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COVID-19: patients with stroke or risk of stroke

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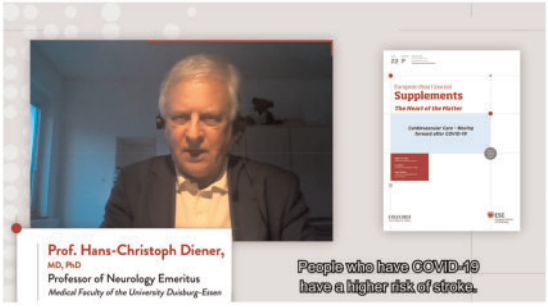
In the context of COVID-19 infection, 0.5–2% of affected patients will suffer a stroke. The strokes are usually severe with an unfavourable prognosis. Most patients suffer from occlusion of the large brain-supplying arteries caused by the COVID-19 induced coagulation disorders. In the context of COVID-19 infection, there has been a dramatic temporary decrease in the number of stroke patients treated in stroke units.



Video 1 (Video is clickable in the HTML version).

Introduction

In August 2020, COVID-19 had infected 17 million people worldwide, resulting in more than 700 000 deaths. The main manifestation of the viral disease is an atypical pneumonia. In addition, many other organ systems are affected, with 0.5–2% of patients suffering a stroke.[1]

Impact of the COVID-19 pandemic on stroke care

Shortly after the beginning of the pandemic, it was reported in many European countries as well as in the USA and Canada that the number of patients admitted to stroke units was declining dramatically.[2,3] The decrease was mainly in patients with transient ischaemic attack (TIA) and a mild stroke. Both the patients themselves and the doctors treating them often refused a referral to a hospital for fear of infection. However, patients with severe strokes continued to be admitted. A further problem was that in many hospitals, beds from the stroke unit were converted into ventilation beds for the treatment of COVID-19 patients. The decrease in the number of patients screened for thrombectomy in the USA with the RAPID software is impressive. RAPID identifies patients who, on magnetic resonance imaging (MRI) imaging have preserved penumbra and are candidates for mechanical thrombectomy. The use of the RAPID software decreased by more than 50% in April 2020 in the USA.[4] In the meantime, the situation has

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returned to normal and all stroke units in most countries are back in normal operation. In the current situation, it remains crucial that the acute treatment of severe stroke with thrombectomy is performed under appropriate protective measures due to the proximity to the patient and the danger of aerosol spread.

Impact of the COVID 19 pandemic on stroke research

During the COVID-19 pandemic, most of the ongoing studies on acute stroke therapy and secondary prevention had to be interrupted until the end of June 2020.[5] However, this hardly affected any registry studies. Most of the studies have since resumed recruitment. Patient follow-up is performed via telemedicine or phone calls.

Pathophysiology

COVID-19 infection leads to disorders of the coagulation system with an increased risk of thrombosis and embolism.[6] This could explain why most strokes that occur during COVID-19 infection are caused by occlusions of the large brain-supplying arteries.[7]

Lacunar infarctions occurred in a minority of patients. In individual cases, it is difficult to differentiate, whether the COVID-19 infection was the cause of the stroke or whether the stroke would have occurred independently of the infection.

Stroke as a complication of COVID-19 infection

Several studies have shown that the incidence of stroke in patients with COVID-19 infection ranges from 0.9% and 2.7%.[8] COVID-19 infection primarily leads to severe interstitial pneumonia. Some patients also develop neurological manifestations, including stroke. Most patients are severely affected, with a mortality rate of about 40%.[9,10] Regardless of the presence of infection, patients who arrive at the hospital within the appropriate time window were treated with systemic thrombolysis or mechanical thrombectomy.[8]

In 86 severely ill COVID-19 patients from China, 6 had a recent ischaemic stroke and 1 patient had a cerebral haemorrhage. A significantly higher prevalence of antiphospholipid antibodies was described in the seven brain-infarct patients (83.3 vs. 26.9%, $P < 0.05$).[11] In a cohort study including 187 patients at Montefiore Medical Center in the Bronx, New York, an increased incidence of Lupus Anticoagulans (LA) positivity was found in patients with COVID-19 after adjusting for C-reactive protein (CRP) levels. In addition, of the 30 patients who were LA positive, 19 had documented thrombosis (arterial and venous) including 2 strokes, an event rate of 63%, as compared with a rate for LA-negative patients of 34% ($P = 0.03$).[12]

A multicentre international registry (the Global Covid-19 Stroke Registry) performed a 1:1 propensity score matching analyses comparing stroke severity and outcomes in 174 patients with acute ischaemic stroke and COVID-19 with 336 non-COVID-19 ischaemic strokes registered in the Lausanne Registry. The median National Institute of Health Stroke Scale was higher in patients with COVID-19 (10) vs. 6 (IQR 3–14), $P = 0.03$; [odds ratio 1.69; 95% confidence interval (CI) 1.08–2.65]. Patients with COVID-19 had a higher risk for sever disability [median mRS 4 (IQR 2–6) vs. 2 (inter quantile range (IQR) 1–4), $P < 0.001$] and death (odds ratio 4.3, 95% CI 2.22–8.30) compared with patients without COVID-19.[13]

A working group from Spain presented its results on strokes in the context of the COVID 19 pandemic.[7] In March and April 2020, 1683 patients with COVID-19 infection were admitted to the hospital, 23 (1.4%) of whom had a stroke. Seventeen patients had cerebral ischaemia (73.9%), two of whom had arterial dissection. Five patients had an intracerebral haemorrhage (21.7%) and one patient had leukoencephalopathy of the posterior reversible constriction syndrome. Patients with haemorrhage included subarachnoidal haemorrhage, parieto-occipital leukoencephalopathy, multiple microbleeds, and focal haematomas. The prognosis was unfavourable in 74% of the stroke patients.

