

## COVID-19 流行と脳卒中

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要旨：新型コロナウイルス感染症 (corona virus disease 2019, 以下 COVID-19 と略記) の流行により、脳卒中診療は大きく変貌しており、受診数減少、受診遅延、recombinant tissue plasminogen activator 静注療法や機械的血栓回収療法の施行数減少などが報告されている。既報告では COVID-19 患者の 1.1 (0.4~8.6) %程度に脳卒中が合併している。特徴は、虚血性脳卒中、特に潜因性脳梗塞や大血管病変合併例が多く、D-ダイマー高値例が多く、心血管危険因子を持つ患者での発症が多く、転帰不良例が多いことなどである。また本疾患では動脈血栓塞栓症より静脈血栓塞栓症が多く、急性冠症候群より脳卒中発症が多い。安全で有効かつ迅速な治療を完全な感染対策下で行う protected code stroke が提案されている。

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Key words : COVID-19, 脳卒中, 大血管閉塞, 潜因性脳梗塞, protected code stroke

### 1. はじめに

脳卒中、特に脳梗塞は recombinant tissue plasminogen activator (rt-PA) 静注療法による血栓溶解療法 (intravenous thrombolysis, 以下 IVT と略記) や機械的血栓回収療法 (mechanical thrombectomy, 以下 MT と略記) の登場により、治療可能な時代となってきた。これらの治療を多くの脳梗塞患者に提供するためには、専門性と時間との戦いの両立が必要であり、救急搬送段階から code stroke 発令の下で脳卒中診療が開始されるような地域や院内のシステム構築が、全世界で行われ始めている。

2020 年になると新型コロナウイルス感染症 (corona virus disease 2019, 以下 COVID-19 と略記) が流行し、患者増加につれて呼吸器感染症の範疇にとどまらず、様々な病態を引き起こすことが報告され、COVID-19 患者に発症する脳卒中、特に脳梗塞も注目されるようになった。COVID-19 は、脳卒中診療体制にも大きな影響をあたえ、医療従事者の感染防御を考慮した protected code stroke (PCS) の提案がなされるなど、COVID-19 流行下の脳卒中診療のあり方も変わりつつある<sup>1)</sup>。

ここでは、各国からの報告をもとに、COVID-19 患者の脳卒中の特徴、COVID-19 流行下の脳卒中診療体制の変化、わが国における今後の課題についてまとめた。

### 2. COVID-19

2019 年 12 月に中国武漢で原因不明の肺炎患者が報告され、2020 年 1 月にはその原因が新種のコロナウイルスであることが確認された。1 月 9 日には最初の死者が報告され、同症が生命をも脅かす疾病であることが伝えられた。同症は中国から世界へ拡大、1 月 16 日に日本でも初の感染者が確認された。2 月 1 日「新型コロナウイルス感染症を指定感染症として定める等の政令」が施行され、「新型コロナウイルス感染症」と定められた。2 月 11 日には、International Committee on Taxonomy of Viruses (ICTV) がこのウイルスを severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) と分類、命名した。WHO がその感染による疾患を COVID-19 と命名した。3 月 11 日には、ついに WHO が世界各地での流行についてパンデミック相当との見解を示した。

### 3. 初期の COVID-19 の報告

2020 年 1 月の武漢 Chen らの報告では、99 例の COVID-19 患者の重症肺炎という特徴を中心に述べられ、神経症候や脳卒中の記載はほとんどなかった<sup>2)</sup>。同時期の武漢 Wang らの 138 例の報告、中国全土の情報をまとめた Guan らの 1,099 例の報告でも、主に呼吸器症状に言及しており、血栓症や脳卒中の記述はなかった<sup>3)4)</sup>。

3 月には韓国の Kang らが 70 歳以上、心筋梗塞 (myocardial

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infarction, 以下 MI と略記) や脳梗塞の既往, 不整脈, 高血圧などの基礎疾患がある患者の死亡率が高いことを報告し, Aggarwal らは脳卒中の既往があると COVID-19 が 2.55 倍重症化しやすいことを示した<sup>56)</sup>. Qin らも同様に脳卒中の既往があると COVID-19 患者は, 急性呼吸窮迫症候群になりやすく, 退院率が低く, 死亡率が高いことを示した<sup>7)</sup>.

#### 4. 初期の脳卒中の報告

Mao らは武漢で COVID-19 患者 214 例中 78 例 (36.4%) が神経症候を呈し, 6 例 (2.8%) が脳卒中を発症, 重症例では 88 例中 5 例 (5.7%) が脳卒中を発症したと報告した<sup>8)</sup>. Li らによる同施設の報告では, 5.8% で脳卒中が発症し, 高齢者, 重症例に多い傾向にあり, 高血圧, 糖尿病, 脳卒中既往を有する例に多く, 死亡率は 38% と報告された (のちに脳卒中発症率 4.6%, 死亡率 55% に修正)<sup>9)</sup>. Zhou らは, COVID-19 発症から 2 週間頃に虚血性脳卒中発症が多いとしている<sup>10)</sup>.

