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Covid-19 Post-Acute and Chronic Disease

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Abstract

A new coronavirus emerged in Wuhan-China at the end of 2019, apparently originating in a wholesale seafood market in that city due to the passage of the virus from a wildlife animal, probably a bat or pangolin, to humans. This coronavirus achieved an important adaptation in the body and generated a new disease that was called COVID-19, which causes Acute Respiratory Distress Syndrome (ARDS). Little is really known about the possible medium and long-term consequences of this new disease. Many of the patients, due to the severity of their disease and/or due to the invasive management established in them, will develop squeal that could be permanent and that in one way or another are plausible through extensive tests requested by the health personnel. Likewise, it is essential to take into account the knowledge provided by past epidemics caused by other similar coronaviruses, which at the time generated the Severe Acute Respiratory Syndrome (SARS) of 2003 and the Middle East Respiratory Syndrome (MERS) of the 2012. Therefore, in this bibliographic review, the medium and long-term consequences that other coronaviruses have generated and that could generate the one that has been called severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2) will be exposed.

Keywords: Syndrome; Covid-19; Persistent Covid; Post-acute; Chronic; Long covid; covid Long haulers; Long haul covid

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Introduction

Due to the recent appearance and identification of a new coronavirus at the end of 2019, little is known about the possible consequences in the medium and long term. Many of the patients due to the severity of their disease and/or due to the invasive management established in them will develop squeal that could be permanent and that in one way or another are plausible through extension tests requested by health personnel. However, the concern lies not only in them, but also in those people who carry symptoms for months and who in their vast majority were initially classified as "mild" and managed on an outpatient basis. It is worth mentioning that, in some of them; it has not been possible to identify an apparent structural or functional damage that justifies the symptomatology. It is based on the latter, on patterns of symptomatology that are evident and on the association of chronicity with the number of symptoms and their characteristics during the acute phase, that it has begun to speculate on the possible causes, within them: the existence of a viral persistence, an unbalanced immune response characterized by post-viral hyperactivity of the same, presence of autoantibodies, due to entities such as small fibre neuropathy, or to pathophysiological processes similar to myalgic encephalomyelitis / chronic fatigue syndrome (ME/CFS), fibromyalgia (FM), central sensitization syndrome (CFS), orthostatic postural tachycardia syndrome (POTS), autoimmune autonomic ganglionopathy (GAA), the disease of small vessels (microangiopathy), deconditioning, a deficiency state perpetuated mainly by a vitamin deficit such as those of the B complex, psychiatric disorders that eventually lead to the somatization of the symptomatology even reaching to mimic the symptoms of COVID-19, among others [1,2].

On the other hand, it is interesting the knowledge that the past epidemics caused by other similar coronaviruses have provided us, that is the Severe Acute Respiratory Syndrome (SARS) of 20031 and the Middle East Respiratory Syndrome (MERS) of 2012 on persistent symptoms and post-viral syndromes. On the one hand, it has come to identify countless studies that corroborate the fact that coronaviruses are very versatile viruses, with a surprising ability to adapt to organisms and endowed with extremely effective immune system evading mechanisms, thus generating very diverse symptoms, variable in intensity and that could last for an indefinite time. On the other side of the coin, we have post-viral syndromes, which have already been documented, but which, nevertheless, remain little known and recognized

by health personnel. This is probably due to the fact that the scientific community in one way or another has ignored research in this regard due to how infrequent or rather how infrequent they used to be, the complexity of them and the need to solve problems that at the time, were more emerging or priority for health systems. This pandemic may be the opportunity to interfere in depth in the research of both persistent infectious diseases and post-viral syndromes, in order to better understand these processes, and thus provide affected patients with a more effective and efficient treatment than has been done so far.

Without further ado, we will present in the following section a bibliographic review of the past and present regarding the medium and long-term consequences that other coronaviruses have generated and that could generate what has been called coronavirus type 2 of severe acute respiratory syndrome (SARS-CoV-2).

Materials and methods

To carry out this article, a bibliographic search was carried out in various databases such as Elsevier, Scielo, Medline, PubMed, Science Direct and Ovid, thus selecting original articles, case reports and bibliographic reviews from 2018 to 2021, in Spanish and English using MeSH terms: Syndrome, covid-19, persistent covid, post-acute, chronic, long-distance carriers, long distance covid, and Boolean operators and and or. Thus including all the documents that will deal with post-acute and chronic covid-19 disease, the data found were between 35-45 records, thus using 40 articles for the realization of this document.

Review

Definition

Given the attempt of countries to avoid the greatest number of deaths from COVID-19, the attention and research of a group of patients who persist with signs and symptoms after 3 weeks from the beginning of the picture has been reduced. These patients are very heterogeneous, which is why it has been difficult to pigeonhole them into a definition and classify them given that COVID-19 generates a significant multisystem condition with a temporal course that, to date, is unclear. Many patients have not even necessarily had a "moderate" or "severe" disease, but they have not managed to resume their lives in a normal way, because in many cases, the symptomatology is so flowery that it is detrimental to the quality of life, even, in a not inconsiderable subgroup, it has become disabling. That is why, in search of defining them, they have come to be called in different ways; in Spanish as "covid-19 persistent", "covid-19 chronic" and in English as "long haul COVID-19", "covid long-haulers" or simply as "long covid".

According to two published articles, the first by the Department of Biology and Biomedical Sciences at Aga Khan University in Pakistan and the second published in the journal Jama Network, there is no clear consensus on the definition of the medium and long-term effects generated by COVID-19. Well, according to the first, it is of the utmost importance to designate a name that has been called "long covid" or "covid long haulers", thus proposing the possibility of naming it as other existing syndrome processes, either of infectious or non-infectious etiology that exceed 3 weeks from its beginning, that is, as chronic COVID-192. According to the second article and supported by the Spanish Society of Physicians of

Primary Care, it has been considered to opt for a variation to the aforementioned one, defining COVID-19 in two ways: as post-acute and as chronic [3].

According to the duration of the symptomatology

- Post-acute Covid-19: It is one that exceeds 3 weeks from the onset of the disease.
- Chronic Covid-19: It is one that exceeds 12 weeks from the onset of the disease3.

At the moment, we believe that this classification is the most appropriate, because considering it as chronic after 3 weeks could be precipitous since many patients will present a complete resolution of their symptoms before 3 months, as we will see later.

According to the clinical characteristics of the affected patients

It is important to emphasize that those patients who suffer from both post-acute-chronic COVID-19 are very heterogeneous in their vast majority. Through an attempt to classify them, we will divide them into three groups:

1. Those that have a nonspecific disease. Most cases usually present with fatigue and/or dyspnea as cardinal symptoms4. The damage and symptoms are not necessarily permanent, but recovery may take extended periods of time. Mostly, they are those patients who have been managed on an outpatient basis with symptomatic treatment [4].

2. Those who have squeal as a result of the disease4, such as, for example; pulmonary fibrosis, complications associated with a pulmonary embolism, a stroke, among others. These tend to be permanent. They are patients who have mostly been hospitalized. In any case, it has been evidenced that, after discharge, some of them have developed thrombotic events in the weeks or even months after the acute phase.

3. Those patients who have required intensive care and who develop after discharge, a post-intensive care syndrome4. These patients present temporary and/or permanent symptoms caused both by the same hospital stay, as well as by invasive and non-invasive procedures established in the Intensive Care Unit (ICU).

is worth mentioning that this classification is not absolute. Eventually they can overlap each other.

Possible causes

In this article, we will focus on point one according to the classification made previously, because as we have seen, it is a group in one way or another little recognized and that needs immediate answers.

