



Review

“LONG COVID” - DEFINITION, SYMPTOMS, WHAT TO LOOK FOR AND HOW TO TREAT?

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ABSTRACT

"Long COVID," also referred to as "Long-Haul COVID or Post-COVID syndrome" is a condition where a person continues to experience symptoms of COVID-19 after their body has defeated the virus. On the bases of couple of clinical studies, we have attempted to describe the most common clinical symptoms that are present 12 weeks or more after having COVID-19, if these symptoms are not explained by another diagnosis. As can be seen, the long COVID is not an easy topic. There are many aspects to this issue because SARS-CoV-2 affects many organs in the human body. However, with the fast increase of data emerging from the vast variety of clinical studies that are currently underway, a better understanding will be obtained of how to treat patients with COVID-19 that have symptoms which have lasted for more than 12 weeks.

Key words: Long COVID ,SARS-CoV-2,Post COVID.

Definition

"Long COVID," also referred to as "Long-Haul COVID or Post-COVID syndrome" is a condition where a person continues to experience symptoms of COVID-19 after their body has defeated the virus [1-3]. Long COVID is a Post-COVID condition, which the Centers for Disease Control and Prevention (CDC) of the United States describes as "new, returning or ongoing health problems" caused by the disease more than a month after infection.

In the current review we are going to look into the long term effects of COVID-19, and potentially what we can do about them. The symptoms of long-term COVID-19 are complicated, and we will attempt to simplify them. There are a lot of terms that we use for "persistent COVID-19 symptoms":

- Long COVID or long haulers,
- Post acute sequelae of SARS-CoV-2 infection (PASC),
- Post acute COVID-19,

- Chronic COVID-19,
- Post COVID syndrome.

The definition for persistent COVID-19 symptoms is any symptoms that are present 12 weeks or more after having COVID-19, if these symptoms are not explained by another diagnosis [3].

The length of these symptoms depends on whether or not, the patients have had severe COVID-19 whether or not, they were inpatient or outpatient. They can also depend on the type of symptoms. For instance fevers typically go away pretty quickly, whereas shortness of breath or fatigue can linger.

Clinical studies

The first study enrolled about 2000 health care workers in Sweden. In this study, there were compared SARS-CoV-2 positive patients with SARS-CoV-2 negative patients. When they looked at them 60 days post, they found that those that were SARS-CoV-2 positive - 26% of those had at least one symptom that was persistent versus just 9% in the SARS-CoV-2 negative. After 8 months that number had gone down from 26% to 15% but it was still lingering

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and for the other group from 9% in the placebo down to just 3%. About 8% to 15% of patients versus just 4% in the placebo said that the symptoms, that they had interfered with their work social or home life. These are significant [4].

The second study was looking at 60 days outcomes among patients hospitalized with COVID-19 [5]. This was a little bit of a bigger study including about 1600 subjects admitted to 38 hospitals in the United States. After 60 days post discharge, 33% of them had persistent symptoms and 19% had actually worsening symptoms. The prevalence showed that 24% of the patients had dyspnea or shortness of breath, 17% had shortness of breath or chest tightness, 15% cough, interesting here 13% loss of taste or smell [5]. Interesting regarding those 13% of the patients appears to be a smaller number than what actually may be the case, because among people who have had a change in their taste or in their smell - it's a much larger number, but not complete loss of taste or smell.

The most common symptoms up to three months - 15 to 87% of patients had fatigue and this happens to be the longest-lasting symptoms [3]. In general, 10 to 71% had shortness of breath lasting up to two months. About 12 to 44% had Chest discomfort, again usually up to and including about two or more months. Cough 17 to 34% - about two months. No taste or smell 10-13% - I'm sure a much higher percentage had problems with taste or smell and that generally speaking a month or so, but there are patients clearly that have had the symptom for much longer than that and this is not unusual. There are other infections, where people have lost their sense of taste or smell. It seems however to be a little bit more common in COVID-19. Other less common physical symptoms that you could see and with a much different variable time in terms of weeks to months are - joint pain, headache, sicca syndrome, rhinitis, poor appetite, dizziness, vertigo, myalgias, insomnia, alopecia, sweating, and diarrhea [3].

In terms of common neurological symptoms - 7 to 24% had PTSD flashbacks, 18 to 21% had impaired memory, 16% had poor concentration and 23% had anxiety and depression. The vast majority of these last about one to two months, with some exceptions lasting longer [6].

There was a study that was done in Vancouver Canada which was a prospective study looking at patients that were discharged from a hospital with SARS-CoV-2. They contacted 100 and 78 of them fulfilled the questionnaire. What they found was some interesting data - 51% of these patients had a quality of life reduction, because of these persistent symptoms, 50% had dyspnea or shortness of breath, 23% had cough, the drawback to this study was that there was no baseline to compare it to, but there it is nonetheless [7].

Examination and management of long COVID

And so as we are progressing and hopefully around the world the incidence of acute SARS-CoV-2 infections are going down, we're now emerging into this post COVID world, where we are seeing patients with lingering symptoms, showing up in the waiting room, waiting to be seen. The main question is what do we do with such patients?

