

Web headline: Trapped by the coronavirus: a conundrum with no quick fix

Newspaper headline: Long covid is a riddle without a quick solution

Some corona patients stay ill for a long time. They are tired, short of breath, they have a headache or brain fog. What is going on? Much is unclear. Scientists are frantically searching for the cause, but there may not be one single mechanism that explains everything.

Niki Korteweg, 10 June 2022 – NRC

<https://www.nrc.nl/nieuws/2022/06/10/langdurig-gevangen-door-het-coronavirus-een-raadsel-zonder-snelle-oplossing-a4133083>

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Coronavirus waves come and go, but one reservoir just keeps swelling: that of people who have long-term complaints after an infection with SARS-CoV-2. The vast majority of people recover from Covid-19 within a week or two, but some still have symptoms after a few weeks or develop new ones, which can last for months or even years. This prolonged aftermath of the disease is called Long covid, post covid syndrome or PASC (Post-Acute Sequelae of Covid-19).

People can experience all kinds of symptoms – in all kinds of organs, and in all kinds of combinations. The most commonly reported ones are extreme tiredness, shortness of breath and problems with thinking - a lack of concentration and forgetfulness, so-called 'brain fog'. But also palpitations, chest pain, muscle aches, headaches, dizziness, abdominal pain, persistent elevation, loss of sense of smell and sleep problems - over 200 symptoms have been reported.

The persistent complaints are more common in people who have been seriously ill and have been hospitalized or who were in the ICU with pneumonia. But it also occurs in people who initially had hardly any symptoms - sometimes young fit people. Many healthcare workers who were at the frontline during the first wave have become infected themselves, and thousands are unable to work to this day. More than six thousand people who work in healthcare and education have already reported to the trade union FNV with long covid.

The hopelessness, the lack of treatment and the lack of recognition by their employers drives people with post-covid syndrome to despair. Tatjana van Run (37), an art historian, did PhD research at TU Delft. After visiting a conference in March 2020, she fell ill, and ever since she has had the whole palette of nasty and ever-changing symptoms. “The GP initially blamed it on stress, the occupational health physician said: it must be something else. Every time there was that struggle to be taken seriously.”

Together with eleven other people with long-term symptoms, Van Run founded the website longcovidnederland.nl. Last year they submitted a petition to the House of Representatives, signed by more than 10,000 patients, doctors and family members. “A call for recognition, coordinated research and better treatments.” It helped: 7.8 million euro was made available for research into long covid.

“ In two-thirds, we still see lung damage on CT scans and reduced lung function after six months”

Joachim Aerts, Professor of Pulmonary Medicine

But conducting scientific research into long covid is not easy. To begin with, there is no unanimous definition. The World Health Organization WHO describes a 'post-covid condition' as having complaints three months after the onset of Covid-19 that have lasted at least two months and cannot be explained by another diagnosis. The US CDC draws the line at one month after a corona infection. And the British health organization NICE distinguishes two groups: 'persistent Covid-19' if it lasts between 4 and 12 weeks, and 'post-Covid-19 syndrome' if it lasts longer.

It is therefore difficult to determine how many people get long covid after an infection. Most studies show estimates of 10 to 30 percent. That is a significant part of the population: the British Office for National Statistics ONS calculated in May that 2.8 percent of the British people reported long-haul covid complaints that lasted longer than a month. For two-thirds, this significantly hindered their daily activities.

In the available studies, different groups of patients can be discerned. People who have been in ICU face by far the highest risk of long-term complaints after covid, followed by people who were in hospital. The percentage of people who stayed at home with the disease and then developed long covid complaints is much lower, but because so many people have had covid-19, their number is greater. In a recent American study, three-quarters of people with long-term complaints after Covid-19 had not been hospitalized.

Tissue damage

The nature of the complaints differs between these groups: long covid patients who have stayed in the hospital more often suffer from shortness of breath, whereas people who went through the disease at home most often report extreme fatigue and cognitive complaints. The long covid patients in this group more often are women around the age of 50.

Which biological processes are causing the slew of long-term symptoms after Covid-19 is still a mystery. But scientists do have hypotheses. They could be due to organ damage, from the viral infection, a dysregulated immune response or autoimmune antibodies. A disbalance of the microbiome is also suggested, or the reactivation of a dormant virus in the body. In particular for the first three hypotheses, scientific evidence is trickling in. And for a suspicious process that may lie beneath all these explanations: the formation of tiny blood clots, microclots.