According to an article published in The BMJ, it is not known exactly what generates the persistence of the symptomatology. However, some hypotheses have been raised, which will be presented in the following section:

1. Viremia due to a weak or absent antibody response.
2. Relapse or reinfection.
3. Inflammatory reactions and other immune reactions.
4. Deconditioning.

Mental factors such as post-traumatic stress4. On the other hand, according to a video published by Dysautonomia International, the possible mechanisms of persistence of symptomatology are the following:

1. Persistent SARS-CoV-2 infection.
2. Secondary infection.
3. Resolution of infection, but persistence of tissue damage.
4. Resolution of infection, but persistence of the immune response.
5. Deconditioning
6. Other things still unknown

A combination of them: probably point 3, 4, and 5 according to the author's opinion5.

On the analysis of these points and the evidence acquired in the literature review, we believe that the **persistence of the symptomatology is probably due to**

1. A persistent-chronic viral infection caused by an inadequate immune response of the host during the acute phase (includes viral persistence in the same inflammatory and nerve cells), accompanied by tissue injury probably triggered by the same viral replication and consequently an acute inflammatory state that ultimately progresses into a chronic, low-intensity inflammatory process, but significant enough to generate signs and symptoms. In addition, it is possible that there is a deficiency state and a state of deconditioning either due to the same disease and / or inactivity.

2. Denervation or neuronal loss and/or endothelial damage during the acute phase, accompanied by a chronic post-viral inflammatory state probably due to immune system disease, perhaps with autoimmune behavior, accompanied by a deficiency state, and a state of deconditioning caused either by the disease itself and/or by inactivity [5].

Viral persistence

Persistent viral infection is a condition caused by the entry of a certain virus into the body generating or not symptoms in the acute phase and that can last in the body for an indefinite time (weeks, months or years). These infections may or may not generate clinical manifestations without killing quickly or causing excessive damage to the body.

According to the evidence currently available, viruses not only generate acute illness, but can also generate persistent infection due to their ability to remain in cells after the end of the acute phase of the disease. This persistence allows the virus to replicate constantly without generating cell death [6].

Persistent infections can be classified as

• Chronicles: Those that can manifest as a long-term infection, in which the virus continues to replicate even at low levels for an indefinite time despite the immunity generated, and may also produce fluctuating symptoms or even appear after several years.

• Latent: They are characterized by being inactive within a cell, that is, they can remain hidden after the initial infection probably because it does not provide transcription factors necessary to produce viral replication. Reactivations may occur one or more times under certain circumstances, such as; hormonal changes, physical or psychological stress, etc. Both the first infection and the reactivation can lead to symptoms and these remain throughout life.

• Slow/prion infections: these affect only the central nervous system because there is no or mild immune response. Generally the first infection is asymptomatic however after several years it can trigger a severe, progressive picture that can even lead to death.

• Transforming infections: They are those in which the virus is able to infect cells, but cannot produce viral particles in a significant way that leads to cell destruction, however, part of its genes are translated into viral proteins which cause cellular changes through interaction with genes and proteins which could lead to the formation of tumour's whether benign or malignant.

In the event that we consider the possibility that SARS-CoV-2 generates a persistent infection, it would probably be chronic due to its characteristics.

According to Boggs W, it is possible that SARS-CoV-2 is eliminated slowly, especially in those patients suffering from primary or secondary immunodeficiency. It is believed that they can prolong both the disease and infectivity because their degree of dissemination, immune clearance kinetics and disease severity are different from that of immunocompetent patients [7].

In any case, we previously verified the fact that this cannot necessarily occur in people with some degree of immunosuppression, but also in immunocompetents by unclear mechanisms. However, it could be caused by an ineffective immune response in the acute phase of the disease, especially in those patients managed on an outpatient basis [8].

Viral persistence in body fluids

Importantly, many patients over the weeks and months shed the virus through various fluids. It should be noted that it has even been identified in various tissues of the body. We will describe in the next section, some studies that prove it.

In a 2003 cohort study in Beijing, patients who were likely infected with SARS-CoV-1 were recruited from a hospital, based mainly on criteria stipulated by the World Health Organization (WHO). Stool and sputum samples were taken for several weeks

of hospitalization and for months after discharge (6 months after disease onset). 514 stool samples and 493 sputum samples were collected from 56 patients during the study period. The results showed that sputum and stool samples by RT-PCR did not show negative results until day 14 and day 16 after the onset of the disease, respectively. An average duration of viral excretion of 3 weeks in sputum and 4 weeks in feces was evident. In addition, a prolongation in excretion (> 100 days after the onset of symptoms) was observed in the feces of 4 patients, which probably suggests that viral replication may take place in the intestinal tract. 3 of these 4 patients had co-existing conditions (pulmonary tuberculosis, diabetes, and pulmonary hypertension), a known risk factor for prolonged SARS-CoV-18 disease. The striking thing is that viral excretion can be persistent in the feces even exceeding 3 months from the onset of the disease. Something to note is that the excreted virus appears not to have been infectious. Something that has not been fully clarified with the new coronavirus as we will see later.

In a study conducted in China, between January and March, respiratory and fecal samples were collected and analyzed from 74 patients infected with SARS-CoV-2 by RT-PCR. It was evidenced that in about 55% of patients, their fecal samples remained positive for SARS-CoV-2 RNA for an average of 11.2 days longer than respiratory samples, even lasting in some cases about 5 weeks after the respiratory tract samples became negative for SARS-CoV-2 RNA. It is worth mentioning that severity was not associated with the prolonged duration of viral RNA positivity of the fecal sample [9].

A study conducted in Guangdong - China, a total of 49 patients with SARS-CoV-2 were recruited. Mostly (43 patients) with a mild course of the disease. Samples of pharyngeal smear, nasopharyngeal, sputum and feces were obtained every 3 days for 4 weeks, which were analyzed by RT-PCR. In the study, persistent viral RNA spread was evidenced in both nasopharyngeal and stool samples. The estimated time to loss of viral RNA detection ranged from 45.6 days for nasopharyngeal smear samples to 46.3 days for stool samples in mild cases, and 48.9 days for nasopharyngeal smear samples and 49.4 days for stool samples in severe cases. This was longer than evidenced with other coronaviruses, i.e. SARS-CoV-1 and MERS-CoV. In this study, virus isolation and sample infectivity tests were not carried out [10]. It is again evident that viral excretion can last longer than expected.

Of positive results and symptoms in patients recovered from Covid-10

According to Read S, the detection of SARS-CoV-2 can occur in several scenarios

• In people who have recovered from the disease completely and after it, viral RNA has not been detected in the upper respiratory tract.

• In people in whom viral RNA continues to be detected after a complete resolution of the symptomatology, even reaching in some cases to persist for weeks.

• In people in which, after an apparent elimination of the virus objectified by obtaining 2 negative viral RNA tests in the upper respiratory tract, and after that, they return to positivity, but without presenting symptoms.

• Those people who have not presented clinical recovery and who persist or resort to viral RNA positivity in nasopharyngeal samples [11].

In those who do not present symptoms, the persistence of viral RNA may not generate much concern. Based on other viruses and with the evidence available to date on SARS-CoV-2, these people would no longer be contagious. The concern basically lies in those that do not present a resolution of the clinical picture or that, after an apparent recovery, present new symptoms with positive detection tests for SARS-CoV-2.

According to Syrek R, it is unclear why many patients continue to test positive for long periods of time. As reported, some of them, after having tested negative, with the passage of time come out positive again, however, it is believed that they are probably no longer infectious.

A German study mentions that patients with less than 100,000 copies of viral RNA/ml of sputum 10 days after symptoms have "little residual risk of infectivity [12].

