrombi and initiated a special therapy called Triple therapy, which uses direct oral anticoagulants, dual antiplatelet therapy, and gastric protection, from which encouraging results are expected[28,29].

Other research efforts fall on two researchers, Tamara Romanuk and Ale Frost, who address the theory of dysbiosis secondary to long COVID and that it conditions a gut-brain axis disorder with subsequent neuropsychiatric dysfunction (@remissionbiome on twitter); In their study, they have implemented the study of the microbiota and are using a treatment scheme with the antibiotics doxycycline and amoxicillin with clavulanate, taking advantage of properties against neuroinflammation and neuroimmunology; something similar occurs with the study of dectin-1 as a therapeutic target for the treatment of stress-induced behaviors[30,31].

In Spain, researchers address the theory of damage to the vagus nerve in patients with long COVID, based on the prevalence of inappropriate sinus tachycardia in these patients, they have devised an ultrasound protocol to identify vagus nerve disorders, which would corroborate the viral neurotropism that affects to said nerve, conditioning dysautonomia and disorders in other spheres such as neuropsychiatric, cardiopulmonary, gastrointestinal and endocrinological (Table 1)[32].

Finally, in Switzerland, a research protocol has begun with a monoclonal antibody called Temelimab focused on chronic fatigue and cognitive alterations, whose target is a protein called HERV-W-End, which has been associated with autoimmune diseases and chronic fatigue; encouraging results are expected for long COVID patients. The investigation has been extended to Spain and Italy (Clinical-Trials.gov Identifier: NCT05497089)[33].

CONCLUSION

There is still much to be deciphered in the etiopathogenesis and pathophysiology of long COVID, however current efforts clarify these conditions on which treatments are tested in the real world, in order to limit the pathological manifestations that affect the population affected by long COVID. With the study of etiopathogenic theories, diagnostic and treatment strategies can begin to be created.

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