

BRIEF REPORT

Treatment of Acute Ischemic Stroke due to Large Vessel Occlusion With COVID-19

Experience From Paris

Simon Escalard¹, MD*; Benjamin Maier, MD*; Hocine Redjem, MD; François Delvoe, MD; Solène Hébert, MD; Stanislas Smajda, MD; Gabriele Ciccio, MD; Jean-Philippe Desilles, MD, PhD; Mikael Mazighi, MD, PhD; Raphael Blanc, MD; Michel Piotin, MD, PhD

BACKGROUND AND PURPOSE: Higher rates of strokes have been observed in patients with coronavirus disease 2019 (COVID-19), but data regarding the outcomes of COVID-19 patients suffering from acute ischemic stroke due to large vessel occlusion (LVO) are lacking. We report our initial experience in the treatment of acute ischemic stroke with LVO in patients with COVID-19.

METHODS: All consecutive patients with COVID-19 with acute ischemic stroke due to LVO treated in our institution during the 6 first weeks of the COVID-19 outbreak were included. Baseline clinical and radiological findings, treatment, and short-term outcomes are reported.

RESULTS: We identified 10 patients with confirmed COVID-19 treated for an acute ischemic stroke due to LVO. Eight were men, with a median age of 59.5 years. Seven had none or mild symptoms of COVID-19 at stroke onset. Median time from COVID-19 symptoms to stroke onset was 6 days. All patients had brain imaging within 3 hours from symptoms onset. Five patients had multi-territory LVO. Five received intravenous alteplase. All patients had mechanical thrombectomy. Nine patients achieved successful recanalization (mTICI2B-3), none experienced early neurological improvement, 4 had early cerebral reocclusion, and a total of 6 patients (60%) died in the hospital.

CONCLUSIONS: Best medical care including early intravenous thrombolysis, and successful and prompt recanalization achieved with mechanical thrombectomy, resulted in poor outcomes in patients with COVID-19. Although our results require further confirmation, a different pharmacological approach (antiplatelet or other) should be investigated to take in account inflammatory and coagulation disorders associated with COVID-19.

Key Words: coagulation disorder ■ COVID-19 ■ outbreak ■ stroke ■ thrombectomy

Higher rates of strokes have been observed in patients with coronavirus disease 2019 (COVID-19),¹ and large-vessel stroke has been reported as a presenting feature of COVID-19 in the young.² Here, we describe our initial experience in the treatment of patients with COVID-19 presenting with acute ischemic stroke (AIS) due to large vessel occlusion (LVO) during the first 6 weeks of the COVID-19 outbreak in Paris, France.

METHODS

According to the Transparency and Openness Promotion Guidelines, the authors declare that the data which support the findings of this study are available from the corresponding author upon reasonable request.

All consecutive patients with COVID-19 with AIS due to LVO treated in our institution during the 6 first weeks of the COVID-19 outbreak, between March 1st and April 15th, 2020, were included. All patients had RT-PCR confirmed COVID-19.

Correspondence to: Simon Escalard, MD, Interventional Neuroradiology Department, Rothschild Foundation Hospital, 25 rue Manin 75019 Paris, France. Email sescalard@for.paris

*Drs Escalard and Maier contributed equally.

For Sources of Funding and Disclosures, see page XXX.

© 2020 American Heart Association, Inc.

Stroke is available at www.ahajournals.org/journal/str

Nonstandard Abbreviations and Acronyms

AIS	acute ischemic stroke
COVID-19	coronavirus 2019
LVO	large vessel occlusion
MT	mechanical thrombectomy

Patients could have a Chest computed tomography at admission to provide early screening before mechanical thrombectomy (MT). Baseline clinical and radiological findings, treatment, and short-term outcomes were prospectively gathered. Our local ethics committee approved the use of patient data for this research protocol. In accordance with French legislation, informed consent was not needed from patients because this study analyzed anonymized data collected prospectively as a part of routine clinical care.

RESULTS

Among 37 patients treated for an AIS with LVO in our institution between March 1st and April 15th, 2020, 10 patients with confirmed COVID-19 were included. All data regarding clinical and radiological features and medical management are reported in the Table. The median age of patients with COVID-19 with AIS and LVO was 59.5 years, 8 patients were men.

Two patients were asymptomatic, and 5 had mild symptoms of COVID-19 before stroke onset. All patients with chest computed tomography at admission (80%) had radiological findings consistent with a COVID-19 infection. Median time from COVID-19 symptoms onset to stroke onset was 6 days (range 2–18 days). Three patients had a stroke during hospitalization for COVID-19.