The case of a patient suffering from refractory mantle cell lymphoma (MCL) and COVID-19 is reported concomitantly, the patient was admitted several times due to a worsening of the symptomatology after an apparent remission. On day 156 of the disease, when the patient had been readmitted for progression of his lymphoma, the SARS-CoV-2 test remained positive. It is worth mentioning that samples grown in Vero E6 cells demonstrated the presence of SARS-CoV2 from day 7 to 119 of the disease. Virus sequencing demonstrated a progressive evolution with additional substitutions over time, but phylogenetic analysis basically ruled out reinfection7. For now, the question must be asked whether this actually occurs exclusively in immunocompromised patients or also occurs in those immunocompetent, as we will see below.

According to Rong Yang J, et al, by reporting one case, it was possible to demonstrate that SARS-CoV-2 infection can have a clinical course of more than two months. Well, in a 44-year-old male patient, without precondition of immunosuppression, after overcoming the acute phase evidencing clinical improvement from day 15 to 32 approximately, with the negativization of viral RNA by taking a pharyngeal swab and the formation of antibodies, there was a reappearance of viral RNA approximately on day 36 of the disease, which persisted for more than 40 days (74 days after the onset of the picture). In addition, something striking is that viral persistence was identified in other types of samples, especially in saliva with extremely high titers [13].

Gousseff et al presented a series of cases of 11 patients infected with SARS-CoV-2 who presented two acute episodes of the disease confirmed clinically and virologically. The median duration of symptomatology was 18 days for the first episode and 10 days for the second. 4 of the 11 were health care workers, with a median age of 32.5, with no previous comorbidities, with mild illness and made a full recovery. However, they had a relapse that did not require hospitalization, with a symptom-free mean interval of 9 days. On the other hand, 7 patients with previous comorbidities,

who underwent a second episode presenting new tomographic findings. 4 of the 7 worsened, including one, leading to pulmonary thromboembolism. There was no evidence of super infection and no differential diagnosis. Here the possibility arises that both health personnel due to their prolonged exposure and their immune weakness, have been able to acquire a new infection. On the other hand, the second group was vulnerable people, in one way or another immunosuppressed and may also have acquired a new infection by chance. Despite this, the possibility of reactivation due to immunosuppressive factors, such as the use of corticosteroids or due to an inflammatory rebound due to an inadequate immune response, is also considered. However, the fact that viral RNA has been detected in all patients – some of them with a low cycle threshold – and that a viral strain could be cultured during the second episode for one of them, supports rather reinfection or reactivation [14].

We must be cautious with the last thing they mention, because so far there is no solid evidence of the existence of new strains and reinfection. It is likely that in reality they are genetic variations of the same virus that are not enough to generate a change in the behavior of the same and therefore a new immune response and even less, in such a short period of time. However, reactivation or replication of greater intensity resulting from a persistent viral infection could justify the symptomatology.

According to an article published by Xia J, there are two possibilities in cases where patients come back positive in tests for SARS-CoV-2 RNA. The first reinfection, this is considered unlikely because of the little evidence available in this regard, and two, that there have been false negatives and that there is really a viral persistence. The latter could be given by viral persistence in immunologically privileged sites.

Means that there are places in the body that can tolerate the existence of an antigen, without triggering an immune response. This is probably due to an evolutionary mechanism that aims to preserve the structures of the organism in the face of a possible immune response, which, if it exists, would be detrimental to its functionality. These sites are mainly: the eyes, placenta and fetus, testicles, central nervous system (CNS) and hair follicles. This is not something new, as it has been seen with other types of viruses, such as Zika and Ebola. Ebola was detected in semen even 3 years after the onset of infection, while Zika was detected 134 days in semen after resolution of symptoms caused by the disease. Interestingly, SARS-CoV-2 shares characteristics with these [15].

On the other hand, as described in an article published in The Bmj, it is necessary to mention that long-term respiratory, musculoskeletal and neuropsychiatric "squeal" have already been previously documented in other coronaviruses (SARS and MERS). In addition, it is emphasized that mild patients can prolong their symptoms, within it cough, fever and fatigue, which tends to be fluctuating, with eventual relapses and remissions, with variation in intensity and form, even on the same day. They consider that, for the majority of these patients, who do not present significant evidence of structural or functional damage, they will not need to be referred to a rehabilitation service and that, with a progressive, controlled activity associated with adequate follow-up with symptomatic treatment for the time being, it is sufficient until the results of the long-term studies are available. In addition, a slow, gradual and complete recovery is expected based on other causes of viral pneumonitis and ARDS in most of them 7. Something that fortunately has been observed in one way or another in patients who have been diagnosed with COVID-19 and who persist with symptoms.

In another sense, this may be strengthened by Syrek R, who mentions that even in those who are not considered to have persistent symptoms; recovery after overcoming COVID-19 can be difficult. Exercise tolerance can take 2 to 3 months or even take longer to return to pre-COVID-1916 fitness [16].

Now, from our point of view, patients who have developed post-acute COVID-19 may take a while to resume their normal lives because it can be difficult to overcome convalescence not only because of the ravages generated by the infection, but also because of a process of deconditioning that can be resolved in weeks or months. It is worth mentioning that in those who have developed chronic COVID-19, this process could be longer and more complex because both doctors and patients struggle not only against deconditioning, but also against sequelae, deficiency states and against a non-specific viral or post-viral disease that is still unknown.

On the other hand, according to the study described in previous paragraphs published in the journal Jama Network, the most frequent symptoms after the end of the acute phase are fatigue and dyspnea3. While in another study conducted by the Spanish Society of Primary Care Physicians, it was demonstrated through a survey that fatigue and cough are the main symptoms [17].

So, the list is not limited to a few symptoms that persist after the acute phase, rather it extends in the same way as the number of patients who suffer from them increases. Well, support groups have even been created on various websites, social networks, and instant messaging services, mainly Facebook (e.g. Long Covid Support Group, which currently has more than 50,000 members) and Whatsapp (e.g. persistent COVID Spain), most likely caused by the neglect they receive, or by the same incomprehension and impotence of health personnel in the face of the difficulty of their diagnosis and therefore of their management. It is worth mentioning that, in these groups, stigmatization by their relatives is emphasized because they were mostly classified as "mild" cases and did not require hospitalization. This undoubtedly makes management difficult, since the lack of support, ignorance and lack of recognition by the family and health personnel can eventually lead to or worsen the psychological/psychiatric problems of the affected patients.

As we have shown, in part the rejection of doctors, and therefore of the family towards patients, is given by the scarce evidence of alterations in extension examinations, many of them even being classified as "anxious" or as "patients who somatize" without any foundation. This must be taken with tweezers, it is likely that it is due to a real ignorance of the picture, because anxiety may be part of the disease of patients but is not the cause of it. Aptly, as Avindra Nath describes it in an article published in the journal Neurology on post-acute-chronic COVID-19, "We discovered the biological basis of diseases such as epilepsy and dystonia, to name a few, that for centuries had been called 'hysteria'.

Psychological/psychiatric disorders in patients affected by post-acute-chronic COVID-19 are not only caused by the disease, but are also caused by the pain and discomfort generated by being in one way or another misunderstood, abandoned and stigmatized by both their loved ones and their doctors. It is worth mentioning that as described in previous paragraphs, although many doctors have lacked the tools to deal with the problems of "long-haulers", these should be accompanied with symptomatic treatment, should be recognized and should receive the warmest and most honest care possible until long-term results are available. For the ignorance of science does not necessarily reflect the absence of a morbid condition in these patients. To end the paragraph, I will quote Avindra Nath again where she says the following "let us remember that we must study and treat not the disease that affects the patient, but the patient who is affected by the disease".

