

## ORIGINAL ARTICLE

# Neurological complications in COVID-19 patients admitted to a general ICU in the Netherlands

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## Abstract

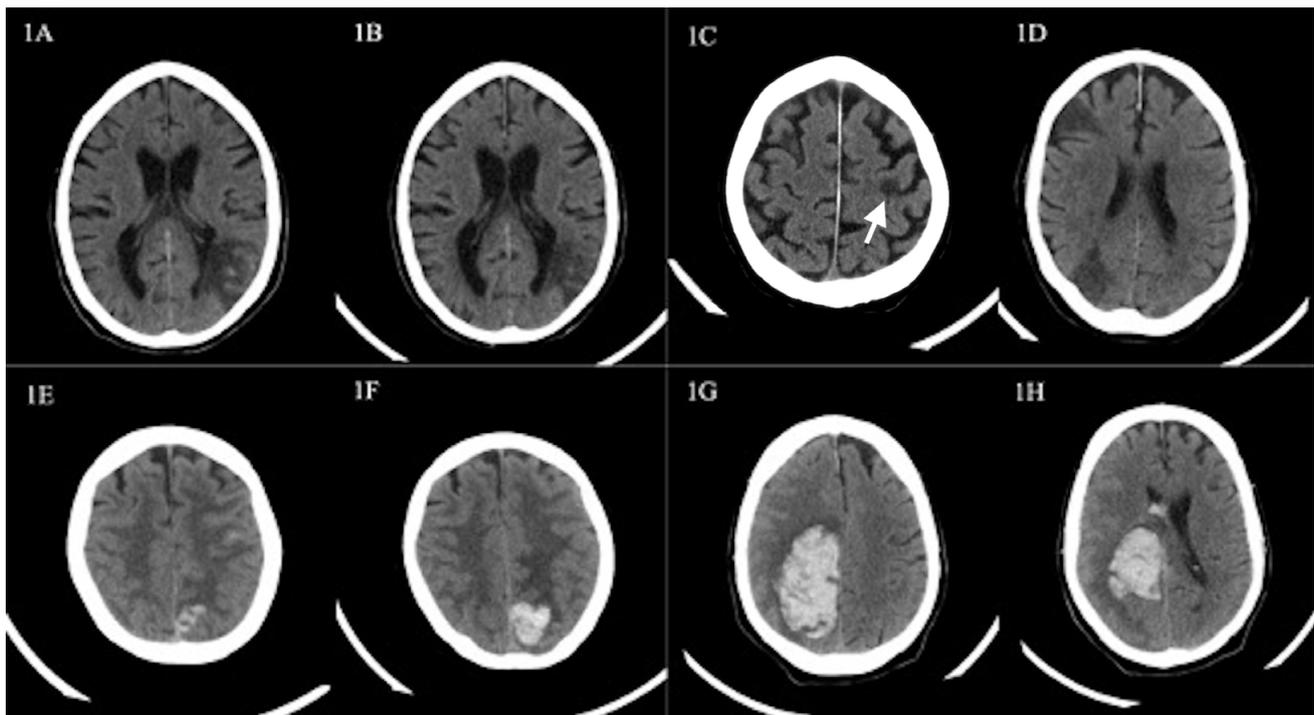
Coronavirus disease 2019 (COVID-19) predominantly affects the respiratory system. However, the viral infection has been associated with brain involvement. In the literature multiple routes are described through which this neurotrophic virus enters the central and peripheral nervous system, including direct and indirect pathways. This can cause various neurological complications, mostly in the advanced stages of the disease. In this case series we present four patients with COVID-19 and stroke out of 59 COVID-19 patients admitted to the intensive care unit in Ede, the Netherlands, before October 2020. Patients had two to five risk factors for cerebrovascular disease. In conclusion, COVID-19 itself might be a risk factor for neurological complications, particularly stroke in patients with cerebrovascular risk factors. Although the underlying pathophysiology remains to be fully understood, physicians should be aware of these neurological complications while treating critically ill patients with COVID-19.