So from a physician's standpoint what should be the follow up? What should be done with these patients, which have gotten COVID-19 infection? The data and the recommendations seem to be - if anybody is hospitalized with these symptoms of SARS-CoV-2, whether they are older or younger, with comorbidities, or without. The consensus is that the latter patients should be followed up within a week. If they got their SARS-CoV-2 in the outpatient world, to begin with and never needed to be hospitalized, then if they are older - (greater than 60 years of age), or they have comorbidities (kidney problems, congestive heart failure, diabetes, hypertension) then generally speaking they should be followed up at about 3 weeks. It is really important when they are seen back the physician should get information about how that COVID-19 was treated - did they get monoclonal antibodies, did they get Remdesivir (it is thought to cause kidney problems). It is also important to know did they get steroids - because it should be known whether or not they have been made immunocompromised, or if they have been tapered appropriately off the steroids, or whether or not they were still on those steroids. It should be known about the duration of illness and the types of interventions that they had - were these patients on the ventilator, did they have ARDS [7].

It is important to understand that there is no need of rechecking them for SARS-CoV-2

routinely, to see whether or not they are negative. There is no evidence that that is beneficial in these types of situations.

The next issue –which should be asked, are the symptoms. The patients should be separated in a few groups - 1 cardio pulmonary symptoms / 2 neurological / 3 blood / 4 problems with olfaction / 5 fatigue. The physician should go through them step by step and look at the evidence to see what could be done about them.

For cardio pulmonary symptoms it should be asked about shortness of breath. It could mean a lot! - Shortness of breath could be a result of a lung disease, it could be a result of heart disease, it could be a result of deconditioning. It should be also known if it is happening at rest, or on exertion, or when lying down. If it's when lying down, that is usually suggestive of Congestive heart failure. Also it should be asked about cough, because a lot of these patients have a cough. It can be a symptom of other pathological diseases like a cough variant asthma. Chest pain is usually related to a pleuritic pain due to inflammation of the pleural cavity. Edema is a very common situation in the lower legs or feet that can be related to Congestive heart failure. It could also be related to blood clots in the legs or lungs. These are serious issues and should be evaluated. Palpitations - that's the term that is used for what it feels like there's a butterfly in the chest. This can often mean that there is arrhythmias going on and again that needs to be evaluated especially in light of the fact that the SARS-CoV-2 can affect the cardiovascular system.

Dizziness is a very non specific symptom that could be related to the neurological or cardiovascular issues. It's important to ask the patient if they feel like they are going to pass out or if they feel like the room is spinning. If the patient feels like the room is spinning that is usually more of a neurological issue whereas, if they feel like they are going to pass out or blackout that is usually a cardiovascular issue.

Other important information is while they were in the hospital or sometimes even as an outpatient – was the chest X-ray abnormal. If so, the physician has to follow it through to make sure that the abnormality is resolved, and if it not he/she has to follow it up to make sure that it's not a tumor or any kind of mass. In some cases patients are clinically and symptomatically getting much better, but the chest X-ray is very

delayed in its resorption – in such cases it is not recommended repeating the chest X ray for at least 12 weeks. In 12 weeks it should be seen resolution of those infiltrates and a normal chest X ray. If it is not seen, then the physician has to be concerned about a persistent problem in the lungs, such as tumors or masses and etc. Then it should be obtained more advanced imaging analyses like a CAT scan to see what else is going on.

Another very informative study that can be easily done is ECG; it is a very cheap test to be done and it gives a lot of information (myocarditis or pericarditis). Echocardiogram is an ultrasound of the heart; experts do not routinely recommend getting these. But if COVID-19 patients have swelling in the legs that's new, if there is a chest pain especially if in the hospital the patient had a history of elevated cardiac enzymes, all these are indicative that there was heart muscle injury. If the patient has ongoing symptoms of shortness of breath and signs and symptoms of congestive heart failure, the Echocardiogram may give a diagnosis and it may explain what is going on. Echocardiography can also show what the pulmonary artery systolic pressure is. It is also sometimes suggestive of a pulmonary embolism. That is important because the autopsies in patients with COVID-19 were nine times more likely to have blood clots than patients without COVID-19 [8].

Pulmonary function tests with diffusion capacity are very informative in hospitalized patients especially if they had acute respiratory distress syndrome (ARDS). This means that there is going to be damage to the lungs, potentially even fibrosis.

Other test that can also be done as a baseline, especially in patients with fatigue, is a “6 minute walk test”. Based on that it can be obtained an assessment about what their functional capacity is.

Laboratory and other assessments in long COVID patients

In the case of a “Long COVID” symptomatic patient another important test is the D-dimer test (D-dimer is a product of coagulation in the body). It is a very sensitive test; if negative it is very helpful at telling that there is no risk for this patient to have blood clot issues as an outpatient, but if it is positive there are so many reasons that can cause it. So, it could not be

really told for sure that it is related to blood clots. At that point what the physician would do is getting further tests with a bilateral lower extremity ultrasound Doppler, to look for blood clots to make sure that that is not the case. Furthermore it could be done a CT scan with a contrast day which is often what is done when there are suspicions for blood clots in the lungs (unfortunately those CT scans are not very sensitive for chronic clots).