On the other hand, it is worth mentioning that many of the members of these groups mentioned above, have developed a flu process in their homes, which were never tested for SARS-CoV-2, because they were mostly afraid of contracting the infection or in turn thought that the origin, it was the product of a different virus than the one mentioned. After overcoming the acute phase in their homes, the symptomatology persisted for months, within them myalgias, arthralgias, thermal elevation, asthenia, hyposmia, dyspepsia, etc. They dedicated themselves to looking for information about the cause of the persistence of the symptomatology on the internet, coming to meet these groups by chance, where they have come to ask if "the members believe that they have been able to contract the infection by SARS-CoV-2 weeks or even months ago." This is complex, because they are also not recognized, and less considering that they do not have previous tests that have shown a SARS-CoV-2 infection. For many doctors, the absence of a previous positive test excludes the diagnosis of post-acute-chronic COVID-19. We must not forget as doctors, that clinical and epidemiological data are relevant in the diagnosis of most pathology and those complementary examinations is just that, complementary.

According to a publication made by the World Health Organization (WHO), a monitoring was carried out between August 27 and September 2 on the most discussed topics around the long-term effects of COVID-19 in social networks, where it was evidenced that around 12,000 interactions corresponded to the long-term effects on the lungs, 8,000 in the heart and 3,000 in the brain.

The top tweets referencing a review of several studies related to the possible long-term effects at the heart of COVID-19 by Scientific American, generated 104,000 interactions on social media (of which 60% on Reddit, 35% on Facebook, 5% on Twitter).

An article published in the journal "Undark" on the prolonged disease caused by COVID-19 in children generated around 2,000 interactions on social networks [18].

Among the signs and symptoms that have been evidenced in these groups we have those described in the following table **(Table 1)**.

Table 1:

General Symptoms	Neurological	Sense organs	Otolaryngological	Cardiovascular
Fever -Chills with or without thermal rise -Hypothermia	- Headache -Confusion -Retrograde & anterograde amnesia -Bruxism -Tooth hypersensitivity -Bladder dysfunction (retention or incontinence) -Fasciculations -Intercostal neuritis -Parestesias - Monoplegia -Hemiplegia -Erectile dysfunction -Alteration of sweating pattern -Orthostatic intolerance -Hiccups -Vertigo	- Tinnitus -Blurred vision -Myodesopsias -Anosmia -Hyposmia -Ageusia -Dysgeusia	- Rhinorrhea -Odynophagia -Nasal obstruction -Otalgia -Vertigo	-Inappropriate sinus tachycardia -Sinus bradycardia -Chest tightness -Chest pain -Dyspnea -Hypertension -Hypotension
Pulmonary	**Gastrointestinal**	**Genitourinary**	**Dermatological**	**Rheumatologic**
- Cough -Wheezing -Roncus -Shallow breathing -Apneas -Hypopneas -Chest tightness -Dyspnea -Tachypnea -Central and peripheral cyanosis -Difficulty inspiring deeply or sighing	-Nausea -Vomiting -Abdominal pain -Meteorism -Diarrhea -Hiccups	- Dysuria -Oliguria -Bladder tenesmus -Urinary incontinence -Urinary retention -Dysmenorrhea -Metrorrhagias -Menometrorrhagia -Amenorrheas	-Chilblains -Bruising -Skin peeling	Dryness ocular -Xerostomia -Enanthema -Glossodynia -Glossitis -Arthralgias -Myalgia -Urticaria -Loss of nail lunula -Alopecia

According to Lambert N, who collected and analyzed data obtained from a survey published on the "Survivor Corps" Facebook page about the symptoms of post-acute-chronic Covid-19, the symptoms are more numerous compared to those described by the CDC, since the problems not only cover the lungs and heart, but also countless organs and tissues. It was evidenced that skin and eye problems, in addition to muscle, joint and nerve pain, are common in this group of patients. In addition, it was estimated that approximately 26.5% of the symptoms are described as painful by the participants. On the other hand, it is emphasized that there is a lack of agreement between the available evidence, regarding the symptoms actually presented by patients affected by post-acute-chronic COVID-19 [19].

It is likely that even the symptoms described in your survey will still be reduced compared to those that actually afflict this group of patients. It is of the utmost importance to pay due attention and carry out an adequate follow-up by a multidisciplinary group to solve the needs of those affected. In addition, research on these patients who in one way or another have been bypassed both by severe cases and by the little evidence available on post-acute-chronic COVID-19 in the literature should be encouraged.

Below is the comparative table between the symptoms described by the CDC and the symptoms collected through the survey of long-haulers **(Figure 1)** [19].

To an article published in the journal ERJ open research, 2113

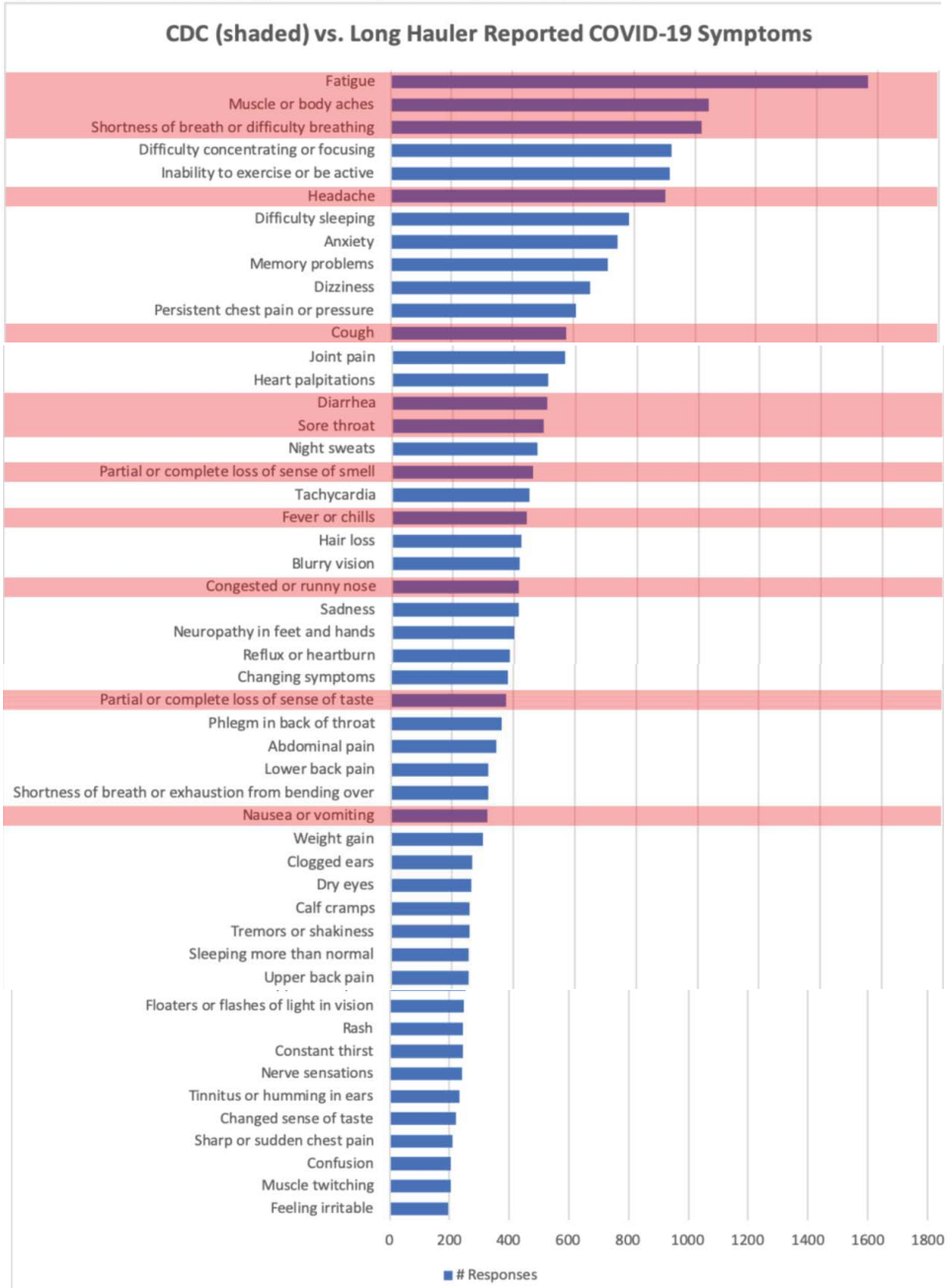

Figure 1 CDC verses long hauler reported Covid 19 symptoms.