## Background

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), causing coronavirus disease 2019 (COVID-19), predominantly affects the respiratory system. Common symptoms of COVID-19 patients are fever, dry cough, shortness of breath, diarrhoea and fatigue.<sup>[1,2]</sup> Neurological symptoms are also frequently observed among COVID-19 patients. Headache and dizziness are considered non-specific minor symptoms associated with COVID-19.<sup>[3]</sup> Both the peripheral nervous system and the central nervous system (CNS) can be affected, mostly in advanced stages of the disease.<sup>[3]</sup> Possible CNS manifestations include meningitis, encephalitis, acute myelitis, stroke, and encephalopathy.<sup>[1,4-9]</sup> Manifestations of the peripheral nervous system may include Guillain-Barré syndrome, anosmia, chemosensory dysfunction and skeletal muscle damage.<sup>[5,10,11]</sup>

Nervous system disorders due to SARS-CoV-2 accompanied by the immune system are positively correlated with the degree of severity of COVID-19 symptoms.<sup>[6]</sup>

In the literature, multiple routes are reported through which SARS-CoV-2 may enter the brain, including direct and indirect pathways. The virus may gain access to the CNS through a synapse-connected route after invading peripheral nerve terminals of the respiratory or enteric network.<sup>[12-14]</sup> SARS-CoV-2 invades host cells through the angiotensin-converting enzyme 2 (ACE2) receptor, which is expressed in various cell types including the brain and capillary endothelium.<sup>[15]</sup> The interaction on capillary endothelium may damage the blood-brain barrier through which the virus gains bloodstream access into the CNS.<sup>[16]</sup> Together with hyperinflammatory responses and cytokine storms caused by the virus, this might result in acute myelitis, meningitis, encephalitis and severe encephalopathy.<sup>[6,17]</sup> As with other neurotrophic viruses, SARS-CoV-2 may spread transneuronally to distant brain targets.<sup>[18]</sup> Beside pathways to infiltrate the CNS, a procoagulant tendency may lead to CNS thromboembolisms resulting in ischaemic stroke.<sup>[9]</sup> Endothelial dysfunction and cytokine storm in combination with immobilisation leads to microangiopathy, hypercoagulability and blood stasis.<sup>[4,9,19]</sup> Haemorrhagic stroke has been reported in COVID-19 patients as well. Damaged intracranial arteries due to the interaction of SARS-CoV-2 and ACE2 receptors could lead to vessel wall rupture.<sup>[20]</sup> Coagulation disorders seen in COVID-19 patients result in disseminated intravascular coagulation, which accompanies this damage to intracranial arteries. Together these disorders could be the cause of haemorrhagic stroke.<sup>[20,21]</sup> COVID-19 related stroke may cause focal inflammation in the injured brain region causing substantial secondary brain injury.<sup>[22]</sup>



**Figure 1.** CT brain of four ICU patients with coronavirus disease 2019 and stroke. 1A and 1B: patient 1 with ischaemic stroke, 1C and 1D: patient 2 with ischaemic stroke (white arrow indicates lesion), 1E and 1F: patient 3 with haemorrhagic stroke, 1G and 1H: patient 4 with haemorrhagic stroke.

Serious neurological complications of COVID-19 are increasingly reported, primarily in small case series and a few cohort studies. The aim of this study was to report the observed neurological complications of COVID-19 in the ICU of Gelderse Vallei Hospital during the first COVID-19 crisis.

**Table 1.** TOAST classification

Types of ischaemic stroke
Large-artery atherosclerosis
Cardioembolism <sup>3</sup>
Small-vessel occlusion
Stroke of other determined aetiology
Stroke of undetermined aetiology

\*Adapted from Goldstein et al.<sup>[25]</sup>

## Methods

Consecutive COVID-19 patients admitted to the ICU of Gelderse Vallei Hospital from 18 March to 12 October 2020 were retrospectively analysed. A confirmed case of COVID-19 was defined as a positive result on polymerase chain reaction (PCR) analysis of throat swab specimens or a CO-RADS score of at least 5 on chest CT scan with clinical symptoms of COVID-19.<sup>[23]</sup> Radiological assessments and laboratory testing were performed according to the clinical care needs of patients. We retrospectively reviewed medical records of all patients with confirmed SARS-CoV-2 infection. We collected data on

