Evidence check

27 May 2020

Rapid evidence checks are based on a simplified review method and may not be entirely exhaustive, but aim to provide a balanced assessment of what is already known about a specific problem or issue. This brief has not been peer-reviewed and should not be a substitute for individual clinical judgement, nor is it an endorsed position of NSW Health.

Large vessel occlusion strokes in COVID-19 patients

Rapid review question

1. Is there evidence of large vessel occlusion stroke in patients with COVID-19?
2. Are stroke patients with COVID-19 more likely to bleed post alteplase (tPA)?

In brief

Large vessel occlusion stroke in COVID-19

- Small series of stroke in COVID-19 patients have been reported:
    - A letter in the *New England Journal of Medicine* (NEJM) featured five COVID-19 positive cases of new-onset symptoms of large-vessel stroke in patients younger than 50 years of age, who presented to a New York health system over a two-week period.
    - A letter in the *British Medical Journal* (BMJ) describes six consecutive cases of acute ischaemic stroke and COVID-19, all of which had large-vessel occlusion (LVO).
    - An article published in *Brain, Behaviour and Immunity* identified four patients with acute stroke and COVID-19 in New York, including two with LVO.
- Other case series have reported acute ischaemic stroke in patients with COVID-19 suggesting neurological manifestation of COVID-19. In two of these cases, patients had severe COVID-19 infections.

Bleeding post alteplase

- A single case report of administration of intravenous rt-PA to an ischemic stroke COVID-19 positive patient has been published, with no bleeding reported.
- Other than this case report, there are no studies in stroke patients with COVID-19 looking at outcomes post alteplase treatment.
- Guidance for stroke patients with COVID-19 state that despite the concern of impaired recombinant tissue plasminogen activator (rt-PA) hepatic clearance, no data are available to suggest a greater risk or benefit with intravenous rt-PA.

Limitations

New evidence on this topic is emerging. The evidence is generally based on small case studies and may differ due to disparate stage and extent of the pandemic in different countries.

Background

Patients with COVID-19 may have an increased risk of stroke related to a systemic inflammatory and prothrombotic state.(1) Additionally, cerebrovascular disease was found to be associated with an approximately 2.5-fold increased disease severity in patients with COVID-19.(2)

Alteplase (tPA) for stroke patients with COVID-19

An international panel have released guidance on the management of ischemic stroke in patients with COVID-19. Current stroke guidelines do not recommend treatment with intravenous recombinant tissue plasminogen activator (rt-PA) in patients with acute ischemic stroke and infective endocarditis, because of the increased risk of intracranial haemorrhage. The guidelines recommend:

- That the relatively high prevalence of elevated concentration of inflammation and hypercoagulabilty markers, such as leukocytosis and C reactive protein and D dimers in patients with COVID-19 infection, should be recognised. While these aren't contraindications to intravenous rt-PA, previous studies in patients without COVID-19 infection demonstrated a higher rate of death or disability and post thrombolytic intracranial haemorrhage.
- A single case report of administration of intravenous rt-PA to an ischemic stroke COVID-19 positive patient has been published, with no bleeding reported.(3)
- Hepatic dysfunction without coagulopathy can occur in patients with COVID-19 infection.
    - Despite the concern of impaired rt-PA hepatic clearance, no data are available to suggest a greater risk or benefit with intravenous rt-PA.
    - Current guidelines specify certain eligibility thresholds based on PT, INR, APTT, or reduced platelet counts, although there is ambiguity regarding thresholds associated with greater risk or benefit with intravenous rt-PA.
    - For patients with COVID-19 and other organ involvement, a detailed assessment of coagulation profile should be conducted to determine risk benefit ratio is preferable prior to intravenous rt-PA administration.(4)

Methods (appendix 1)

PubMed and Google were searched on the 8 May 2020.

Results (Table 1 and 2)