オランダの Klok らは, ICU 治療患者 184 例の血栓性合併症発生率が 31% で, 静脈血栓塞栓症が多いものの, 脳梗塞 5 例 (2.7%) を含む動脈系にも生じることを示した<sup>11)</sup>.

フランスの Helms らは, ICU 治療患者の 84% に神経合併症が見られ, MRI を施行した 13 例中 3 例で無症候性脳梗塞が見られたと報告した<sup>12)</sup>.

イタリアの Lodigiani らは, 血栓塞栓性合併症は低分子ヘパリンによる予防にも関わらず 7.7% に見られ, 静脈系に多く, 動脈系では MI より脳梗塞が多いことを示した<sup>13)</sup>.

#### 5. COVID-19 患者に発症する脳卒中の特徴

世界各国が都市のロックダウンを実行し, 日本も緊急事態宣言下だった 4 月下旬, ニューヨークで「COVID-19 患者で脳卒中, しかも若年の脳卒中が多い」と報道され, 論文でも報告された. パンデミック期の 2 週間に, 50 歳未満の large vessel occlusion (LVO) 患者 5 例が入院し, 全員 SARS-CoV-2 陽性だった. 非パンデミック期の 50 歳未満の LVO 患者は 2 週間平均 0.73 例で, パンデミック期はその約 7 倍と強調していた<sup>14)</sup>.

このころになると, 各国から COVID-19 患者に発症した脳卒中の症例報告が続くことになる. Table 1 に 42 報告 102 例を公開された順に, 国や地域, 都市とともにその特徴を示す<sup>14)~55)</sup>. この 102 例のうち, 虚血性脳卒中が 90 例 (男 63 例, 女 26 例, 性別不明 1 例, 平均 61.4 歳) と大半を占めており, 脳内出血が 6 例, 脳静脈血栓症が 3 例, くも膜下出血, 網膜中心動脈閉塞症, posterior reversible encephalopathy syndrome (PRES) が 1 例ずつだった.

なお, COVID-19 の診断は, 102 例中 96 例では, SARS-CoV-2 RT-PCR (reverse transcription-polymerase chain reaction) で, 3 例では胸部 CT で行われていた. また, 虚血性脳卒中 90 例の脳画像診断は, 67 例では CT で行われており, 23 例では MRI も施行されていた.

#### 5-1. 年齢と背景因子

全 102 例のうち年齢が明示してある 82 例で, 50 歳未満は 12 例 (14.6%), 50 歳以上が 70 例 (85.4%) となっていた. 通常期, 全脳卒中患者のうち若年成人が占める割合は 10~15% とされ, 報告された COVID-19 関連脳卒中患者が極端に若いとは言いがたかった<sup>56)</sup>.

Annie らは, 多国籍データベースを用いて, 50 歳以下の COVID-19 患者 9,358 例を解析した<sup>57)</sup>. 33.2% は COVID-19 重症で入院した. 虚血性脳卒中は 64 例 (0.7%) で発症し, 男女差はなかった. 発症例では, 高血圧, 糖尿病, 心不全, ニコチン依存, 肥満, 慢性閉塞性肺疾患, 脳卒中の既往歴, 腎不全が有意に多く, 死亡率は 15.6% で, 非発症例の 0.6% より有意に高かった. 若年でも脳卒中を発症すると COVID-19 の転帰不良となる可能性はある.

#### 5-2. 大血管病変と超急性期治療

Table 1 の 102 例中 90 例が虚血性脳卒中だったが, そのうち 72 例と大半を LVO が占めていた<sup>14)16)~19)21)~38)40)~42)47)50)~55)</sup>. 転帰の記載がある LVO 患者 58 例中 18 例 (31%) が死亡, 33 例 (57%) が転帰不良 (mRS: 4~5), 7 例 (12%) が転帰良好 (mRS: 0~3) だった<sup>14)16)~19)21)~26)28)31)~33)35)~37)40)~43)47)52)~55)</sup>. なお, 転帰良好 7 例中 1 例は IVT, 2 例は MT, 3 例は IVT と MT 併用で治療されていた. また, 全体でも, IVT は 8 例, MT は 9 例, 併用例が 3 例報告されているが, LVO の患者が多くを占めていることを考慮すると, 施行率は必ずしも高くない. 受診の遅延などもあり, IVT や MT に至らない例も少なくない可能性がある.

なお, Kihira らは, COVID-19 患者を含む虚血性脳卒中患者 329 例で検討し, COVID-19 患者であることは, LVO を来す独立した危険因子であると示している (odds ratio, 2.4; 95% CI, 2.1~2.7;  $P = 0.011$ )<sup>58)</sup>. ただ, 2003 年に Paganini-Hill らは, 1 週間以内に呼吸器感染症の病歴がある虚血性脳卒中患者は, 病歴がない患者よりも LVO の割合が多いことを示しており, COVID-19 に LVO が多いことの特異性についてはさらに検討を要す<sup>59)</sup>.

Escalard らによると 10 例の LVO 患者 (中央値 59.5 歳) 中 5 例が MT 単独, 5 例が IVT と MT の併用治療を受け, 9 例に再灌流 (TICI 2B-3) を得たものの, 6 例 (60%) が死亡しており, COVID-19 に発症した LVO では再灌流療法を施行し得た場合でも転帰不良となる可能性もある<sup>60)</sup>.

