

Covid-19: Neuropsychiatric symptoms

MESSAOUDI Abdelkrim (1), SI AHMED Hakim (1), DAOUDI Smail (2).

Faculty of Medicine, University Université Mouloud Mammeri Tizi-Ouzou. Algeria.

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I. Introduction:

Covid-19 refers to "Coronavirus Disease 2019", the disease caused by a virus in the Coronaviridae family, SARS-CoV-2. This infectious disease is a zoonosis, the origin of which is still debated, which emerged in December 2019 in the city of Wuhan, in Hubei province in China. It quickly spread, first throughout China, and then abroad, causing a pandemic.

Covid-19 is a respiratory disease that can be fatal in patients who are frail by age or another chronic illness. It is spread through close contact with infected people. The disease could also be transmitted by asymptomatic patients. Current scientific data is very uncertain.

Since the late 1960s, human coronaviruses have been recognized as being able to affect the lower respiratory tract and to be associated with more serious pathologies such as severe acute respiratory syndrome, SARS. During the following three decades, the neuro-invasive and neurotropic potential of human coronaviruses (HCoV) has been clearly demonstrated: The neurons of the central nervous system (CNS) are often the target cell of infection, which causes their degeneration and possibly their death. In addition, by participating in poorly controlled activation of the immune system, coronaviruses could trigger an autoimmune process in the CNS in some individuals.

According to several Chinese medical teams, all of the clinical data shows that one must be vigilant in the presence of neurological symptoms. Caregivers should discuss the diagnosis of Covid-19, even in the absence of fever and respiratory symptoms, so as not to delay the diagnosis. It is particularly important that clinicians learn as much as possible about the neurological symptoms of patients before admission to hospital (impairment of consciousness). To take all protective measures and limit the risk of exposure to healthcare staff and other patients.

Clinic:

Symptoms of Covid-19 disease are fever, fatigue and a dry cough. Some patients have also experienced pain, congestion and runny nose, sore throat and diarrhea. These symptoms are generally mild. But about one in six people have more severe symptoms, including dyspnea. Pneumonia is the most common complication of Covid-19. There are also asymptomatic cases, that is, patients have no apparent symptoms despite detection of the virus.

People most at risk

Those most at risk are the elderly and those with other health conditions such as high blood pressure, heart problems and diabetes. The mortality rate increases with age: it is 0.2% for the youngest people (10 to 39 years old), but reaches 14.8% for people aged 80 and over. The average mortality rate is estimated between 1 and 3%.

There is currently no treatment capable of eradicating the virus. Patient care is only intended to treat symptoms. Researchers around the world are exploring many avenues to find an antiviral drug or vaccine, with no convincing results to date. Antibiotics are ineffective against viral infections, as are some traditional herbal or food remedies.

In about 80% of cases, patients recover spontaneously, without needing any special treatment. The most serious cases are managed in intensive care units in the hospital where they are closely monitored.

Prevention measures to prevent the spread of the epidemic

According to the WHO, the effective means of prevention not only to contract Covid-19, but also to prevent its spread, are:

- Frequent washing of hands with soap or with an alcoholic solution;
- Avoid close contact, like kissing or shaking hands, with people who cough or sneeze;
- Cover your mouth with the crease of the elbow, or a disposable handkerchief, during a cough or sneeze;

- Do not touch your eyes, nose or mouth;
- In case of respiratory symptoms and fever, wear a mask and stay confined so as not to contaminate those around you. Call your doctor and follow their instructions.

Neuropsychiatric table:

Although coronaviruses are essentially respiratory viruses, several studies have reported their ability to also infect the central nervous system and cause neurological disorders.

The neurotropism of coronaviruses is known, in particular for the family of beta-coronaviruses to which SARS-CoV, MERS-CoV and SARS-CoV-2 belong. The neurons of the central nervous system are often the cell targeted by the virus which causes their degeneration. HEV 67N, a porcine coronavirus, was the first to be identified in the brains of pigs. There is 91% homology between this strain and a human beta-coronavirus, HCoV-OC43, responsible for the common cold.

The path taken by coronaviruses is not precisely known, but it seems that viruses use synaptic pathways to pass from the cardiorespiratory center to the spinal cord. The mechanoreceptors and chemoreceptors of peripheral nerve endings in the lower respiratory tract are thought to be the gateway through which the virus reaches the central nervous system.