patients were evaluated by a questionnaire, who were members of two Facebook groups from both the Netherlands and Belgium and a panel of people registered on the website of the Lung Foundation Netherlands (a total of 12,200 members combined), of which 112 were hospitalized patients and 2001 were non-hospitalized patients.

During the acute phase they presented an average of 14 symptoms. 97% of patients had more than 5 symptoms at this stage. Something striking was that the mean of symptoms by subgroups was small but significant, being higher in patients who were not hospitalized compared to those who were [20].

It was also evidenced in the follow-up, after an average period of 79 +-17 days, an average of approximately 7 symptoms. This shows a reduction in symptoms over time [20].

It was also possible to verify the presence of multiple symptoms approximately 3 months after the onset of the disease. Fatigue and dyspnea were the most prevalent symptoms both during the acute phase and at follow-up [20].

0.7% of all patients were symptom-free at 79 days after infection. And something striking and surprising is the fact that approximately 2% of patients had an increase in symptoms compared to the number of symptoms during the acute phase of infection. It is worth mentioning that most were adult patients, previously healthy, without evidence of pre-existing pathologies. It is also evident that both severe and mild patients are affected by what was called in the article a "post-COVID-19 syndrome" [20].

This highlights several points. The first, that the "mild" can present even more symptoms compared to moderate-severe cases. Second, the symptoms diminish with the passage of time, even in a small percentage, manages to resolve their symptoms completely before 3 months, this corroborates the fact that certain patients should be classified as post-acute and not as chronic. Third and most striking of the study, a percentage of those affected may present even greater symptoms in follow-up than in the acute phase. Definitely, this last point should be considered for future research.

Likewise, in a study published in. the journal Jama Network, 143 Italian patients were evaluated in an average of 60.3 days after the onset of the first symptom. At the time of evaluation, only 12.6% were completely free of any symptoms, while 32% had 1 or 2 symptoms and 55% had 3 or more. In the study, none of the patients had fever or any signs or symptoms of acute illness. Deterioration in quality of life was evidenced in about 44% of patients. In addition, it was observed that a large proportion of patients presented fatigue (53.1%), dyspnea (43.4%), joint pain (27.3%) and precordial pain (21.7%) [21].

According to a cohort study conducted internationally by Davis H et al, in about 3,762 people from 56 countries through a survey, where only 8.4% had been hospitalized, it was evident that the ages most affected by persistent symptoms were between 40 and 49 years, with the female sex also being the most affected. A prevalence of 205 symptoms was estimated in 10 organ systems, with 66 symptoms tracked over 6 months. The most frequently observed symptoms after 6 months were fatigue, post-exertional discomfort, and cognitive dysfunction. Something striking is that of those who presented symptoms for more than 6 months, they experienced an average of 13.8 symptoms when they reached the seventh month [22].

In an article published by Nath A, symptoms such as mental confusion, sleep disturbances, exercise intolerance, autonomic symptoms, lymphadenopathies, even fever, are highlighted as the main ones [23]. The latter, like the autonomic symptoms, are currently poorly described in the literature. It is worth mentioning that the persistence of fever is relevant to the extent that it could suggest the persistence of SARS-CoV 2 within the body or correspond to an overactive response of the immune system, as we will see later. In addition, this study, by mentioning fever as one of the persistent symptoms, contrasts in one way or another with what was suggested in the study published in the journal Jama Network by Carfi A et al.

Now, in a publication made in the journal Nature, a disturbing but revealing title stands out: "The lasting misery of coronavirus long-haulers". This title translated into Spanish "the lasting misery of long-distance carriers of the coronavirus", highlights the ordeal that is lived day by day with a condition still unknown and little recognized. It is mentioned that, in reality, it is a multisystem disease because ACE2 receptors are found throughout the body and are also the main target of the virus. It should be noted that the infection can generate significant immune damage generating a certain degree of persistent immunosuppression probably given by a reduction in interferon's, or quite the opposite, generating that parts of the immune system become overactive and lead to inflammation harmful to the body, both things demonstrated already in the SARS-CoV-1 epidemic in 2003. In a study conducted at the Peking University People's Hospital in Beijing on SARS-Cov-1, in which 71 people who had been hospitalized after acquiring the virus were tracked, it was evidenced that after 15 years 4.6% of people still had visible lesions in the lungs and that 38% had a reduced diffusion capacity. On the other hand, a study of patients in China showed that 25% had abnormal lung function after 3 months, and that 16% were still fatigued [24].

Several posts made on the Medscape website regarding post-acute-chronic COVID-19. The website usually identifies main search terms, with which, it is dedicated to investigating what originated the popularity of them and makes info graphic about it. Something striking is that, during the last weeks, the terms associated with the long-term consequences of COVID-19 have prevailed.

According to Ellis R, a study was conducted at the British hospital North Bristol NHS Trust, where it was shown that 81 out of 110 patients still experienced dyspnea, asthenia, myalgias and sleep disorders months after discharge. Something important to note is that in many of these patients it was not possible to demonstrate alterations in tests of image or lung functionality, but that, nevertheless, their quality of life was deteriorated to such an extent that a subgroup of them could not perform tasks as simple as bathing, dressing or even resuming their working life. According to the Centers for Disease Control and Prevention (CDC), people who continue with fever, chills, cough, myalgia, odynophagia, nausea, vomiting, among other symptoms, may

eventually continue with the viral process [25]. It is worth mentioning that there are patients who after 7 or 8 months of discharge, persist with symptoms such as chills, cough and fever.

1. In a comparison of the symptomatology between the acute phase and the "post-covid syndrome" as it has been catalogued by its author, it was evidenced that 66% did not present any improvement in the symptomatology. Interestingly, 34% of the participants have even stated that their symptoms have worsened. On the other hand, it has been evidenced that 66% of the respondents have remained ill after 6 months since the onset of symptoms. This is important in the sense that "covid long-haulers" could be classified within post-viral syndromes. In any case, caution is suggested, because as we will see, there is a possibility that it is not a post-viral disorder but rather, that its symptomatology is due to a persistent viral infection. It is worth mentioning that in this survey there is a higher percentage of participants who have presented a worsening of symptoms, as demonstrated by the survey described in the article published by the journal ERJ open research, which was described above.

2. According to a video published on the website of Dysautonomia International, dysfunction of the autonomic nervous system is caused by structural damage to the nerves, by their loss, by a malfunction of the same without structural damage or by a combination of them. This alteration could be:

• less than 1 month

• Transient: 1 to 6 months after infection

• Chronic: 6 months or more after infection

Among the most frequent infectious causes that trigger alterations of the autonomic nervous system we have:

HIV, rabies virus, Human T-cell lymphotropic virus, West Nile virus, enter virus 71, herpes virus, tick-borne viral encephalitis, bacteria such as borrelia burdorgferi, mycobacterium leprae, Corynebacterium diphteriae, clostridium botulinum, clostridium tetani, parasites such as trypanosome cruzy and prions. It is currently believed that coronaviruses should be included within the viral etiology causing dysautonomia5.