Liang らは悪性脳浮腫 (malignant cerebral edema) を来した若年患者 3 例に早期減圧開頭術を施行し, 2 例を救命しており, 「COVID-19 患者ということで, 救命処置の可能性のある患者を除外するべきではない」と述べている<sup>61)</sup>.

#### 5-3. 脳卒中の発症時期

Table 1 に示すように, COVID-19 診断のタイミングの記載がある 100 例中 34 例は COVID-19 診断後の入院中に脳卒中を発症しており, 残りの 66 例は脳卒中発症をきっかけに病院を受診した後に COVID-19 と診断されている<sup>14)~50)52)~55)</sup>.

Table 1 Case reports of strokes in patients with corona virus disease 2019 (COVID-19).

No.	Epub Date	Author	City, Country/Region	Number of cases	Age/Gender	Method for COVID-19 definitive diagnosis	COVID-19 Severity	Intubation/ICU management	Brain imaging for diagnosis	Stroke Subtype	Reperfusion therapy (IVT/MT)	COVID-19 diagnostic timing	serum D-dimer level (reference range, unit)	Outcome	Characteristic
1	2020/3/27	Sharif-Razavi A <sup>15)</sup>	Sari, Iran	1	79M	PCR+	Mild	NR	CT	ICH	NP	S → C	NR	NR	ICH with no anticoagulation
2	2020/3/31	Zhao J <sup>16)</sup>	South of China	1	60M	NR	Mild	NR	MRI	LVO	NP	S → C	NR	Severe	Right LVO, MT indication, Pandemic did not allow MT.
3	2020/4/21	Moshayedi P <sup>17)</sup>	Los Angeles, CA, United States	1	80sM	PCR+	Severe	Intubation - ICU +	CT+MRI	LVO	NP	C → S	NR	Death	Stroke developed during hospitalization for MI MCA(MI) occlusion
4	2020/4/22	Zhou B <sup>18)</sup>	Xian, China	1	75F	PCR+	Severe	Intubation - ICU +	CT	LVO	NP	C → S	0.83 (0-1.5 µg/ml)	Poor	Brain infarcts in right ACA, MCA, left ACA distribution Subsequently developed VTE
5	2020/4/28	Avula A <sup>19)</sup>	New York, NY, United States	4	73M, 83F, 80F, 88F	PCR+	Severe: 3 Mild: 1	Intubation +; 3/4 ICU NR	CT: 1 CT+CTA: 2 CT+MRI: 1	LVO: 4	NP	S → C: 4	13,966 3,442 (0-230 ng/ml)	Death: 3 Poor: 1	All cases are elderly patients and LVO.
6	2020/4/28	Oxley TJ <sup>16)</sup>	New York, NY, United States	5	33F, 37M, 39M, 44M, 49M	PCR+	Mild: 5	Intubation NR ICU +; 1/5	CT+CTA+CTP+MRI: 2 CT+CTA+MRI: 2 CT+CTA+CTP: 1	LVO: 5	IVT+MT: 1 MT: 3	S → C: 5	460 52 2,230 13,800 1,750 (0-500 ng/ml)	Poor: 4 Good: 1	2020.3.23-2020.4.7 (2 weeks): 5LVOs <50 years of age were hospitalized Average for the past year: 0.73LVOs hospitalized in 2 weeks
7	2020/4/29	Hughes C <sup>20)</sup>	Bangor, Wales, United Kingdom	1	59M	PCR+	Mild	Intubation - ICU -	CT+CT venogram	CVT	NP	S → C	NR	Good	Stroke developed 4 days after the onset of respiratory symptoms Improved with anticoagulant therapy
8	2020/4/30	Beyrouth R <sup>21)</sup>	London, United Kingdom	6	64M, 53F, 85M, 61M, 83M, 73M	PCR+	Severe: 5 Mild: 1	Intubation NR ICU + 2/6	CT: 2 MRI: 3 CT+CTA: 1	LVO: 6	IVT: 2	C → S: 5 S → C: 1	>80,000 7,750 16,100 27,190 19,450 1,080 (<1,000 µg/l)	Death: 1 NR: 5	Lapus anticoagulant was positive in 5/6 patients.
9	2020/4/30	Al-Saiegh F <sup>22)</sup>	Philadelphia, PA, United States	2	31M 62F	PCR+	Mild	Intubation +; 2 ICU NR	CT: 1 CT+CTA: 1	SAH LVO	NP	S → C: 2	NR	Poor: 2	Patient with SAH underwent placement of an EVD Patient with LVO underwent a decompressive hemicraniectomy Negative for SARS-CoV-2 in CSF even positive with nasal swab
10	2020/4/30	González-Fruto I <sup>23)</sup>	Cruces, Bilbao, Spain	1	36F	PCR+	Mild	Intubation - ICU -	CT+CTA	LVO	NP	S → C	7,540 (ng/ml)	Death	A free-floating thrombus in the ascending aorta with no signs of aortic atheromatosis revealed with CTA
11	2020/5/4	Viguier A <sup>16)</sup>	Toulouse, France	1	73M	PCR+	Mild	Intubation - ICU -	CT+CTA+CTP	LVO	NP	S → C	2,220 (ng/ml)	Good	Large intraluminal floating thrombus was revealed with CTA. It has disappeared with anticoagulant therapy. Antiphospholipid antibodies were negative.
12	2020/5/6	Tunç A <sup>23)</sup>	Sakarya, Turkey	4	45F, 67F, 72M, 77M	PCR+	Mild: 4	Intubation - ICU -	CT+MRI: 4	LVO: 2 SVO: 2	NP	S → C: 4	803 1,040 644 378 (0-500 µgFEU/l)	Poor: 2 Good: 2	One patient had DM at the age of 45 and developed LVO. 3 patients were 67-77 years of age, relatively older.
13	2020/5/8	Sahabuddin H <sup>23)</sup>	Toledo, OH, United States	1	75M	Thorax CT findings	Severe	Intubation - ICU -	CT+CTA+CTP	LVO	NP	S → C	NR	Death	The patient was diagnosed with COVID-19 after stroke diagnosis, required intubation and died from respiratory failure within 2 days.