age, sex, duration of ICU admission, nervous system symptoms and risk factors for neurological complications of all patients. Risk factors include hypertension, diabetes mellitus, obesity, smoking, alcohol, dyslipidaemia, atrial fibrillation, history of cerebrovascular or cardiovascular events, and physical performance.<sup>[24]</sup> For patients with neurological symptoms, we collected laboratory findings (triglyceride level, low density lipoprotein cholesterol and non-fasting glucose) and radiological examinations. Neurological manifestations were reviewed and confirmed by a neurologist. TOAST classification was used to classify ischaemic stroke subtypes (*table 1*).<sup>[25]</sup> Written informed consent was obtained from each patient described.

## Results

Fifty-nine patients with a confirmed COVID-19 diagnosis were admitted to the ICU. Of these patients, 19 were females and 40 males, with a median age of 69 years (range 29-83). Eleven patients died during admission to hospital, nine of whom died during their ICU stay. Five patients died after discharge from hospital. The median ICU stay was eight days (range 1-50). Cerebrovascular risk factors were present in 56 patients, with a median of two risk factors per patient (range 0-7). Four patients developed neurological symptoms during their ICU stay, all were diagnosed with ischaemic or haemorrhagic stroke (based on clinical examination and CT brain). Their characteristics including their risk factors are summarised in *table 2*. All cases are reviewed in detail below. At the beginning of the pandemic the normal doses of thromboprophylaxis based on body weight of 2850 IU or

**Table 2.** Characteristics of patients and cohort with coronavirus disease 2019 (COVID-19) who developed neurological symptoms during their stay at the ICU

	Patient 1	Patient 2	Patient 3	Patient 4	Cohort
<b>Age, years</b>	78	74	62	68	73 [29-83]
<b>Gender</b>	Male	Male	Female	Male	Male 37 (67.3%) / Female 18 (32.7%)
<b>ICU stay, days</b>	42	18	46	27	8 [1-50] 8 [1-50]
<b>Duration of hospitalisation, days</b>	46	30	83	28	16 [1-63]
<b>COVID-19 diagnosis before onset of neurological complication, days</b>	30	20	28	33	NA
<b>Neurological complication</b> TOAST classification	Ischaemic stroke Large-artery atherosclerosis	Ischaemic stroke Cardioembolism	Haemorrhagic Stroke NA	Haemorrhagic Stroke NA	NA
Subtype haemorrhagic	NA	NA			
<b>Hypertension</b> Blood pressure at admission, mmHg	No 150/58	No 146/91	De novo 158/66	Yes 112/65	Yes 24 (43.6%) / No 31 (56.4%)
<b>Dyslipidaemia</b> Triglyceride, mmol/l LDL-cholesterol, mmol/l	No 1.7 -	No 1.1 -	No 1.2 2.69	Yes 1.1 1.98	Yes 23 (41.8%) / No 32 (58.2%)
<b>Diabetes mellitus</b> Non-fasting glucose, mmol/l	No 8.2	No 7.3	No 5.2	Type 2 diabetes 10.3	Yes 16 (29.1%) / No 39 (70.9%)
<b>Atrial fibrillation</b>	No	No	De novo during admission	No	Yes 5 (9.1%) / No 50 (90.9%)
<b>History of cerebrovascular or cardiovascular events</b>	CVA (2 times)	TIA	No	No	Yes 17 (30.9%) / No 38 (69.1%)
<b>Smoking</b>	Stopped at 40 years old	Unknown	Unknown	Stopped at 65 years	Yes 15 (35.7%) / No 27 (64.3%)
<b>Obesity, BMI</b>	26.2	24.9	29.0	31.7	29.4 [22.5 – 56.9]
<b>Physical status, Barthel score</b>	100	100	90	80	100 [70 – 100]
<b>Alcohol</b>	Incidental	2-3 units/day	Unknown	No	Yes 23 (54.8%) / No 19 (45.2%)
<b>Deceased</b>	No	No	No	Yes	Yes 15 (27.3%) / No 40 (72.7%)
<b>Anticoagulation before event</b>	Clopidogrel 75 mg po per day and nadroparin 2850 IU sc per day	Nadroparin 2850 IU sc twice daily till PE, then 7600 IU sc twice daily	Nadroparin 2850 IU sc per day till PE, then 7600 IU sc twice daily	Nadroparin 5700 IU sc twice daily till DVT, then 9500 IU sc twice daily	NA

Variables are shown as mean with range, or as number with percentage per subgroup. Note that the four patients reported were excluded from the cohort column.