Table 1: Stroke in COVID-19 positive patients

Source title and author	Findings	Source link
Large vessel occlusion in COVID-19		
Large-Vessel Stroke as a Presenting Feature of Covid-19 in the Young Oxley, et al. 2020 (5)	• Five cases of new-onset symptoms of large-vessel stroke in patients younger than 50 years of age presented to the health system in New York City over a two-week period in March-April. • Severe COVID-19 infection was diagnosed in all five patients. • Comparatively, this service treated on average 0.73 patients during the same time period over the previous 12 months.	Click here
Characteristics of ischaemic stroke associated with COVID-19 Beyrouti, et al. 2020 (6)	• All six patients had large vessel occlusion with markedly elevated D dimer levels (≥1000µg/L). Three patients had multi-territory infarcts, two had concurrent venous thrombosis, and two had schaemic strokes, despite therapeutic anticoagulation.	Click here
Triage of Acute Ischemic Stroke in Confirmed COVID-19: Large Vessel Occlusion Associated With Coronavirus Infection Moshayedi, et al. 2020 (7)	• A case report of a COVID-19-positive patient with a left middle cerebral artery syndrome. MRI showed evidence of hemorrhagic conversion in the left fronto-temporal territory. MR angiogram showed occlusion of the left middle cerebral artery proximal M1 segment. • The patient was not a candidate for thrombolysis as he had elevated activated partial thromboplastin time (PTT) on heparin.	Click here
COVID-19 Presenting as Stroke Avula, et al. 2020 (8)	• This study identified four patients presenting with imaging confirmed acute strokes and PCR confirmed SARS-CoV-2 infection. Two patients had large vessel occlusion including left and right middle cerebral arteries.	Click here
Coexistence of COVID-19 and acute ischemic stroke report of four cases (9)	• The report describes a small case series of simultaneously diagnosed COVID-19 and acute ischemic cerebrovascular event. Two of the four patients had large vessel stenosis with elevated D dimer and CRP. Both cases were treated with aspirin and low dose LMWH.	Click here

Table 1: Stroke in COVID-19 positive patients

Source title and author	Findings	Source link
Ischemic stroke in COVID-19		
Incidence of thrombotic complications in critically ill ICU patients with COVID-19 Klok, et al. 2020 (1)	• 184 patients with proven COVID-19 pneumonia and admitted to ICU of three Dutch hospitals. • Of these patients, 23 died (13%), 22 were discharged alive (12%) and 139 (76%) were still on the ICU on 5 April 2020. The median duration of observation per patient was seven days (IQR 1-13). The cumulative incidence of the composite outcome was 31% (95% CI: 20-41%), of which CTPA and/or ultrasonography confirmed venous thromboembolism (VTE) in 27% (95% CI: 17-37%) and arterial thrombotic events in 3.7% (95% CI: 0-8.2%). Acute pulmonary embolism (PE) was the most frequent thrombotic complication (*n* = 25, 81%). Age adjusted hazard ratio (aHR) of 1.05 per year, 95% CI: 1.004-1.01 and coagulopathy, defined as spontaneous prolongation of the prothrombin time >3s or activated partial thromboplastin time >5s (aHR 4.1, 95% CI: 1.9-9.1), were independent predictors of thrombotic complications. Three patients were identified to have arterial thrombosis resulting in ischemic stroke. • Authors concluded that the 31% incidence of thrombotic complications in ICU patients with COVID-19 infections is remarkably high**.**	Click here
Neurologic Manifestations of Hospitalized Patients with Coronavirus Disease 2019 in Wuhan, China Mao, et al. 2020 (10)	• In a study of 214 COVID-19 cases from Wuhan, China, 36.4% had neurological symptoms, which were more frequent in patients with severe disease. • Stroke occurred in six cases (2.8%), all but one case was seen in the severe infection group, most strokes were ischemic but one case of intracerebral hemorrhage occurred.	Click here
Venous and arterial thromboembolic complications in COVID-19 patients admitted to an academic hospital in Milan, Italy Lodigiani, et al. 2020 (11)	• Symptomatic patients with laboratory-proven COVID-19 admitted to a university hospital in Milan, Italy between 13 February and 10 April 2020. • Ischemic stroke was diagnosed in 9 (2.5%) patients, of which, 3 were on the ICU and 6 on the general ward. One patient developed both stroke and acute pulmonary embolism (PE). In 6 (67%) patients, stroke was the primary reason for hospitalisation. • Venous and arterial thromboembolic events occurred in 8% of hospitalised patients (cumulative rate 21%) and 50% of events were diagnosed within 24 hours of hospital admission.	Click here

Appendix

PubMed:

((2019-nCoV[title/abstract] or nCoV*[title/abstract] or covid-19[title/abstract] or covid19[title/abstract] OR "covid 19"[title/abstract] OR "coronavirus"[MeSH Terms] OR "coronavirus"[title/abstract] OR sars-cov-2[title/abstract] OR “severe acute respiratory syndrome coronavirus 2”[Supplementary Concept])) AND (stroke) AND (2019:2020[pdat])

Google: ‘COVID-19 and stroke and bleeding complications post thrombolysis’

References

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