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14	2020/5/11	Co COC <sup>(27)</sup>	Manila, Philippines	1	62F	PCR+	Mild	Intubation - ICU -	CT+CTA	LVO	IVT	S → C	1.160 (0-246 ng/ml)	NR (still In hospital)	The patient developed stroke during hospitalization for mild COVID-19. First reported IVT in a patient with COVID-19 (according to the author).
15	2020/5/12	Valderrama EY <sup>(28)</sup>	New York, NY, United States	1	52M	PCR+	Mild	Intubation - ICU -	CT+CTA+CTP	LVO	IVT+MT	S → C	>10,000 (ng/ml)	Good	Stroke developed 7 days after the onset of respiratory symptoms. The patient with left MCA occlusion was treated with IVT and transferred to CSC. Reperfusion was achieved with MT.
16	2020/5/14	Goldberg MP <sup>(29)</sup>	Baltimore, MD, United States	1	64M	PCR+	Severe	Intubation + ICU +	CT+CTA	LVO	NP	S → C	Increased (no numerical description)	NR	The first case of COVID-19-related brain infarcts that includes brain imaging at multiple time points and CTA (according to the author).
17	2020/5/19	Gill I <sup>(30)</sup>	Queens, NY, United States	1	79F	PCR+	Mild	Intubation - ICU -	CT+CTA+CTP	LVO	MT	S → C	8.24 (units)	NR (still In hospital)	Reperfusion was achieved with MT. Pulmonary embolism also developed and treated with anticoagulation.
18	2020/5/20	Morassi M <sup>(31)</sup>	Brescia, Italy	6	64M, 75M, 82M, 79F, 57M, 57M	PCR+	Severe: 5 Mild: 1	Intubation +2 ICU +:2	CT:2 CT+CTA:3 CT+MRI:1	LVO:2 SVO:2 ICH:2	NP	C → S:5 S → C:1	7,744 NR 1,381 2,866 NR	Death: 5 Poor: 1	4 ischemic strokes, 2 hemorrhagic strokes during anticoagulant therapy
19	2020/5/25	Seabra CS <sup>(32)</sup>	Penafiel, Portugal	1	82F	Thorax CT findings	Severe	Intubation - ICU -	CT+CTA	LVO	NP	S → C	NR	Death (renal dysfunction)	Hospitalized for left MCA occlusion. SARS-CoV-2 negative on admission. After the respiratory condition worsened, it turned positive.
20	2020/5/26	Duroi I <sup>(33)</sup>	Ronse, Belgium	1	74F	PCR+	Severe	Intubation + ICU NR	CT	LVO	NP	C → S	2,504-3,941 (0-500 ng/ml)	Death	Hospitalized with COVID-19. Left ICA occlusion developed after intubation.
21	2020/5/28	Fara MG <sup>(34)</sup>	New York, NY, United States	3	33F, 77F, 55M	PCR+	Mild	Intubation - ICU -	CT+CTA+MRI:1 CT:1 CT+CTA:1	LVO:3	NP	S → C:3	only pt.2 increased (no numerical description)	NR	Patients with intracranial vascular occlusion due to thrombus in ICA and CCA. Thrombus disappeared with anticoagulant therapy in 2/3 patients.
22	2020/6/5	Agarwal A <sup>(35)</sup>	New Delhi, India	2	56M, 72M	PCR+	Severe: 1 Mild: 1	Intubation + ICU NR	CT:2	ICH	NP	S → C S → C	NR	Poor: 1 Death: 1	11 ischemic, 14 hemorrhagic stroke patients were hospitalized during the pandemic, including 2 COVID-19 patients with hemorrhagic stroke
23	2020/6/6	Chibane S <sup>(36)</sup>	Montreal, Canada	1	66F	PCR+ (post-mortem)	Severe	Intubation - ICU NR	CT	LVO	NP	S → C	>4,400 (µg/l)	Death	SARS-CoV-2 negative on admission for respiratory symptoms. Left MCA occlusion developed. SARS-CoV-2 positive confirmed after death.
24	2020/6/6	Cavallieri F <sup>(37)</sup>	Reggio Emilia, Italy	1	33M	PCR+	Severe	Intubation + ICU +	CT+CTA	LVO	NP	S → C	3,728 (<250 ng/ml)	Poor	Because of bilateral cerebellar infarction, the patient underwent a neurosurgical decompression of the posterior cranial fossa.
25	2020/6/9	Guillam M <sup>(38)</sup>	Madrid, Spain	1	67M	PCR+	Mild	Intubation - ICU -	CT+MRI	LVO	NP	C → S	1,777 (µg/l)	NR (still In hospital)	Patient of multiple brain infarction without embolic source SARS-CoV-2 is negative, cells and proteins are increased in CSF.
26	2020/6/9	Williams OH <sup>(39)</sup>	London, United Kingdom	1	38F	PCR+	Mild	Intubation - ICU -	CT+CTA+MRI	SVO	NP	S → C	NR	Good	Multiple internal border zone infarcts in a patient with COVID-19 and CADASIL diagnosed by mutations in the NOTCH3 gene and family history. Anticoagulant antibodies was elevated.
27	2020/6/11	Khan M <sup>(40)</sup>	Dubai, United Arab Emirates	22	Ave. 46.3 M: 20	PCR+	NR	CT:3 CT+CTA:19	CT:3 CT+CTA:19	LVO:16 Other:6	IVT:2 MT:2	C → S:4 S → C:18	4.4 ± 6.4 (mean ± SD) (ng/ml)	Death:6 Poor:14 Good:2	The majority of patients were young men who developed LVO with poor outcome.