Eight patients (80%) had at least one risk factor for stroke. Two patients were younger than 50 years old and had no known risk factor for stroke. The median National Institutes of Health Stroke Scale at admission was 22. AIS diagnosis imaging was performed within 3 hours from stroke onset for all patients. Five patients (50%) had multi-territory LVO at baseline (with proximal middle cerebral artery occlusion and either anterior cerebral artery or posterior cerebral artery occlusion), with a median admission Alberta Stroke Program Early Computed Tomography Score of 5.

Five patients (50%) were treated with intravenous thrombolysis, within a median time of 175 minutes.

All 10 patients were treated with MT, all procedures were started within 6 hours from stroke onset. Overall, 9 patients (90%) had successful recanalization defined by a modified Thrombolysis in Cerebral Infarction score $\geq 2B$, with a median time from stroke-onset to recanalization of 302 minutes. None of our patients achieved

complete recanalization after one pass (ie, first-pass effect), with a median number of 3.5 passes per patient.

Overall, 4 patients had early intracranial proximal artery reocclusion within 24 hours. Altogether, 6 patients (60%) died during hospitalization. Despite high angiographic recanalization rates and timeframes, none of our patients had dramatic neurological improvement 24 hours after MT. No patient experienced symptomatic intracranial hemorrhage at 24 hours.

DISCUSSION

Our series highlights new important insights into patients with COVID-19 who suffer from AIS due to an LVO. First, most of them (70%) had mild or no respiratory signs at the time of stroke, which could suggest the absence of correlation between the severity of respiratory symptoms and the risk of AIS with LVO. Second, all patients for whom a Chest computed tomography was performed (80%) at the time of admission had radiological features consistent with a COVID-19 infection, suggesting that Chest computed tomography could be relevant for early screening of COVID-19 in patients with AIS. Half of them presented with multiple LVO on initial imaging, which is much higher than what is usually observed in patients with LVO,³ and could be explained by the coagulation and microcirculation disorders described in patients with COVID-19.^{4,5}

More important, our series shows the devastating prognosis of patients with COVID-19 with AIS due to LVO and is in line with a recent publication displaying COVID-19 cardiovascular impact.⁴ Indeed, although successful recanalization rates reached 90%, which seems in line with everyday practice,^{6,7} MT procedures were more complex with 50% multi-territory LVO, no first-pass effect and 4 patients with early reocclusions, altogether resulting in high in-hospital mortality rates (60%) and no clinical improvement among survivors. Of note, 4 of our patients had prestroke anticoagulation (1 patient under oral anticoagulant combined with dual antiplatelet therapy for recent acute coronary syndrome, 3 patients were treated with therapeutic dose of heparin in hospital for COVID-19), which did not prevent the occurrence of an AIS with LVO in the particular setting of COVID-19. Recent works have shed light on the endothelial cell and neutrophil extracellular traps involvement of COVID-19,^{8,9} suggesting that our patients have been recanalized without successful reperfusion, possibly due to microvascular thromboinflammation damages or endotheliitis.⁹ In addition, reocclusions might be promoted by a procoagulant state, an association that has already been described with infections.^{10,11} In the COVID-19 setting, a recent study highlighted this finding with venous and arterial thromboembolic complications.¹²

Table. Characteristics of Patients With and Without COVID-19 and Acute Ischemic Stroke due to Large Vessel Occlusion*