However, it is necessary and fundamental to highlight certain pathologies that are closely related to the symptomatology of post-acute-chronic Covid-19. Because these syndromes are little known even to health personnel. In addition, the problem is that all this leads to certain patients being diagnosed with an anxiety disorder.

Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS)

This is perhaps the most diagnosed chronic or post-viral viral disorder in the world. So far, most of the literature seems to support the fact that a large part of the patients who have studied and who will undergo SARS-CoV-2 infection, will develop this disorder that, in the same way as the rest of the disorders exposed in this article, can also generate autonomic alterations. Well, as we have shown, fatigue in most cases is the main manifestation.

It should be remembered that in the SARS-CoV-1 epidemic of 2003, a study was evidenced where it was found that 22 health workers who had been infected by this virus, had a post-viral syndrome, which was called "chronic post-SARS syndrome" in which chronic fatigue was reported within the main symptoms as a cardinal symptom, in addition to musculoskeletal pain, sleep disturbances characterized by non-restorative sleep with apneas and hypopneas, among others similar to fibromyalgia and ME/CFS up to three years after the disease, without any returning to work within the first year [26].

On the other hand, according to E. Tucker M, the persistent symptoms caused by SARS-CoV-2 overlap with chronic fatigue syndrome, similar to what we have already described with SARS-CoV-1 of 2003, which is why he mentions that the association between the two is being sought, especially since it is presumed that the origin of this disorder, it is also of viral etiology in a large number of patients.

Among the diagnostic criteria for ME/CFS, are:

• Substantial and deep fatigue for at least 6 months

• Post-exertional discomfort

• Non-restorative sleep and one or both of orthostatic intolerance and/or cognitive impairment.

There is no presence of other pathologies that may occur with chronic fatigue Vale clarify, that not all those patients with persistent symptoms will develop chronic fatigue. One way perhaps to distinguish them early is to ask if there is a dramatic exacerbation of post-exercise symptoms, such as fatigue, pain, and cognitive decline a day or two after exercise rather than immediately afterward. The objective measures supporting the diagnosis of ME/CFS are a low natural killer cell count and autonomic dysfunction assessed by the tilting table test.

Fibromyalgia is a disease characterized by generalized, chronic pain, accompanied or not by joint stiffness, sleep disorders, cognitive dysfunction given by difficulty in concentration, memory problems and depression that affects approximately 2% to 4% of the general population, however of utmost importance since it represents a high cost for the health system given the high number of consultations per year (approx. 10) and the lack of productivity of diagnosed patients [27].

The pathophysiology of fibromyalgia is given by a disorder in the regularization of pain and central sensitization; among which is an excess of excitatory neurotransmitters and low levels of inhibitory neurotransmitters in the descending ant nociceptive pathways of the spinal cord and alteration of endogenous opioids. Among the risk factors identified are genetic, environmental, hormonal, neural and immunological factors28.

Due to the high number of under diagnostics, in 2010 the American College of Rheumatology updated the diagnostic criteria of the disease; among which are:

Pain index (WPI) greater than or equal to 7 and severity symptom scale (ESS) greater than or equal to 5 or WPI between 3-6 and ESS greater than or equal to 9.

1. Presence of: Fatigue, non-restorative sleep, cognitive symptoms

2. Symptoms have been present for at least 3 months

3. Other diagnoses that explain pain have been excluded.

A relationship between fibromyalgia and some viral infections such as Epstein-Barr virus, parvovirus, among others, has been found, which is why in the current context in which the world is going through a pandemic due to the SARS Cov 2 virus, the relationship between it and fibromyalgia is not ruled out [28].

Following a review of the currently available literature, it was observed that

1) Fibromyalgia patients are considered as a vulnerable population in this pandemic.

2) It is common knowledge the existence of countless stressors (physical, mental, emotional and financial) to which the human being is being subjected during this pandemic, it has been seen that these stressors generate a direct and negative impact on the central awareness that is the causal mechanism of FM [29].

3) Patients with central sensitization have inadequate control in the limbic system intensifying the symptoms of depression and anxiety; which in the context of the pandemic could increase suicidal ideation

4) Half of patients with FM establish the worsening of their symptoms after confinement [30].

However, the information reviewed does not establish fibromyalgia as a consequence of INFECTION by SARS Cov 2 virus, however, it has been shown that there are several epidemiological and socioeconomic factors such as insomnia, uncertainty, decreased physical activity which we go through during this pandemic that are also involved in the pathophysiology of FM. A worsening of symptoms was demonstrated in patients with a previous diagnosis of FM secondary to the large number of current stressors. Further research is needed in this relationship in order to establish or not a direct causal link [31, 32].

Central sensitization syndrome

On the other hand, another hypothesis that is handled regarding the persistence of covid-19 symptoms is the Central Sensitization Syndrome. This syndrome corresponds to a set of frequently painful disorders that contribute to the increased risk of opioid abuse and that tends to decrease the quality of life of patients [33].

Central sensitization syndrome is understood as an increased response due to stimulation mediated by an amplification of signaling in the central nervous system [34].

The International Association for the Study of Pain defined central sensitization syndrome as an increase in the responsiveness of nociceptive neurons of the central nervous system to normal or subnormal afferent entry [35].

The central desensitization syndrome currently includes diagnoses such as Fibromyalgia, Chronic Fatigue Syndrome, Migraine or Tension Headache, Restless Legs Syndrome, Multiple Chemical Syndrome33.

This syndrome is characterized by a generalized sensory sensitivity that contributes to hypersensitivity to pain and polysomatization [36].

This process is apparently due to synaptic neuroplasticity, which is characterized by the alteration of neurons depending on factors, both environmental and genetic, and which has been of great interest in chronic pain syndromes [37].

This process of synaptic neuroplasticity occurs in neurons within the limbic region of the brain37.

This mechanism begins with peripheral sensitization, and progresses to the early phase and then moves to the late phase leading to allodynia (pain with mild touch) and diffuse hyperalgesia (generalized increase in sensitivity to painful stimuli) [37].

Sensitization syndrome is divided into acute and late phase. In the acute phase, the activation potential of neurons in the dorsal horn of the spinal cord is reduced by increased transmission of glutamate by N-methyl-D-aspartate (NMDA) and A-amino-3-hydroxy-5-methyl-4-isoxazol-propionic receptors. This increase in the amino acid glutamate and substance P lowers the activation threshold and intensifies the opening of several channels, leading to increased neuronal excitability. Another characteristic is that this increase in glutamate causes the death of inhibitory neurons, thus reducing the modulation of pain signals. These inhibitory neurons are replaced by more afferent excitatory neurons allowing pain signals to increase.

In the late phase there is an alteration in gene expression within the neurons of the dorsal horn, in this way it becomes more difficult to recover from hyperalgesia. This causes changes in the dorsal root ganglia that give these neurons the ability to induce pain without the entry of nociceptors. This continuous afferent outflow without the relevant inhibition results in a greater transmission of pain to the brain, specifically in the insula, which is the area responsible for the interpretation of sensory information [37].

Due to the pandemic caused by COVID 19 there has been a decrease in the physical and emotional condition of people, however, this picture may be more marked in those who suffer from central sensitization syndrome.

Although COVID 19 can be a very stressful circumstance for all patients, those with central sensitization syndromes may be more affected and have an increased risk of developing symptoms of psychological distress36.