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28	2020/6/16	Mahboob S <sup>(41)</sup>	Reno, NV, United States	1	58F	PCR+	Severe	Intubation + ICU +	CT+CTA	LVO	NP	S → C	NR	Death	The patient was diagnosed with COVID-19 after stroke diagnosis. Respiratory failure rapidly deteriorated and died.
29	2020/6/17	Sharifa-Razavi A <sup>(42)</sup>	Sari, Iran	3	88F, 85F, 55M	PCR+	Severe	Intubation +3 ICU +3	CT:3	LVO:3	NP	S → C:3	NR	Death: 1 Poor: 2	The patients were diagnosed with COVID-19 after stroke diagnosis. Respiratory failure rapidly deteriorated.
30	2020/6/18	Chougar L <sup>(43)</sup>	Paris, France	1	72M	PCR+	Severe	Intubation + ICU +	CT+CT venogram	CVT	NP	S → C	NR	Death	CVT (hemorrhagic brain infarction) developed with paralysis/convulsion Negative for SARS-CoV-2 in CSF even positive with nasal swab
31	2020/6/18	Hanafi R <sup>(44)</sup>	Sacramento, CA United States	1	65M	PCR+	Moderate	Intubation - ICU -	CT+MRI	Other	NP	C → S	NR	NR	The patient had extensive cerebral small-vessel ischemic lesions resembling cerebral vasculitis in a characteristic combined imaging pattern of ischemia, hemorrhage, and punctuate postcontrast enhancement.
32	2020/6/18	Acharya S <sup>(45)</sup>	Staten Island, NY, United States	1	60M	PCR+	Severe	Intubation + ICU +	CT+CTA	CRAO	NP	C → S	42,131 (no unit description)	NR	CRAO secondary to COVID-19 disease
33	2020/6/24	Princiotra Carriddi L <sup>(46)</sup>	Varese, Italy	1	64F	PCR+	Severe	Intubation + ICU +	CT+CTA+MRI	PRES	NP	C → S	NR	NR	PRES in a COVID19 patient
34	2020/6/24	D'Anna L <sup>(47)</sup>	London, United Kingdom	8	63F, 83M, 88M, 77M, 71M, 55M, 79M, 70M	PCR+	Severe: 4 Moderate: 4	NR	CT:4 CT+CTA:3 CT+CTA+MRI:1	3LVO 4SVO 1ICH	IVT:1	C → S:5 S → C:3	9,709 1,256 >2,000 3,846 1,557 NR NR 5,952 (≤500 ng/ml)	Poor: 1 Good: 7	58 patients developed during hospitalization NIHSS median is 5
35	2020/6/27	Baudard C <sup>(48)</sup>	Brussels, Belgium	1	33F	PCR+	Mild	Intubation - ICU -	MRI	CVT	NP	S → C	902 (≤500 ng/ml)	Good	The patient was on oral contraceptives. BMI 34.6. Comorbidity is the onset symptom. SARS-CoV-2 positive after CVT diagnosis. Improved with anticoagulant treatment.
36	2020/6/29	Zhai P <sup>(49)</sup>	Wuhan, Hubei, China	1	79M	PCR+	Mild	Intubation - ICU -	CT	SVO	NP	S → C	NR	Good	The patient hospitalized for right limb mild weakness and was later diagnosed with COVID-19.
37	2020/7/1	Lima CFC <sup>(50)</sup>	Fortaleza CE, Brasil	1	89F	PCR+	Mild	Intubation - ICU -	CT+CTA	LVO	NP	S → C	NR	NR	The patient had a cold-like symptom for 2 weeks, developed right hemiplegia, aphasia, and was diagnosed with left M2 obstruction by CTA.
38	2020/7/2	Gulko E <sup>(51)</sup>	New York, NY, United States	2	53F, 49M	NR	NR	NR	CT+CTA+MRI CT+CTA	LVO	NR	NR	NR	NR	1) Right proximal ICA thrombus (1 cm) was visualized. 2) Thrombus extending from the left CCA to ICA was visualized. No risk of atherosclerosis in both patients
39	2020/7/2	Mohammad AY <sup>(52)</sup>	Detroit, MI, United States	6	55M, 78F, 62M, 74M, 59M, 67M	PCR+: 5 Thorax CT findings: 1	NR	NR	CT+CTA:3 CT+CTA+CTP:2 CT+CTA+MRI:1	6LVO	IVT:1 MT:3	C → S:6	3.02 3.95 14.17 >20,000 4.88 >20,000 (≤0.5 mgFEU/ml)	Poor: 4 Good: 2	All patients had vascular risk factors including diabetes (63%), hyperlipidemia (100%), and smoking (17%). NIHSS 24-30
40	2020/7/2	Morjana JB <sup>(53)</sup>	Harefield, United Kingdom	1	75M	PCR+	Severe	Intubation - ICU +	CT+MRI	LVO	NP	C → S	1,034-8,974 (0-240 ng/ml)	Poor	Paraplegia with bilateral ACA occlusion.