Characteristics	Total (n=37)	COVID-19 (n=10)	Non COVID-19 (n=27)
Median age (IQR), y	70 (57–79)	59.5 (54–71.5)	72 (60–81.5)
Male sex, no. (%)	21 (57)	8 (80)	13 (48)
Median baseline mRS (IQR)	0 (0–1)	1 (0–1)	0 (0–1)
Risk factor			
Hypertension, no. (%)	20 (54)	5 (50)	15 (55)
Diabetes melitus, no. (%)	10 (27)	4 (40)	6 (22)
Hypercholesterolemia, no. (%)	13 (35)	3 (30)	10 (37)
Smoking, no. (%)	8 (22)	1 (10)	7 (26)
Atrial fibrillation, no. (%)	9 (24)	1 (10)	8 (30)
Prestroke anticoagulation, no. (%)	8 (22)	4 (40)	5 (18)
Symptoms of COVID-19 and chest computed tomography around the time of stroke			
Fever, no. (%)	5 (13)	5 (50)	0
Cough, shortness of breath, respiratory distress, no. (%)	9 (24)	7 (70)	2 (7)
No or mild symptoms / no oxygen requirement, no. (%)	32 (86)	7 (70)	25 (93)
Dyspnea with saturation <94% on room air, no. (%)	5 (13)	3 (30)	2 (7)†
Anosmia, no. (%)	0	0	0
No symptom, no. (%)	27 (73)	2 (20)	25 (93)
Time from COVID-19 symptoms onset (range), d	...	6 (2–18)	...
Chest computed tomography		8 (80)	2 (7)†
Opacities consistent with a COVID-19 infection		8 (100)	0
Stroke characteristics			
Median NIHSS (IQR)	18 (13–22)	22 (19–25.7)	16 (12.5–19.5)
Diagnosis imaging			
MRI, no. (%)	29 (78)	8 (80)	21 (78)
Computed tomography, no. (%)	8 (22)	2 (20)	6 (22)
Median ASPECT score (IQR)	7 (5–8.5)	5 (3–7)	7 (6–8.75)
Occlusion site			
Carotid terminus, no. (%)	9 (24)	3 (30)	6 (22)
M1, no. (%)	15 (40)	6 (60)	9 (33)
M2, no. (%)	11 (30)	0	11 (41)
Basilar, no. (%)	2 (5)	1 (10)	1 (4)
Multiterritory LVO, no. (%)	7 (19)	5 (50)	2 (7)
Median Clot Burden Score (IQR)	7 (5–9)	6 (5–7)	7 (5–9)
Median time from onset to imaging (IQR), min	152 (115–216)	119 (104–143)	177 (128–228)
Intravenous thrombolysis, no. (%)	18 (49)	5 (50)	14 (52)
Median time from onset to IV-thrombolysis (IQR), min	175 (137–192)	175 (160–185)	175 (120–195)
Mechanical thrombectomy			
Median time from onset to arterial puncture (IQR), min	321 (258–399)	251 (220–303)	334 (278–450)
Median time from onset to recanalization (IQR), min	340 (294–430)	302 (277–340)	392 (309–438)
Median number of passes (IQR)	2 (1–4)	3.5 (3–4.75)	3 (1–4)
First pass effect, no. (%)	9 (24)	0	9 (33)
Successful recanalization, no. (%)	32 (86)	9 (90)	23 (85)
Follow-up and outcome			
Median 24 h NIHSS (IQR)	18 (8–22)	25 (19.75–42)	15 (5–20)
Dramatic early neurological improvement, no. (%)	6 (16)	0	6 (22)
In-hospital all-cause mortality, no. (%)	9 (24)	6 (60)	3 (11)
Sepsis associated mortality, no. (%)	2 (5)	2 (20)	0
Malignant brain edema associated mortality, no. (%)	4 (11)	2 (20)	2 (7)
Acute respiratory failure associated mortality, no. (%)	2 (5)	2 (20)	0
Early cerebral re-occlusion, no. (%)	4 (11)	4 (40)	0
Symptomatic intracranial hemorrhage, no. (%)	1 (3)	0	1 (4)

Successful recanalization was defined by a TICI (Thrombolysis in Cerebral Infarction) score of 2B–3, first pass effect was defined as a successful recanalization achieved after one pass, dramatic early improvement was defined as an improvement of ≥ 8 NIHSS points, symptomatic intracranial hemorrhage was defined as intracranial hemorrhage associated with an increase by ≥ 4 points on the NIHSS. ASPECT indicates Alberta Stroke Program Early Computed Tomography; COVID-19, coronavirus disease 2019; IQR, interquartile range; LVO, large vessel occlusion; MRI, magnetic resonance imaging; mRS, modified Rankin Scale; and NIHSS, National Institutes of Health Stroke Scale.

*Percentages may not total 100 because of rounding.

†Two non COVID-19 patients had acute pulmonary edema resulting in dyspnea.

Our study does not support the fact that COVID-19 was primarily responsible for AIS with LVO as most of our patients had at least one known risk factor for stroke and no proper etiological investigations could be performed (mostly due to rapid clinical deterioration leading to death). Nevertheless, further studies are urgently needed to assess the potential role of microthrombotic disorders in the occurrence of strokes and the relevance in this setting of a combined approach with a mechanical (MT) and medical treatment (ie, antiplatelet therapy or neutrophil extracellular traps targeting therapy), to limit neurological disabilities for COVID-19 survivors.

ARTICLE INFORMATION

Affiliations

From the Interventional Neuroradiology Department, Rothschild Foundation Hospital, Paris, France.

Sources of Funding

None.