TOAST = Trial of Org 10172 in Acute Stroke Treatment; LDL = low-density lipoprotein; CVA = cerebrovascular accident; TIA = transient ischaemic attack; BMI = body mass index; PE = pulmonary embolism; DVT = deep venous thrombosis; NA = not applicable; po = orally; sc = subcutaneously

5700 IU nadroparin once a day were given. After the thrombotic tendency in COVID-19 patients was established in the literature, we adopted an intermediate-intensity dose strategy of nadroparin twice daily 2850 IU or 5700 IU for thromboprophylaxis. If at the time of admission a haemorrhage was clinically suspected, the thromboprophylaxis strategy was individually adjusted to the patient after consultation with a neurologist.

### Patient 1

A 78-year-old male with a past medical history of stroke presented to the emergency room (ER) of another hospital with dyspnoea, headache, fever and a cough for two weeks. He was transferred to Gelderse Vallei Hospital for an ICU bed. Due to progressive respiratory failure, the patient was intubated and mechanically ventilated. After regular daily wakeup the sedation could be completely stopped on day 11. Due to severe ICU-acquired weakness, confirmed by electromyography on day

15, a tracheostomy was performed. On day 16, the patient still experienced persistent reduced consciousness (E1M4Vtube) and absent response to pain stimulus on his right side. CT brain showed semi-recent ischaemic changes in the left parieto-occipital lobe (*figure 1A*). No atrial fibrillation or thrombosis were observed during admission. EEG showed a diffuse slow background rhythm, with lowered left parieto-occipital amplitude, but no epileptic activity. On day 22, no haemorrhagic transformation or extension of the infarction was seen on second CT brain (*figure 1B*). During ICU admission the patient improved to a maximal EMV score with improving ICU-acquired weakness after which he could be decannulated on day 40. After 42 days, he could be transferred to the neurology ward. Upon discharge, the patient was able to get out of bed for one hour twice daily. He returned to his initial hospital for further rehabilitation. Duplex ultrasound was not performed to diagnose possible carotid stenosis as this would have no clinical consequences given the patient's unstable condition.

### Patient 2

A 74-year-old male with a medical history of sick sinus syndrome, transient ischaemic attack (TIA) and first-degree atrioventricular block, presented to the ER with progressive dyspnoea for three weeks, and possibly mild loss of strength of his right hand for one day. Because of acute respiratory failure he could not be properly neurologically evaluated. Brain imaging was postponed and patient was admitted to the ICU. The patient was intubated and mechanically ventilated in the prone position for two days. On day 2, CT angiography showed extensive subtotal and segmental pulmonary embolisms in all lung lobes, for which therapeutic anticoagulation was initiated. After discontinuation of sedation, the right-sided hemiparesis persisted. On day 7, CT brain showed multiple subacute infarction areas on both sides (*figures 1C and 1D*). Ultrasound showed an atrial septal defect potentially contributing to the cerebral embolisation of thrombi causing infarctions. No atrial fibrillation was observed during admission. He improved after two weeks, after which he could be discharged to the neurology ward on day 18. On the ward a normal carotid duplex was performed. On day 30, the patient could be discharged to a rehabilitation centre with a right-sided hemiparesis Medical Research Council (MRC) scale grade 3 to 4.