No.	Epub Date	Author	City, Country/Region	Number of cases	Age/Gender	Method for COVID-19 definitive diagnosis	COVID-19 Severity	Intubation/ICU management	Brain imaging for diagnosis	Stroke Subtype	Reperfusion therapy (IVT/MT)	COVID-19 diagnostic timing	serum D-dimer level (reference range, unit)	Outcome	Characteristic
41	2020/7/7	Suggese CE <sup>60</sup>	Rome, Italy	1	62M	PCR+	Mild	Intubation - ICU -	CT+CTA	LVO	IVT	S → C	1,510 (<278 ng/ml)	Good	Patient with multiple vascular risk factors was treated with rt-PA with improvement of neurologic deficits and was diagnosed with COVID-19 after stroke diagnosis,
42	2020/7/7	Maldonado Sotoijs S <sup>60</sup>	Brussels, Belgium	1	74unknown	NR	Mild	Intubation - ICU -	CT+CTA	LVO	IVT+MT	C → S	NR	Good	Sudden onset with left hemiplegia and aphasia. NIHSS 16 → 25. ICA T occlusion with CTA. IVT was performed within 3 hours, and TICB was achieved in MT. NIHSS after 72 hours.

M: male, F: female, Ave.: average, unknown: gender unknown, PCR+: positive for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) using the reverse transcription-polymerase chain reaction, NR: not reported, CTA: CT angiography, CTP: CT perfusion, ICH: nontraumatic intracerebral hemorrhage, LVO: large vessel occlusion, CVT: cerebral venous thrombosis, SAH: subarachnoid hemorrhage, SVO: small vessel occlusion, CRAO: central retinal artery occlusion, PRES: posterior reversible encephalopathy syndrome, NP: not performed, MT: mechanical thrombectomy, IVT: intravenous thrombolysis, S → C: patient diagnosed with COVID-19 after the onset of stroke, C → S: patient who developed stroke after diagnosis of COVID-19, FEU: Fibrinogen Equivalent Units, MI: myocardial infarction, MCA: middle cerebral artery, ACA: anterior cerebral artery, VTE: venous thromboembolism, EVD: external ventricular drain, CSF: cerebrospinal fluid, CSC: comprehensive stroke center, CCA: common carotid artery, CADASIL: cerebral autosomal dominant arteriopathy with subcortical infarct and leukoencephalopathy, BMI: body mass index, NIHSS: National Institutes of Health Stroke Scale, rt-PA: recombinant tissue plasminogen activator.

前者は COVID-19 が重症化した際に、脳卒中を発症している例が多い。後者は受診時には COVID-19 は軽症であったと推察される。このように、COVID-19 合併脳卒中患者が非 COVID-19 患者に紛れて受診することを考慮すると、医療従事者の感染防御に配慮した PCS の実践が極めて重要である。また、この中には、入院後に COVID-19 が重症化し死亡した例もある<sup>19)26)36)41)</sup>。

Moshayedi らは COVID-19 に伴う MI で入院中に LVO を発症した患者を報告しており、本例は死亡している<sup>17)</sup>。Hughes ら、Chougar ら、Baudar らは脳静脈血栓症を報告している<sup>20)43)48)</sup>。いずれも脳静脈血栓症の診断後に COVID-19 と診断され、1 例は出血性脳梗塞で死亡、2 例は抗凝固療法で改善している。