Severe Covid-19 can wreak havoc in many organs, including the lungs, heart, kidneys and brain. This damage can last for a long time, especially in patients who were in hospital. “In two-thirds, we still see lung damage on CT scans and reduced lung function after six months,” says Joachim Aerts, professor of pulmonary medicine at Erasmus MC in Rotterdam. “In one third there is permanent scarring in the lungs, fibrosis. That results in long-term shortness of breath.”

In a quarter of the covid patients in the ICU, damage to the heart muscle is still visible after six months, says cardiologist Chahinda Ghossein-Doha of Maastricht UMC.

In contrast, long covid patients who experienced covid at home usually show no damage to the lungs, says Aerts. “These patients mainly suffer from long-term fatigue, or loss of smell and taste. Corona really has an effect. But the question is whether it originates from their lungs.” Aerts carries out research into the cause of that fatigue.

The fact that nothing odd is visible on regular scans of the lungs may be because those methods are not suitable. British researchers therefore used a new type of scan: an MRI scan during which participants inhaled xenon gas to determine the gas exchange between lungs and blood. With this method they looked at the lungs of 23 people with long covid and those of 13 healthy people. In 19 long covid patients, they saw a reduced gas exchange six months later compared to healthy people, even when no damage was visible on an X-ray or CT scan.

Microclots

There are ideas about the cause of such a faltering gas exchange. The walls of blood vessels in the lungs may have been damaged by the virus – the ACE2 receptor, the gateway through which the virus enters cells, is also located in these walls. As a result of damaged vessel walls tiny clots could form, which block the blood flow in the capillaries of the lungs. And perhaps not just in the lungs, as blood vessels run throughout the body.

An infection with SARS-CoV-2 can cause problems with blood clotting. Especially in patients with severe Covid-19, the risk of thrombosis or pulmonary embolism is increased: a blood clot in a vein or artery. And that increased clotting tendency remains present for up to six months.

Microclots have also been found in the capillaries of the lungs and brains of deceased people with severe Covid-19. At the Erasmus Medical Centre scientists are investigating whether microthrombosis in the lungs can play a role in the shortness of breath that people sometimes experience after severe Covid-19. “They don't seem to play a role in long-term fatigue,” says Aerts.

However, the South African physiologist Ethersia Pretorius thinks the microclots are more widespread. They could lead to a lack of oxygen in various tissues and thus cause the wide variety of complaints. She discovered small microclots in the blood of long covid patients that are difficult to dissolve with anticoagulants. She did not see those microclots in healthy people. With a patented microscopic technique she is able to visualize those tiny clots, only around 50 micrometres in size. The blood she studied also contained overactive blood platelets, which are important in blood clotting, and two to ten times higher concentrations of various proteins involved in clotting. The normal equilibrium between blood clotting and anticoagulation seems to be out of balance in long covid patients.

Dangerous

Erik Klok, vascular medicine internist at the LUMC in Leiden and specialized in blood clotting, is skeptical. “For now, Pretorius is the only one who has demonstrated this, with a technique that only she can use, in small groups of people, without clearly defining long covid.”

He gets a lot of questions about it from desperate patients. But administering anticoagulants won't help against the microclots, he says. "Those medicines do not dissolve clots, they only prevent the formation of new ones. The body clears clots on its own, just like scabs on a wound." The cocktail of three drugs that Pretorius administered to a small number of patients with long covid is dangerous. "It can lead to severe bleeding. That is why a study with these risky medicines to treat a non-life-threatening condition like covid will not easily be approved by a medical ethics committee."

However, cardiologist Ghossein-Doha does think that chronic formation of microscopic blood clots could play a role in the heart damage that she sees in her ICU covid patients. "The scar tissue in the heart muscle is different from what we see after oxygen deprivation or after an infection of the heart. We want to collaborate with the South African researchers and see whether these microclots are present in the blood samples of our patients."

"Long-term or severe stress can also have strong physical consequences"

Chahinda Ghossein-Doha cardiologist

The disturbed blood clotting may be caused by an increased concentration of inflammatory molecules, Pretorius suspects. This fits with another hypothesis about long covid that scientists are investigating, including Aerts: an aberrant reaction of the immune system to the virus or to lingering viral fragments. Some inflammatory molecules, such as certain cytokines and interferons, are elevated for up to eight months after infection in people with post-covid symptoms, writes American immunologist Akiko Iwasaki in a review article in Science.

Also in the brain, a chronic inflammatory response could play a role, says virologist Debby van Riel of Erasmus MC in Rotterdam, who specializes in the effects of virus infections on the nervous system. "With SARS-CoV-2 you hardly ever see acute brain inflammation, but you do see mild chronic inflammation."