Disclosures

Dr Mazighi reports personal fees from acticor Biotech, personal fees from boeinger, personal fees from air liquide, and personal fees from amgen outside the submitted work.

REFERENCES

- Mao L, Jin H, Wang M, Hu Y, Chen S, He Q, Chang J, Hong C, Zhou Y, Wang D, et al. Neurologic manifestations of hospitalized patients with coronavirus disease 2019 in Wuhan, China [published online April 10, 2020]. *JAMA Neurol*. 2020. doi: 10.1001/jamaneurol.2020.1127
- Oxley TJ, Mocco J, Majidi S, Kellner CP, Shoirah H, Singh IP, De Leacy RA, Shigematsu T, Ladner TR, Yaeger KA, et al. Large-vessel stroke as a presenting feature of Covid-19 in the young. *N Engl J Med*. 2020;382:e60. doi: 10.1056/NEJMc2009787
- Kaesmacher J, Mosimann FJ, Giarrusso M, El-Koussy M, Zibold F, Piechowiak E, Dobrocky T, Meier R, Jung S, Bellwald S, et al. Multivessel occlusion in patients subjected to thrombectomy: prevalence, associated factors, and clinical implications. *Stroke*. 2018;49:1355–1362. doi: 10.1161/STROKEAHA.118.021276
- Bangalore S, Sharma A, Slotwiner A, Yatskar L, Harari R, Shah B, Ibrahim H, Friedman GH, Thompson C, Alviar CL, et al. St-segment elevation in patients with covid-19 - a case series [published online April 17, 2020]. *N Engl J Med*. 2020. doi: 10.1056/NEJMc2009020
- Zhang Y, Xiao M, Zhang S, Xia P, Cao W, Jiang W, Chen H, Ding X, Zhao H, Zhang H, et al. Coagulopathy and antiphospholipid antibodies in patients with Covid-19. *N Engl J Med*. 2020;382:e38. doi: 10.1056/NEJMc2007575
- Goyal M, Menon BK, van Zwam WH, Dippel DW, Mitchell PJ, Demchuk AM, Dávalos A, Majoie CBLM, van der Lugt A, de Miquel MA, et al; HERMES Collaborators. Endovascular thrombectomy after large-vessel ischaemic stroke: a meta-analysis of individual patient data from five randomised trials. *Lancet*. 2016;387:1723–1731. doi: 10.1016/S0140-6736(16)00163-X
- Lapergue B, Blanc R, Gory B, Labreuche J, Duhamel A, Marnat G, Saleme S, Costalat V, Bracard S, Desal H, et al; ASTER Trial Investigators. Effect of endovascular contact aspiration vs stent retriever on revascularization in patients with acute ischemic stroke and large vessel occlusion: the ASTER Randomized Clinical Trial. *JAMA*. 2017;318:443–452. doi: 10.1001/jama.2017.9644
- Barnes BJ, Adrover JM, Baxter-Stoltzfus A, Borczuk A, Cools-Lartigue J, Crawford JM, Daßler-Plenker J, Guerci P, Huynh C, Knight JS, et al. Targeting potential drivers of covid-19: neutrophil extracellular traps. *J Exp Med*. 2020;217:e20200652. doi: 10.1084/jem.20200652
- Varga Z, Flammer AJ, Steiger P, Haberecker M, Andermatt R, Zinkernagel AS, Mehra MR, Schuepbach RA, Ruschitzka F, Moch H, et al. Endothelial cell infection and endotheliitis in covid-19. *Lancet*. 2020;395:1417–1418. doi: 10.1016/S0140-6736(20)30937-5 Published online April 17, 2020
- Paganini-Hill A, Lozano E, Fischberg G, Perez Barreto M, Rajamani K, Ameriso SF, Heseltine PNR, Fisher M. Infection and risk of ischemic stroke: differences among stroke subtypes. *Stroke*. 2003;34:452–457. doi: 10.1161/01.str.0000053451.28410.98
- Subramaniam S, Scharrer I. Procoagulant activity during viral infections. *Front Biosci (Landmark Ed)*. 2018;23:1060–1081. doi: 10.2741/4633
- Lodigiani C, Iapichino G, Carenzo L, Cecconi M, Ferrazzi P, Sebastian T, Kucher N, Studt JD, Clara Sacco C, Alexia B, et al; Humanitas COVID-19 Task Force. Venous and arterial thromboembolic complications in COVID-19 patients admitted to an academic hospital in Milan, Italy. *Thromb Res*. 2020;191:9–14. doi: 10.1016/j.thromres.2020.04.024