#### 5-4. 検査

Al Saiegh らは、COVID-19 に伴うくも膜下出血と脳梗塞で減圧開頭が必要となった患者の開頭手術の報告をしており、いずれも鼻腔ぬぐい液では SARS-CoV-2 陽性でも脳脊髄液では陰性だった<sup>22)</sup>。髄液所見については、Guillan らも検討しているが、SARS-CoV-2 は陰性であった<sup>38)</sup>。また Chougar らは、1,176 例の COVID-19 患者で、脳卒中を含む神経症候を呈した患者 308 例中 36 例で脳脊髄液の SARS-CoV-2 は全例陰性であったことを報告している<sup>62)</sup>。ただ、脳卒中ではなく COVID-19 関連髄膜炎などにおいては、脳脊髄液でウイルスが検出されたとの報告も散見される<sup>63)~65)</sup>。

患者の D-ダイマーについては、42 報告中 24 報告が言及していて、そのいずれでも D-ダイマーは高値を示していた<sup>14)18)19)21)23)~25)27)~31)33)~38)40)45)47)48)52)~54)</sup>。

Beyrouti ら、Viguier ら、Williams らは、ループスアンチコアグラントや抗リン脂質抗体に着目している<sup>21)24)39)</sup>。Tan らは複数の報告の虚血性脳卒中 16 例で解析し、ループスアンチコアグラント検査を受けた 12 例中 5 例 (41.7%) が陽性、抗カルジオリピン抗体は 10 例中 2 例 (20%) で IgM 陽性、7 例中 3 例 (42.9%) で IgA 陽性、IgG 抗体陽性患者なし (9 例中 0 例)、抗  $\beta 2$  グリコプロテイン 1 抗体は 10 例中 1 例 (10%) で IgM 陽性、13 例中 5 例 (38.5%) で IgG 陽性、7 例中 3 例 (42.9%) で IgA 陽性と報告している<sup>66)</sup>。

#### 5-5. 臨床病型と転帰

ニューヨークの Yaghi らの報告では、「COVID-19 を伴う虚血性脳卒中患者」を同時期の「COVID-19 を伴わない虚血性脳卒中患者」や「前年同期間の虚血性脳卒中患者」と比較検討している<sup>67)</sup>。COVID 入院患者 3,556 例中 32 例 (0.9%) が虚血性脳卒中を発症していた。脳卒中中で搬入され COVID-19 と診断された例が 43.8%、COVID-19 治療中に脳卒中と診断された例が 56.2% だった。潜在性脳梗塞の割合が 65.6% と高く、入院中死亡率も 63.6% と高かった。発症時 National Institutes of Health Stroke Scale (NIHSS) スコア高値、D-ダイマー高値、トロポニン高値、赤血球沈降速度亢進、若年男性という特徴も示した。

イタリアの Benussi らは、パンデミック期の「COVID-19

の神経疾患患者」56 例を同時期の「COVID-19 ではない神経疾患患者」117 例と比較している<sup>68)</sup>。COVID-19 の脳卒中患者 43 例中 35 例 (81.4%) は脳梗塞だった。COVID-19 患者では院内死亡率が 37.5%、転帰良好率 25.6% で、対照では各々 4.3%、70.6% であり、彼らも COVID-19 合併脳卒中は転帰不良としている。

フィラデルフィアの Rothstein らは、COVID-19 患者連続 844 例中 20 例 (2.4%) が虚血性脳卒中、8 例 (0.9%) が出血性脳卒中と報告している<sup>69)</sup>。虚血性脳卒中患者は平均 64 歳で、50 歳未満の患者は 1 例 (5%) だった。95% の患者が高血圧、60% が糖尿病だった。COVID-19 症状の発症から脳卒中診断までの期間の中央値は 21 日で、40% が心原性脳塞栓症、5% が小血管病、20% が他の原因の確定された脳梗塞、35% が潜在性脳梗塞だった。血管造影を行った 11 例中 3 例 (27%) が LVO であった。頭蓋内出血患者の 8 例中 5 例は脳内出血、3 例はくも膜下出血だった。

Ntaios らは、16 か国の症例をまとめ、174 例の COVID-19 患者に発症した虚血性脳卒中の転帰を報告している<sup>70)</sup>。NIHSS の中央値は 10、病型を診断し得た 132 例中 30 例 (22.7%) はアテローム血栓性脳梗塞、10 例 (7.6%) はラクナ梗塞だった。174 例中、IVT は 34 例 (19.7%) で、MT は 21 例 (12.1%) で施行された。死亡は 48 例 (27.6%) で、22 例が COVID-19、26 例は脳卒中による死亡だった。障害に関する情報が得られた 96 例中 49 例 (51%) が退院時に重度障害だった。

いずれの報告でも COVID-19 関連脳卒中患者は転帰不良という見解は一致していた。

## 6. 脳卒中の発症率

Table 2 に脳卒中の患者の発症率について、患者を観察した国や地域、都市とともに報告された順に示した<sup>8)9)11)~13)67)69)71)~77)</sup>。なお、トルコの Karadaş らの報告のみが前向き研究だった<sup>75)</sup>。Tsvigoulis らは、6 月 4 日の段階で複数の報告を解析して、虚血性脳卒中の発症率を約 1.6% としている<sup>78)</sup>。