### Patient 3

A 62-year-old female with a medical history of COPD gold 2 and gastric reflux disease presented to the ER with fever, cough and dyspnoea for one week. Due to progressive respiratory failure, she was admitted to the ICU and was intubated. During admission the patient developed type 2 acute coronary syndrome with rapid atrial fibrillation and hypotension for which she was treated. On day 12, CT angiography showed pulmonary embolisms after which therapeutic anticoagulation was started. On day 17, the patient suddenly developed nystagmus, hypertension and a transient conjugated eye deviation to the right. Valproic acid was started because non-convulsive status epilepticus was diagnosed. CT brain showed a small haemorrhage in the left parietal lobe, possibly as a result of sinus thrombosis (*figure 1E*). Labetalol was started to control her blood pressure. Valproic acid was continued because it was effective. The following day a cerebral venous occlusion was excluded. On day 22, she developed a persistent conjugated eye deviation to the right. CT brain showed an increase in the size of the intraparenchymal haemorrhage (*figure 1F*). Therapeutic anticoagulation was continued at a lower dose. Tracheostomy was performed because of an accompanying ICU-acquired weakness. On day 43, a control CT brain showed that the intracerebral haemorrhage had decreased in size, after which full therapeutic anticoagulation was resumed. After decannulation on day 46, the patient was discharged to the nursing ward. Five weeks later, the patient was discharged to a rehabilitation centre. In the following three months, the patient presented multiple times at the ER with focal seizures. To date, she is not able to walk, and is experiencing memory and concentration deficits.

### Patient 4

A 68-year-old male with a past medical history including hypertension, type 2 diabetes and COPD gold 3 with reduced functional lung capacity presented to the ER with dyspnoea, cough and diarrhoea for one week. Due to respiratory failure, the patient was admitted to the ICU and was intubated. Flucloxacillin was initiated due to phlebitis after venous cannulation of the right arm. On day 10, he developed deep vein thrombosis of the right arm for which he received therapeutic nadroparin. Due to ICU-acquired weakness, a tracheostomy was performed on day 16, after which he could be weaned off mechanical ventilation. On day 26, the patient showed decreased consciousness (E1M4Vtube). CT brain showed parenchymal bleeding in the right hemisphere with ventricular breakthrough and mass effect with midline shift (*figures 1G and 1H*), most likely due to hypertension during admission. The consulting neurologist determined that the size and extent of the bleeding was severe. In combination with the patient's impaired physical condition before admission, his prognosis was poor. After a family meeting where prognosis was discussed, palliative care was initiated, and patient died on day 28.

### Discussion

In this case series we present four patients with COVID-19 and stroke in the COVID-19 ICU population. Neurological symptoms were present at presentation in only one patient. Patients had two to five risk factors for cerebrovascular disease, including hypertension, dyslipidaemia, atrial fibrillation, positive medical history for cerebrovascular or cardiovascular diseases, obesity and the use of alcohol or smoking. Patient characteristics correspond to the total COVID-19 ICU population.

Mao et al. reported stroke in 5.7% of non-ICU patients (5/88) with severe SARS-CoV-2 infection admitted to a general hospital.<sup>[5]</sup> In a study by Li et al., stroke was reported in about 5% of non-ICU patients (11/219) admitted to a major tertiary hospital, with an average time of onset 12 days after COVID-19 diagnosis. These patients were associated with severe disease and had a higher incidence of cerebrovascular risk factors. Patients with stroke had an increased inflammatory response and higher D-dimer levels.<sup>[26]</sup> Retrospective observational analysis by Rifino et al. identified stroke in 53 of 1760 (3.0%) patients with COVID-19 admitted to a general hospital.<sup>[27]</sup> The only study in an ICU population is the study by Klok et al.<sup>[9]</sup> They reported a cumulative incidence of stroke of 3.7%. All patients received at least standard doses of thromboprophylaxis, which is comparable with the antithrombotic protocol of Gelderse Vallei Hospital. Moreover, higher age and hypercoagulable state, defined as a prolonged prothrombin time of more than three seconds or activated partial thromboplastin time over five seconds, were risk factors for thrombotic complications.<sup>[9]</sup>

A prospective multicentre cohort study by Koh et al. included a total of 47,572 patients. Thirty-nine patients had neurological manifestations; of these patients 84.4% were asymptomatic or had mild symptoms, 2.2% had severe and 13.3% critical SARS-CoV-2

infection. Sixteen patients had ischaemic stroke, and three had a TIA, with a median age of 53 years. Only three of these 19 patients had critical COVID-19. Fifteen of them had cerebrovascular risk factors. Another two critically ill patients developed an intracerebral haemorrhage. Four cases of young men with cerebral venous thrombosis were identified, two of whom were asymptomatic and two had mild COVID-19.<sup>[28]</sup>