Postural Tachycardia Syndrome (POTS)

Regard to Orthostatic Postural Tachycardia Syndrome (POTS), a similar picture had already been described in the XIII century. In 1871 during the American Civil War, young soldiers developed abnormal postural tachycardia after an intestinal infection, combat wound, or overexertion. In its time, it was referred to as "irritable heart" or "soldier's heart" [5].

Something interesting that Cotelo J reports in his publication is a textual quote from what dr. Ramos mentioned where he says the following "dyspnea during hospitalization was associated with subsequent fatigue, with polypnea post activity and with increased resting heart rate. Also a history of asthma during

hospitalization was associated with the subsequent squeal of polypnea post activity. In addition, having a heart rate greater than 90 beats per minute during hospitalization was associated with an increase in this parameter at rest during convalescence" [32].

With the latter, it may be evident that both the history of patients, such as possible dyspnea, as well as alterations in heart rate during the acute phase, could be crucified if no action is taken. That probably shows us lights, that orthostatic postural tachycardia syndrome can be triggered even from the acute phase of the disease. If this is the case, it could eventually be diagnosed early, before the stipulated 6 months, in order to intervene in a timely manner with the intention of improving the picture and therefore the quality of life of the patients. It is worth mentioning that the especially temporary criteria for the diagnosis of this disease must be revised again.

On the other hand, Syrek R in a publication on COVID-19 syndromes says the following "Heart-related symptoms such as residual palpitations and persistent tachycardia have been reported without any residual inflammation"16.

This again strengthens the fact that "unexplained" cardiac symptoms already appear in early stages of the disease.

Going into orthostatic postural tachycardia syndrome (POTS), it is believed to be one of the possible causes of dysautonomia in patients who have developed COVID-19. It is characterized by being a little-known disorder, which generates orthostatic intolerance. It is estimated that 50% of people who have developed POTS previously had a specific viral exposure5.

The estimated prevalence in 2019 was 1-100/1-1000 people in the United States 5.

It is believed that within the possible mechanisms involved we have: Autoimmune/post-infectious, mast cell activation, a genetic component, deconditioning5.

Other triggering causes: bacterial infections, bruises, pregnancy, traffic accidents 5.

is defined as:

1. heart rate greater than or equal to 30 bpm (40 bpm 12 to 18 years) when standing still after being in supine position for the first 10 minutes (for most patients it exceeds 120 bpm).

2. Absence of orthostatic hypotension defined as a fall greater than or equal to 20/10 mmhg within 3 minutes in standing position.

3. Symptoms of orthostatic intolerance greater than or equal to 6 months.

4. Symptoms that are exacerbated by standing and improved at bedtime.

5. Absence of another cause of orthostatic symptoms or tachycardia5.

Symptoms of POTS

Pronounced tachycardia with standing up, palpitations, difficulty breathing, inability to breathe deeply, confusion "brain fog", light-headedness/presyncope, syncope, gastrointestinal motility disorders, nausea, bladder dysfunction, sensitivity to cold/heat, sensitivity to light and sounds, migraine, pronounced fatigue, weakness, tremor, exercise intolerance, acrocyanosis, flushing, increased allergies/sensitivity to food, medicines and/or environment5.

Something that patients with POTS suffer from is sub occipital and/or paracervical pain, probably caused by low blood flow to the muscles of the upper back and neck5. Interestingly, symptoms manifested by a large proportion of patients with post-acute-chronic COVID-19.

It is believed that it can become as disabling as Congestive Heart Failure (CHF) or Chronic Obstructive Pulmonary Disease (COPD) 5 **(Figure 2)**.

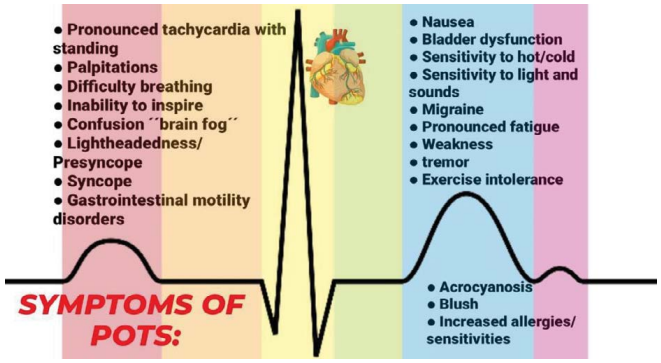

Figure 2 Symptoms of POTS autonomic ganglionopathy (AAG).

It is an autoimmune disease that affects the autonomic ganglia, in half of the cases it is caused by antibodies against the nicotinic acetylcholine receptors of the ganglia that produce their internalization damaged synaptic transmission. The vast majority are preceded by a respiratory infection.

The symptoms described have been classified as autonomic or extra autonomic: within the autonomic ones are: orthostatic hypotension, dry skin, anhidrosis, heat intolerance, pupillary dysfunction, diarrhea or constipation, dysuria, urinary retention, sexual dysfunction. On the other hand, within the extra-autonomic symptoms are sensory alterations (paraesthesia's and dysesthesias), central nervous system involvement, endocrinological disorders (amenorrhea, SIADH, hyponatremia, adrenal insufficiency), autoimmune diseases (Sjogren, systemic lupus erythematous, rheumatoid arthritis, systemic sclerosis, polymyalgia rheumatic, primary biliary cirrhosis, Sill's disease, Hashimoto's thyroiditis, Grave's disease and fibromyalgia), and tumors (ovarian tumor, small cell lung cancer, gastric cancer)

For an adequate diagnosis of this disease, several tests are required, including positive serology for gAChR antibodies and a thorough exploration of autonomic symptoms including tilting table test, measurement of the coefficient of variation of R-R interval, noradrenaline infusion test, levels of catecholamine's in blood, sweat test, pupillary response, Valsalva manoeuvre, study of gastrointestinal motility, urodynamics and customary.

Small fibre neuropathy

The following section is considered fundamental, because a large proportion of patients suffer from symptoms that could be correlated with a viral or post-viral dysautonomia, understood as an over activity or alteration in the sympathetic and parasympathetic components of the autonomic nervous system, which can manifest itself with sinus arrhythmias, profuse sweating, cold, constipation, bronchospasm, chest tightness, alterations in blood pressure, dizziness, presyncope, among others. It is worth mentioning that this symptomatology can simulate panic attacks and in turn, psychological disorders could worsen such dysfunction. This may be due to several factors, perhaps in part due to a hypothalamic alteration mediated by cytokines, due to a small fiber neuropathy, already demonstrated with other viruses such as influenza, viral persistence or viral fragments in leukocytes, such as monocytes, which are easily distributed throughout the body, alteration of the renin angiotensin aldosterone system, by alteration in the hypothalamic-pituitary-adrenal axis, by a microangiopathy, or by direct affection of nerves such as the vagus nerve or glossopharyngeal In a letter to the editor published by The Canadian Journal Of Neurological Sciences, regarding the morbidity of patients recovered from SARS-CoV-1. It was evidenced that, although younger patients tend to survive, they may present with post-infectious disorders, including alterations of the nervous system. In a study conducted in 14 patients who overcame SARS-CoV-1 infection, it was evidenced that 100% of the participants presented fatigue and discomfort and of this group of patients 50% of them presented dysautonomias. It is believed that orthostatic hemodynamic alterations with subclinical behavior could contribute to fatigue and dizziness39.

Novak P mentions that several autoimmune post-infectious complications have been reported, which can affect both the brain and large and small nerve fibers. In it, the case of a patient who developed orthostatic hypo perfusion syndrome (OCHOS) and painful neuropathy of small fibers (SFN) is reported.