SARS-CoV-2 enters brain cells, but does not multiply easily there – except in the olfactory nerve cells in the nose, says Van Riel. "But even if a virus is temporarily present, long-term inflammation can occur. That could be a systemic inflammation that impacts the whole body, or an inflammation impacting a specific organ, or even one single area in that organ."

The brains of deceased Covid-19 patients contain many activated immune cells, so-called microglia. These are also overactive in the brains of mice after they get infected with SARS-CoV-2 in the lab, Iwasaki showed at the beginning of this year. The immune cells seemed to inhibit the production of new brain cells and of myelin, the insulating layer around nerve endings.

Kissing disease

An ongoing or disrupted immune response seems a plausible hypothesis for fatigue complaints: many inflammatory molecules can lead to feeling tired. The chronic inflammation could be caused by virus fragments that the body did not clean up properly, or by the immune system remaining awry after the infection. Another option: dormant viruses in the body may have been awakened by the infection. One candidate is the Epstein-Barr virus (EBV), which

causes mononucleosis - also known as kissing disease-, which is present in over 90 percent of Western Europeans. The presence of EBV in the blood was one of four risk factors for developing post-covid syndrome, American researchers discovered. Next to that, people were more at risk if they had type 2 diabetes, or if they had large amounts of the coronavirus in their blood shortly after infection.

A fourth risk factor also warrants more research: autoantibodies in the blood. These are antibodies that the body accidentally makes against its own tissues or compounds. Some of these can cause tiny blood clots. People with severe covid often have autoantibodies, Iwasaki writes.

A first indication for the role of autoantibodies in long covid comes from a small German study with people with predominantly neurological complaints due to the post-covid syndrome. The researchers found various autoantibodies against a certain type of 'sensor' on cells, so-called G protein-coupled receptors. Such antibodies are rare in healthy people, but have been found in people with pain, chronic fatigue or heart problems, and in people with postural orthostatic tachycardia syndrome (POTS). Some people with long covid also suffer from that syndrome, in which people experience dizziness, faintness and an uncomfortably fast heartbeat as soon as they stand up.

Frustration

Frantically, scientists are searching for leads for explanations for the elusive post-covid syndrome. There is not one clear-cut cause, otherwise it would have been found. The first studies are still small; the palette of possible causes is almost as broad as that of symptoms.

There probably isn't just one mechanism that can explain everything, thinks virologist Van Riel. "It is likely that it is a combination, and perhaps different combinations in different patients."

As long as there is no clear underlying mechanism, research into a possible treatment can hardly be done within the strict rules of scientific research. This frustrates people who have to deal with long covid.

Couldn't people with long covid just take an anticoagulant? Or anti-inflammatory medicines? "I don't recommend that as long as we don't understand the mechanism," says cardiologist Ghossein-Doha. "In any case, never do it without consulting your doctor."

And then there is the poignant question of whether part of the complaints may have been caused or aggravated by stress. To unravel which long-term complaints are caused by Covid-19, cardiologist Ghossein-Doha and colleagues are following covid patients and patients who have not had covid-19 during the pandemic. "It was a confusing and stressful time for many people, in which they might have had less sleep or exercise, they may have lost their jobs or have been lonely. Such long-term or severe stress can also have strong physical consequences."

It is precisely this 'psychologizing' of the complaints that is a major pain point for many people with post-covid complaints, says Tatjana van Run. "It downplays the urgent need for biomedical research, and it puts the blame on the patient. If the complaints don't improve with cognitive behavioral therapy, for example, you get the feeling that it's your own fault."

That is why, despite the lack of knowledge, pulmonologist Aerts in Rotterdam is setting up research investigating the effect of antiviral and immune-enhancing drugs. “Patients desperately need a solution.”

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POSTVIRAL SYNDROMES

It is not surprising that an infectious disease such as Covid-19 has chronic effects in a group of people. Post-acute infection syndromes have also been described for many other infectious diseases. Even after the 'mother of all pandemics', the Spanish flu pandemic of 1918-1919, there were many reports of prolonged fatigue and neurological complaints, as well as after subsequent flu epidemics and after polio.

Little research has been done into the post-acute effects of other viruses, says virologist Debby van Riel. “Most research has been done on myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS), and there are certainly similarities to the symptoms of long covid. And after an infection with the human herpes virus type 6, HIV and the cytomegalovirus, we also see these kinds of long term complaints.”

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