In the literature, neurological syndromes have been reported in patients with a SARS-CoV-2 infection and causality between both entities has been explored. COVID-19 is associated with a wide spectrum of neurological syndromes which affect the entire neuraxis, including cerebral vasculature and inflammatory CNS syndromes with central and peripheral nervous system involvement. The underlying mechanisms of these syndromes may be multifactorial, resulting from combined or independent effects of sepsis, hypoxia, thrombosis and cytokine storms. Valencia-Enciso et al. revealed a trend between the time of onset of ischaemic stroke and severity of the disease. In patients with severe COVID-19, stroke developed late, while in those with mild COVID-19, stroke presented early (mean 23.2 and 5.1 days, respectively).<sup>[4]</sup> These data are in line with the time of stroke onset in the four patients with severe COVID-19 infection presented here, who were admitted to the ICU. Inflammatory markers were related to the development of large vessel occlusion.<sup>[4]</sup> Therefore, together with an increased predisposition to thrombosis,<sup>[29]</sup> the hyperinflammatory state present in patients with severe COVID-19 might be a substantial contributor to the multifactorial underlying mechanisms resulting in stroke. However, data are still emerging and it is too early to draw conclusions.

Besides stroke, other neurological manifestations of COVID-19, such as encephalopathy, encephalitis and epilepsy, have been studied as well. The emergence of a neurological disorder during SARS-CoV-2 infection must be assessed in its complex context and it must be determined whether it could be a direct or indirect effect of viral invasion in the nervous system or represent a random finding. The European Academy of Neurology core COVID-19 Task Force initiated an online survey on neurological symptoms observed in patients with COVID-19. All reported neurological disorders by in total 2343 responders were interpreted as being possibly related to COVID-19. The authors stated that the numbers provided by their survey represent relevant information for the European healthcare system to consider strengthening neurological services.<sup>[30]</sup> Timely neurological assessment of critically ill patients remains important in any case, especially during this COVID-19 pandemic, given the increased risk of neurological complications. A daily wakeup call is important to pursue because intra-arterial thrombectomy can be considered in selected cases of stroke in which the exact start of neurological symptoms is known or not exactly known.

COVID-19 could have substantially contributed to the development of neurological complications of the patients described here. The infection might not have been the direct cause of the neurological complication. However, it could have exacerbated the risk for neurological complications in these critically ill patients, especially

stroke. Patient 1 could have had significant carotid stenosis. However, this was not investigated by duplex ultrasound. So, it is unknown whether this led to the ischaemic stroke or whether it was due to the prothrombotic state in the COVID 19 infection. The infarctions in both hemispheres in patient 2 might also have been exacerbated by a prothrombotic state but could also be caused by the atrial septum defect which was found. In patient 3 no other cause of haemorrhagic stroke was found; COVID-19 may therefore play a major role. The parenchymal haemorrhage in patient 4 was possibly due to a combination of previous chronic hypertension and a higher blood pressure during admission, so COVID-19 might be a lower risk factor. Compared with the total COVID-19 cohort, it is not possible to differentiate based on risk factors between ICU patients with and without neurological complications.

Larger studies are needed to confirm clinical, radiological and laboratory characteristics of neurological complications in patients with COVID-19. Moreover, identifying patients at risk for neurological complications and how to control these risks should be elucidated as well, together with the underlying pathophysiological mechanisms. Given the hyperinflammatory state, it would be interesting to study whether the incidence of neurological complications has changed with standard use of dexamethasone in patients with COVID-19 during the second wave.

## Conclusion

COVID-19, caused by SARS-CoV-2, is associated with neurological manifestations especially in the hyperinflammatory phase. In our small cohort of COVID-19 ICU patients, we experienced a high number of strokes (4/59). COVID-19 itself could be a risk factor for neurological complications. Whether pre-existing risk factors, as present in our patients, contribute to this high number of strokes is suggested in other studies but needs further investigation. So, despite the fact that the underlying pathophysiology remains to be fully understood, physicians should be aware of neurological complications while treating critically ill patients with COVID-19 in ICU.

## Disclosures

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