If a blood clot is suspected in the extremities the recommendation would be to get an ultrasound Doppler, to see whether or not there are any. If patients are taking anticoagulants and it is seen this quite often with discharged patients, the question is how long they should be on that anticoagulation. Generally speaking that has to be determined by the physician himself. It can sometimes be very complicated because they may have other conditions, which may need to keep them on anticoagulation. If a clot is “provoked”, this means that there is some other cause, such as the patient was on a medication, or the patient had a cancer, or the patient was on a long flight. All of these reasons would need three months of anticoagulatory treatment as long as the provoking factor could be removed. If the clot is unprovoked, which means no causes have been suggested, the treatment could be indefinite time [9-12].

Another very informative test is the methacholine challenge test, because in patients with dyspnea symptoms, who have a normal pulmonary function test, normal breathing and they are able to breathe out normally, and on the day that they come in for their tests they are feeling fine. With the methacholine challenge test the lungs will be provoked in order to be seen if they are sensitive to it. Thus finding the diagnosis “cough variant asthma” will be accompanied with starting inhaled corticosteroids.

Complete metabolic panel – creatinine, BUN searching for acute kidney injury (renal failure). Levels of CO₂ are affected adversely when a patient has an active infection for a long period of time which causes acidosis.

Assessment of the neurological implications

To be able to assess the neurological implications of COVID-19 one should do a complete neurological history and examination. If focal deficits are present the physician could order imaging studies like CAT scan or an MRI.

It might be considered also neurocognitive testing, if no focal deficits are present.

Olfaction problems

The olfaction problems are very unique about COVID-19. Such problems are known as post infectious smell loss (PISL). As it was said above about 10 to 13% of patients that were infected have had no smell or taste. The olfactory nerves make a very complicated system, but the neurons have no ACE-2 receptors. So the question had been for a long time is: are the neurons of the olfactory system becoming inflamed, does the virus infect them? - And the answer turns out to be “no” - it is the cells of this supporting tissue, that is around the neurons, that have the ACE-2 receptor, which are being infected. An interesting study that was done on mice expression of SARS-CoV-2 entry genes in the olfactory system suggests mechanisms underlying COVID-19 associated inability to smell [13] After the single cell sequencing it was reported that ACE-2 are expressed in support cells, stem cells and perivascular cells rather than in the neurons themselves. Immunostaining confirmed these results and revealed pervasive expression of ACE-2 protein in dorsally located olfactory epithelial. These findings suggest that COVID-19 infection of non-neuronal cell types leads to anosmia and related disturbances in odor perception in COVID-19 patients [13].

Generally speaking, the olfaction problems usually gets better on its own within a month, but that is not valid for those people that still do not have normal taste and smell. They may need olfactory training.

In a study researching the long term effects of olfactory training in patients with post infectious olfactory loss there were included 111 patients with PISL. The study continued for a total of 13 months. The patients were divided into 2 main groups – with olfactory training with essential oils and without olfactory training. At the end of the follow-up period it was found that 58% of the subjects from the olfactory training group regained their smell in comparison to the 37% from the control group who did not have olfactory training. The conclusion was that the use of these essential oils can help speed up the restoration of the sense of smell and taste [14-16]

Fatigue as a long COVID symptom

Fatigue is a difficult symptom to assess. There is a difference between fatigue and sleepiness; - with fatigue the person is awake. There are a number of various tools that can be used. In addition, there is a lot of data on how to treat chronic fatigue syndrome in order the patients to get adequate rest and to have good sleep hygiene. Although it is not known whether or not fatigue from COVID-19 is similar to chronic fatigue syndrome, there are a number of treatments that are being used for chronic fatigue syndrome that might be applicable in fatigue from COVID-19. Such are the approaches like exercise programs: cardio pulmonary exercise and exercise for cardio pulmonary rehabilitation.

Vaccination as treatment approach for long COVID symptoms

Another potential treatment that is suggested for "long Covid" symptoms is simply vaccination. After 8 months since discharge from hospital from 163 patients screened, 78 of them were followed up, of those only 44 received a vaccine. Every 12 weeks they had a number of questionnaires to answer. When they were vaccinated along this line they were followed up one month later, and this was done blindly so that the people asking the questions on the questionnaire did not know if the patients had been vaccinated or not. So actually out the 159 symptoms that were described before vaccination, 71% stayed the same 6% got worse and 25% got better. When they did the analysis between the two types of vaccines that were available at the time - the Pfizer Biontech and the Oxford AstraZeneca vaccine, there was no statistical significant difference between the vaccines in terms of the outcomes that occurred. Having symptoms worsen from COVID-19 seems to be pretty rare after vaccination [17-21].

CONCLUSIONS

As can be seen, the long COVID is not an easy topic. It is very complicated. There are many aspects to this because SARS-CoV-2 affects many organs in the human body. However, with the fast increase of data emerging from the vast variety of clinical studies that are currently underway, a better understanding will be obtained of how to treat patients with COVID-19 that have symptoms which have lasted for more than 12 weeks.

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