The neurological symptoms of Covid-19 affect only a minority of people: 8% suffer from headaches and 1% from nausea and vomiting. However, loss of consciousness and acute cerebrovascular disorders have been reported in some studies.

An explanation for anosmia?

For several days, doctors have reported that patients complain of anosmia. It is a loss of smell often associated with a loss of taste (ageusia). Anosmia can be caused by damage to the olfactory nerve, the first cranial nerve that connects the nasal cavity to the olfactory bulb located at the base of the brain. When the damage is neurological, the anosmia can be constant.

Anosmia does not necessarily mean the invasion of the central nervous system by the virus, it is a very common symptom in respiratory diseases such as rhinitis or colds. In this case, it is not the olfactory nerve that is involved but a defect in the permeability of the nasal cavities, the stuffy nose in short, which prevents odors from reaching the olfactory receptors. The anosmia is then generally transient.

The virus has not yet been observed in the brainstem of patients, as was the case in a test carried out in mice with MERS-CoV and SARS-CoV. The neurotropism of SARS-CoV-2, responsible for Covid-19, is for the moment only an assumption and scientific data are lacking to attest it with certainty. But being aware of this possibility could have an impact on the care and treatment of the disease.

At the known symptoms of Covid-19 (fever, dry cough, cold ...) are added atypical forms. Particularly in the brain. Cognitive impairment related to coronavirus infection has been confirmed. Anosmia and ageusia, the loss of smell and taste, are indicative of the neurological damage caused by the SARS-CoV-2 virus. They are the first symptoms of neurological damage to be highlighted in Covid-19 disease.

Vigilance disorder

A Chinese retrospective study published on February 22 on the prepublication site medRxiv, conducted with 214 Covid-19 patients hospitalized in mid-February at Union Hospital in Wuhan, evaluated the frequency of neurological manifestations in Covid-19 patients. Such symptoms were observed in 78 patients (36.4%). The most severely affected patients were significantly more likely than the others to present neurological complications: cerebrovascular pathologies (5.7% versus 0.8%), impairment of consciousness (14.8% versus 2.4%).

A study, published March 31 in the British Medical Journal and involving 113 patients from Tongji Hospital (Huazhong University of Science and Technology, Wuhan), indicates that 22% of the patients who died had a disturbance in consciousness at the time of their admission.

In France, vigilance disorders (confusion, drowsiness) are considered to be a criterion of severity during hospitalization but are not among the clinical signs suggesting a SARS-CoV-2 infection. In the United States, the Centers for Disease Control (CDC) mentions on their page titled that a new state of confusion or a disturbance in alertness should immediately encourage them to consult a doctor because these may be warning signs of Covid-19.

Encephalopathy

In early March, US neurologists reported the case of a 74-year-old man infected with SARS-CoV-2 who developed brain damage (encephalopathy). He has a history of Parkinson's disease, cardiac pathology. He suffers from chronic obstructive pulmonary disease, characterized by persistent respiratory symptoms due to the permanent obstruction of the airways. When he visits the emergency room of a hospital in Boca Raton, Florida,

he coughs and has a fever. It has been seven days since he returned from the Netherlands. Blood tests and chest x-rays show nothing special. The patient returns home, the doctors evoking an exacerbation of his chronic pulmonary disease.

The next day, the patient was brought by his family to the emergency room because his condition worsened. His state of consciousness is altered. He has a headache, is feverish and coughs. He is hospitalized and placed in isolation. The chest scanner then shows abnormal images of the two lungs.

The patient is transferred to the neurology department because he no longer speaks and does not respond to simple orders. The brain scan shows nothing in particular, with the exception of the after-effects of a previous stroke. On the other hand, the electroencephalogram is abnormal, with signs suggesting an encephalopathy (diffuse brain damage). The patient is tested for Covid-19. The tests come back positive. The patient is treated with antiepileptics prophylactically and receives antivirals.