Both OCHOS and SFN were confirmed. The first by tilt test with Trans cranial Doppler monitoring and the second confirmed by skin biopsy.

It is striking that these patients have a favourable response to immunotherapy. Well, here a new question arises: Could an early intervention through immunotherapy in those patients who manifest alteration of the autonomous component avoid its chronicity?

It is something that we must consider for the future. Another thing to highlight from what Novak P described is the fact that these disorders are beginning to be described more and more frequently associated with SARS-CoV-2.

A question that must be answered sooner or later is whether fibromyalgia, chronic fatigue syndrome, as well as orthostatic postural tachycardia syndrome, can be pigeonholed with the same name, perhaps as the same disease with slightly different forms of presentation. Well, all three share similar aspects such as viral origin, small fiber neuropathy in many cases, autonomic dysfunction and therefore symptoms such as fatigue, muscle pain, cognitive alterations, alterations in cardiovascular function, etc. In some countries, a "central sensitization syndrome" is beginning to be diagnosed, which includes chronic fatigue syndrome and fibromyalgia, but not orthostatic postural tachycardia syndrome. It would be interesting to see to what extent this last diagnosis can be included in it and thus begin to decipher the pathophysiology behind these disorders to offer an adequate treatment.

Deconditioning

We believe that we cannot fail to address a crucial issue, of vital importance within those patients who are undergoing post-acute-chronic COVID-19. This is post-viral deconditioning.

Deconditioning is a serious alteration of the organism, which can occur to anyone, including athletes in just a few days 5.

Among the symptoms we have

Increased heart rate while lying down or exercising, decreased blood pressure when upright, decreased ability to exercise, weakness, loss of appetite, nausea, constipation, loss of bladder control, electrolyte disturbance, tendency to develop blood clots, impaired response to insulin, elevated blood glucose, impaired balance and coordination, confusion, disorientation, anxiety, depression.

Both deconditioning and dysautonomias can coexist and generate a vicious circle that is detrimental to the health and therefore the quality of life of the people affected. It is worth mentioning that many people in the world live with dysautonomias or post-viral deconditioning. Many of them will fully recover, some will improve over time, and others will not recover.

We believe that viral or post-viral deconditioning is part of the problem of patients suffering from post-acute-chronic COVID-19. However, we believe that it is not the causal axis of his condition.

Discussion

So far, both the persistence of politicization, new politicizations, relapses or the reappearance of symptoms and in many cases the persistence of it with fluctuating intervals of intensity, and variables over time, could suggest the presence of a persistent - chronic viral infection. This is further strengthened in the sense that a large part of those who have these characteristics are patients who have been with mild COVID-19 in which it has been demonstrated, for the most part, low antibody titers and this could justify a real difficulty in eliminating the virus effectively. It is expected if it is the case, that the virus with each replication generates failures that make it disappear from the body and therefore the symptomatology in an indeterminate time.

On the other hand, there is a possibility based on what has been evidenced with other viruses,that this symptomatology is due to a post-viral syndrome such as fibromyalgia, chronic fatigue syndrome, orthostatic postural tachycardia syndrome (POTS) and autoimmune autonomic ganglionopathy. Orthostatic postural tachycardia syndrome (POTS), the most likely cause due to the characteristics of the symptomatology. In any case, it is necessary to analyze to what extent post-viral syndromes are related. Well,

perhaps, they are part of the same disease with slightly different forms of presentation as previously mentioned. In addition, it is necessary to analyse what role deficiency states play in the "long covid", such as deficiencies of vitamins such as B3, B12, vitamin D, amino acids such as acylcarnitine or other disorders such as mastocyte activation syndrome. On the other hand, we do not interfere much in the issue of small fiber neuropathy, however, as we have evidenced, it is believed that it can collaborate with the development of chronic fatigue syndrome, fibromyalgia, orthostatic postural tachycardia syndrome and autoimmune autonomic ganglionopathy. This neuropathy is characterized by the injury of poorly myelinated Aδ peripheral afferent fibers and non-myelinated C fibers.

Also, it is necessary to carry out an exhaustive investigation on what relationship could exist between the infections passed by other viruses such as Epstein Barr, cytomegalovirus, herpes type 1 and type 2 with the subsequent infection by Sars-CoV-2 and the development of persistent symptomatology.

Addition, it is necessary to investigate to what extent they are post-viral syndromes and not chronic viral syndromes.

It is necessary to analyze to what extent the persistence of SARS-CoV-2 in the body is the cause of chronic symptoms. Well, not necessarily the existence of it or its fragments can be the cause of this disorder.

The last possibility that we consider is that SARS-CoV-2, having an important neuroinvasive capacity, could have persisted due to unclear mechanisms in the nerves, perhaps due to the formation of immunocomplexes, generating a process of both central and peripheral neuroinflammation, either at the level of the hypothalamus or perhaps also due to nerve injury such as the vagus, the phrenic and the glossopharyngeal, generating an autoimmune and inflammatory response in these places, thus manifesting with symptoms associated with the autonomic component of the nervous system, which could trigger symptoms similar to postural orthostatic tachycardia syndrome, chronic fatigue syndrome, fibromyalgia, among others. These disorders, whether of viral or post-viral origin, generate similar symptoms and may even overlap with various psychiatric disorders, such as generalized anxiety disorder, post-traumatic stress disorder, or panic attacks, etc. It is important to clarify that psychiatric disorders worsen autonomic symptoms and by coexisting both together with viral persistence, a state lacking nutrients, a state of deconditioning of the individual, could be the cause of the symptomatology, which is confusing and difficult to manage by health personnel. In any case, blood markers in each of the phases of the disease are being investigated, as well as certain important imaging tests for diagnosis such as PET-SCAN or functional magnetic resonance imaging of the brain or heart. In any case, more studies are required to later find the pathophysiological origin and the development of an appropriate treatment.

is not yet clear what percentage of patients and in what time they will recover, in addition, an approximate number of patients suffering from post-acute-chronic COVID-19 is not yet known, given that they have been diagnosed mostly incorrectly, have not had a diagnosis so far by their doctors or because they have not attended them. It is imperative to recognize and assign an ICD-10 to this condition and it is urgently required in the same way, to create "post-covid" clinics or centers, as they have done in some countries.

Conclusions

Both persistent viral infections and post-viral syndromes have been little studied so far. It is perhaps time to interfere in depth in the investigation of chronic infections, their impact on the body, as well as entities that generate dysautonomias and that are usually associated with chronic or post-viral viral pathology, especially chronic fatigue syndrome, fibromyalgia, autoimmune autonomic ganglionopathy and orthostatic postural tachycardia syndrome. The first two are already included in a disorder known as central sensitization syndrome. Well, it would not be uncommon for POTS to end up being part of the latter. More research is needed on blood markers, the presence of viruses in tissues and possible risk factors to prevent chronicity of the disease. Patients with sub-acute-chronic COVID need answers, because the impact on their quality of life, in the workplace, social, psychological has been very great and without a doubt, of not taking action, of not taking corrective prevention measures, of not facilitating vaccination freely worldwide, health systems will be saturated and / or collapsed by a new disease. It is imperative not only to focus on prevention, but also on the treatment of it. Well, we do not know if vaccinated patients are protected against the development of chronic covid.. It is essential to look for a treatment that is equally widespread as the vaccine and at low costs, since the latter is important since most of those who suffer from this chronic disease are people with limited economic resources. It is not possible to dismiss as we have seen, the impact on the nutritional deficiency state generated by the disease nor the deconditioning, which definitely generate repercussions and a worsening of the picture of people who persist with symptoms.

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