A working group from New York conducted a retrospective case–control study in six hospitals.[14] Among all patients admitted to the hospitals between 16 March and 5 April 2020, 126 patients presented with acute ischaemic stroke. The stroke patients were matched with patients without stroke in a ratio of 1:2 with regards to age, sex, and vascular risk factors. This matching resulted in 41 patients with stroke and 82 controls. The mean age of the cases and controls was 65.5 years and 68.8 years. Of the patients with acute ischaemic stroke, 46.3% had COVID-19 infection, compared to 18.3% of the controls ($P < 0.001$). After multivariate adjustment for age, sex and risk factors, patients with COVID-19 infection had a significant association with acute ischaemic stroke compared to controls (odds ratio 3.9, 95% CI 1.7–8.9; $P < 0.001$).

A study group from the National Hospital, Queen Square, UK, established a weekly multidisciplinary COVID-19 conference and collected detailed clinical and laboratory data from 43 patients with polymerase chain reaction (PCR)-confirmed or WHO criteria probable COVID-19 infection. Ischaemic strokes were found in eight patients, four of them with confirmed thrombocytopenia, one of whom died.

In a retrospective multicentre study from Italy, the imaging findings of 108 COVID-19 patients with neurological symptoms were analysed. 107 (99%) received a native CT, 17 (16%) a CT angiography (CTA) and 20 (18%) an MRI. Acute ischaemic infarctions were found in 34 (31%) patients [30 (28%) on CT and 4 (20%) on MRI]. There were 19 (18%) territorial infarctions (15 middle cerebral artery (MCA), 2 posterior cerebral artery (PCA), and 2 anterior cerebral artery (ACA), 11 (10%) were lacunar, 3 (3%) cardioembolic, and 1 (1%) patient showed a pattern of hypoxic–ischaemic encephalopathy. Three of the 6 (6%) intracranial bleedings were subarachnoid haemorrhages.[15]

Anticoagulation

COVID-19 infection leads to coagulation disorders in many patients, with the development of thrombosis and

embolism in both the arterial and venous circulation areas. This explains why COVID-19 patients are more prone to ischaemic strokes, systemic embolisms, deep vein thrombosis, and pulmonary embolism. If a causal relationship exists, anticoagulation should reduce the risk of these thrombo-embolic events and lead to a better prognosis.

A retrospective analysis from five hospitals in New York investigated the association of anticoagulation with mortality in patients with COVID 19.[16] Patients were enrolled between 1 March and 30 April 2020. The primary endpoint of the study was hospital mortality. Secondary endpoints were the need for intubation and serious bleeding complications.

A total of 4089 patients met the inclusion criteria for the registry. The median age was 65 years and 44% of the patients were female. A total of 900 patients received therapeutic anticoagulation, 1959 prophylactic anticoagulation, and 1530 patients did not receive anticoagulation. In total, 1073 patients (20.4%) died during the study.

- Of the patients who did not receive anticoagulation, 931 (60.8%) were discharged alive, 392 (25.6%) died in hospital, and 207 (13.5%) were still in the hospital.
- Of the patients who received prophylactic anticoagulation, 1472 (75.1%) were discharged alive, 424 (21.6%) died in hospital, and 63 (3.2%) were still hospitalized.
- In the group of patients receiving therapeutic anticoagulation, 89 patients (54.3%) were discharged alive, 257 (28.6%) died in hospital, and 154 (17.1%) were still in thes hospital.

Therapeutic anticoagulation resulted in a 47% reduction in in-hospital mortality (HR 0.53, 95% CI 0.45–0.6; $P < 0.001$). Patients who received prophylactic anticoagulation had a 50% reduction in mortality (HR 0.50, 95% CI interval 0.45–0.57; $P < 0.01$) compared to patients who did not receive anticoagulation. The rate of severe bleeding was 3% with therapeutic anticoagulation, 1.7% with prophylactic articulation, and 1.9% in the patient without anticoagulation. Only very few patients received unfractionated heparin.

In conclusion, in hospitalized patients with COVID-19 infection, both prophylactic and therapeutic anticoagulation are able to improve hospital mortality and prognosis.

Future directions

The exact pathophysiological relationships between COVID-19 are infection and the occurrence of stroke are not yet understood. It is also unknown whether treatment of COVID-19 patients with, for example, Remdesivir,[17–19] dexamethasone,[20] or methylprednisolone[21] reduces or anticoagulants[22] the risk of stroke.

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