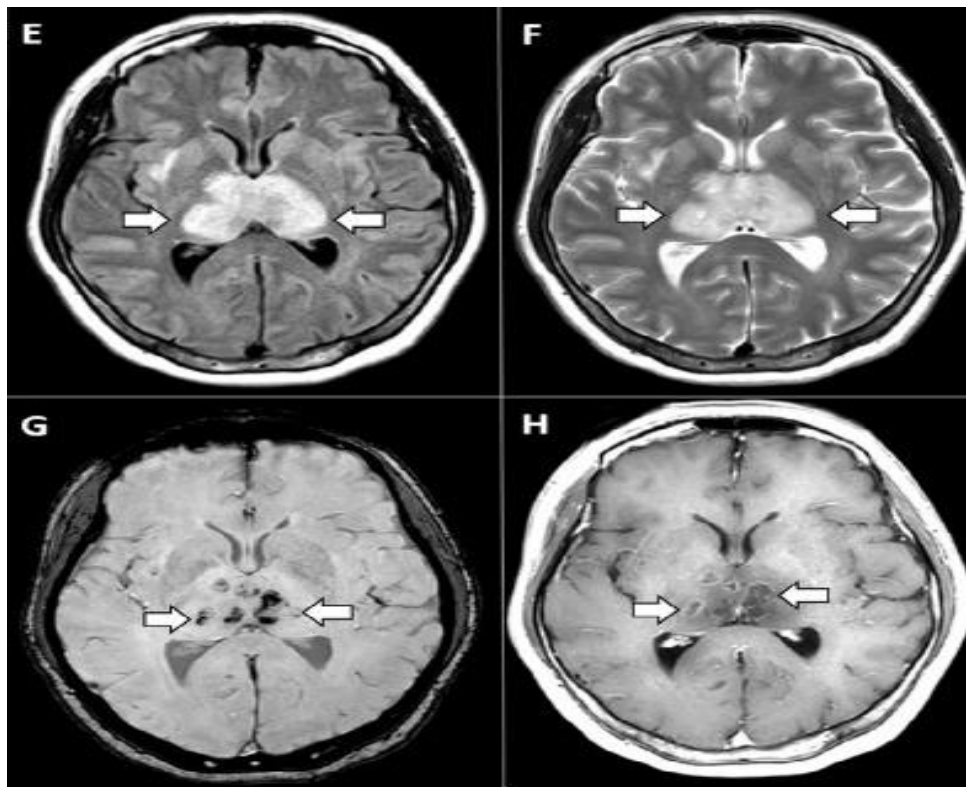
Neurological signs

Covid-19 disease can sometimes manifest itself in a neurological form. This is the finding made by medical teams several weeks after the first clinical descriptions of the SARS-CoV-2 coronavirus infection. As the Covid-19 epidemic progresses, clinicians, radiologists and neurologists are warning about these little-known clinical forms.

These neurological manifestations are in addition to the cardiological, hepatic, renal, ophthalmological, ENT and dermatological lesions recently described. While most patients with Covid-19 develop fever, cough, fatigue, and difficulty breathing, it appears that in some patients, the disease can therefore present itself in a neurological form.

American neurologists from the Henry Ford Health System of Detroit, Michigan published a case of acute necrotizing hemorrhagic encephalopathy in a woman who tested positive for SARS-CoV-2 on March 31 in the journal *Radiology*.

The patient, in her 50s, is an airline employee who has had a cough, fever and altered consciousness for three days. A diagnostic RT-PCR detection test on nasopharyngeal swabs returns positive for SARS-CoV-2. The virus could not be found in the cerebrospinal fluid (CSF) because analysis of the CSF was limited due to a traumatic lumbar puncture. The search for herpes viruses (VHS1 and 2), varicella-zoster virus (VZV), and West Nile virus (West Nile virus) was negative. No bacterial growth was observed on the cultures after three days.



Brain MRI. E and F : bilateral anomalies (T2 / FLAIR hypersignal) in the medial temporal lobe and thalamus. G : hemorrhage visualized on the cerebral MRI by a hyposignal on the magnetic susceptibility sequences (SWI). H: enhancement of the edges of the lesions (post processing of MRI data). Poyiadji N, et al. *Radiology*. 2020 Mar 31:201187.

Magnetic resonance imaging (MRI) of the brain, on the other hand, reveals multiple symmetrical bilateral and hemorrhagic lesions. The patient receives immunoglobulins. This clinical observation represents a suspected case of necrotizing acute hemorrhagic encephalopathy associated with Covid-19.

Acute necrotizing hemorrhagic encephalopathy, a rare complication of influenza and other viral infections, is considered to be due to an intracerebral "cytokine storm". In other words, this pathology does not seem to be due to a direct attack on a virus, or a post-infectious process, but on a flood of inflammatory molecules (cytokines) produced by the immune system and having reached the brain. due to a breach in the blood-brain barrier (blood-brain barrier).

Acute spinal cord injury

On March 18, neurologists at Renmin Hospital at Wuhan University reported a case of acute myelitis after infection with SARS-CoV-2, in other words, spinal cord injury. The patient is a 66-year-old man hospitalized for acute flaccid paralysis, characterized by loss of muscle tone. He has had fever and tiredness for two days. Upon admission, his body temperature is 39 ° C. He does not cough and is not ashamed to breathe. The patient receives antiviral therapy for five days. He then undergoes a thoracic scanner which tests bilateral lung lesions.

The SARS-CoV-2 detection test in nasopharyngeal swabs is positive.

Neurologists believe that this patient developed acute post-infectious myelitis (involvement of the spinal cord one week after onset of fever) and therefore acute paralysis may be a neurological complication associated with Covid-19. It is possible that the inflammatory molecules produced by the immune system that fight SARS-CoV-2 may be involved in the development of spinal cord damage.

Guillain-Barré syndrome

Reported by Chinese neurologists from Central Hospital in Jingzhou and Ruijin Hospital in Shanghai in *The Lancet* on April 1. Doctors described a case of Covid-19, the symptoms of which started with Guillain-Barré syndrome, a condition in which the patient's immune system attacks the peripheral nervous system.

The patient is a 61-year-old woman who presented on January 23, 2020 with acute weakness in both legs and severe fatigue. She returned from Wuhan four days earlier, on January 19, but has no fever, cough, chest pain or diarrhea. Her body temperature was 36.5 ° C. Blood tests show lymphopenia. Neurological examination reveals muscle weakness and an absence of reflexes in both legs and feet. Three days after his hospitalization, the symptoms progress. Doctors observe a decrease in muscle strength in the upper (4/5) and lower (3/5) limbs. The surface sensitivity is reduced.

On January 30, one week after the onset of symptoms, the patient developed a dry cough and fever (38.2 ° C). The chest scanner then shows abnormal lung images (frosted glass appearance). RT-PCR tests on respiratory samples are positive. The patient was immediately transferred to an isolation room and received antivirals. Her clinical condition is gradually improving. Lymphocyte and platelet levels normalize. After discharge from the hospital, 30 days after admission, the muscle strength of the upper and lower limbs returned to normal. The respiratory symptoms have disappeared and the nasopharyngeal tests for SARS-CoV-2 are negative.

Hypotheses:

What are the mechanisms responsible for the associated neurological complications Covid-19. One possibility would be that the coronavirus, after entering the nasal cavity, would reach the olfactory bulb and then go up until reaching the brain. This is only a hypothesis, based solely on an experimental model of encephalitis in mice.

Hypothetical neuroinvasive potential

Based on the neuroinvasive potential observed in mice with coronaviruses other than SARS-CoV-2, Chinese researchers put forward the hypothesis, particularly bold, according to which the acute respiratory failure observed in patients could, in part, may be due to damage to the brainstem, the region between the brain proper and the spinal cord below, in which the centers (nuclei) of breathing control are located. SARS-CoV-2 could travel from the airways to the cardio-respiratory centers in the brainstem. For this, they refer to Japanese work which has shown, in mice inoculated nasally by the influenza virus, that this virus can be transported via the vagus nerve to the central nervous system.

Vascular endothelium

To date, there is no evidence to suggest that viral particles of SARS-CoV-2 can enter the central nervous system via the bloodstream. It can nevertheless be noted that the ACE2 receptor, an enzyme located on

the membrane of many cells and which represents the gateway to SARS-CoV-2, was found on the surface of cells lining the inside of the vessels of the brain (endothelium vascular). This therefore raises the possibility that the strokes associated with Covid-19 are directly linked to the virus and that encephalitis is a complication of viral infection.

"Cytokine storm"

Another hypothesis, probably the most attractive, is attracting the attention of researchers. It is based on the massive release of inflammatory molecules (cytokines) produced by the immune system in response to viral infection. This "cytokine storm" could weaken the blood-brain barrier which normally isolates the brain from undesirable substances which may be present in the blood circulation. This massive release of cytokines would cause persistent neuroinflammation, which causes brain dysfunction. This could explain the occurrence or progression of the cognitive disorders observed in certain patients, sometimes even when the pneumonia is stopped.

Also discussed is the fact that Covid-19 patients with severe infection often have elevated serum D-dimers (coagulation markers), which (in addition to being a risk factor for pulmonary embolism acute), would expose to the risk of developing a cerebrovascular accident by migration of a blood clot in an artery of the brain.

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