Table 2 を元に計算すると、①脳卒中 (一部 transient ischemic attack (TIA) を含む) の発症率は、52,331 例中 588 例で 1.12%、②虚血性脳卒中 (一部 TIA を含む) の発症率は 51,414 例中 560 例で 1.09%、③虚血性脳卒中 (判断可能な TIA を除いた) の発症率は 51,414 例中 555 例で 1.08% となった。対象が全患者の報告も ICU 患者の報告もあり、わずかに TIA 患者の混在もあるが、COVID-19 患者の脳卒中発症率は、おおむね 1.1% 程度でそのほとんどが虚血性脳卒中である。

なお、ICU 患者を除いた解析では、①52,089 例中 581 例で 1.12%、②51,172 例中 553 例で 1.08%、③51,172 例中 548 例で 1.07% となり、ICU 患者のみでは全例脳梗塞で、242 例中 7 例で 2.89% となった。

Merkler らは、COVID-19 患者とインフルエンザ患者の脳梗塞の発症率を比較している<sup>71)</sup>。COVID-19 患者では 2,132 例中 31 例 (1.5%)、インフルエンザ患者では 1,516 例中 3 例

Table 2 Stroke incidence in corona virus disease 2019 (COVID-19) patients.

No.	Epub Date	Author	City, Country/Region	Number of Facilities	Prospective/Retrospective research	Total number of COVID-19 patients	Target	Total number of Stroke patients	Stroke Incidence (%)	Stroke Subtype	Ischemic Stroke Incidence (%)	Etiology	Mortality (%) or Number of Death
1	2020/4/10	Mao L <sup>8)</sup>	Wuhan, Hubei, China	Multicenter research 3 facilities	Retrospective	214	All PT	6	2.8	Ischemic: 5 Hemorrhagic: 1	2.3	NR	NR
2	2020/4/10	Klok FA <sup>10)</sup>	Leiden, Netherlands	Multicenter research 3 facilities	Retrospective	184	ICU PT	5	2.7	Ischemic: 5	2.7	NR	NR
3	2020/4/15	Helms J <sup>12)</sup>	Strasbourg, France	Single-center research	Retrospective	58	ICU PT	2	3.5	Ischemic: 2	3.5	NR	NR
4	2020/4/23	Lodigiani C <sup>10)</sup>	Milano, Italy	Single-center research	Retrospective	362	All PT	9	2.5	Ischemic: 9	2.5	NR	NR
5	2020/5/20	Yaghi S <sup>6)</sup>	New York, NY, United States	Multicenter research	Retrospective	3,556	All PT	32	0.9	Ischemic: 32	0.9	Cryptogenic: 63.6%	63.6%
6	2020/5/21	Merkler AE <sup>7)</sup>	New York, NY, United States	Multicenter research 2 facilities	Retrospective	2,132	All PT	31	1.5	Ischemic: 31	1.5	NR	NR
7	2020/6/9	Camador E <sup>22)</sup>	Madrid, Spain	Single-center research	Retrospective	1,419	All PT	8	0.6	Ischemic: 6 TIA: 2	0.4	LAA: 3 CE: 2 Cryptogenic: 2 UD: 1	1
8	2020/6/16	Nallehale K <sup>20)</sup>	United States	Multicenter research	Retrospective	40,469	All PT	406	1.0	Ischemic: 406 (including TIA)	not calculable	NR	NR
9	2020/6/17	Xiong W <sup>16)</sup>	Chengdu, China	Multicenter research 56 facilities	Retrospective	917	All PT	10	1.1	NR	not calculable	NR	NR
10	2020/6/25	Karadas Ö <sup>20)</sup>	Ankara, Turkey	Single-center research	Prospective	239	All PT	9	3.8	Ischemic: 4 TIA: 3 Hemorrhagic: 2	1.7	NR	NR
11	2020/7/2	Li Y <sup>6)</sup>	Wuhan, Hubei, China	Single-center research	Retrospective	211	All PT	11	4.6	Ischemic: 10 Hemorrhagic: 1	4.7	NR	6
12	2020/7/8	Paterson RW <sup>20)</sup>	London, United Kingdom	Multicenter research	Retrospective	43	All PT	8	8.6	Ischemic: 8	8.6	LVO: 4	1
13	2020/7/9	Hernández-Fernández F <sup>7)</sup>	Alicante, Spain	Single-center research	Retrospective	1,683	All PT	23	1.4	Ischemic: 17 Dissection: 2 Hemorrhagic: 5 PRES1	1.0	LVO: 10 (Stroke in posterior circulation in 6/17 patients)	NR
14	2020/7/20	Rothstein A <sup>6)</sup>	Philadelphia, PA, United States	Multicenter research 3 facilities	Retrospective	844	All PT	28	3.3	Ischemic: 20 Hemorrhagic: 8	2.4	CE 40% SVO 5% Other 20% Cryptogenic: 35%	Ischemic 25% (5/20) Hemorrhagic 75% (6/8)

All PT: consecutive COVID-19 patients, ICU PT: consecutive COVID-19 patients treated in intensive care unit, TIA: transient ischemic attack, NR: not reported, PRES: posterior reversible encephalopathy syndrome, LAA: large-artery atherosclerosis, CE: cardioembolism, UD: stroke of undetermined etiology, LVO: large vessel occlusion, SVO: small vessel occlusion, Other: stroke of other determined etiology.



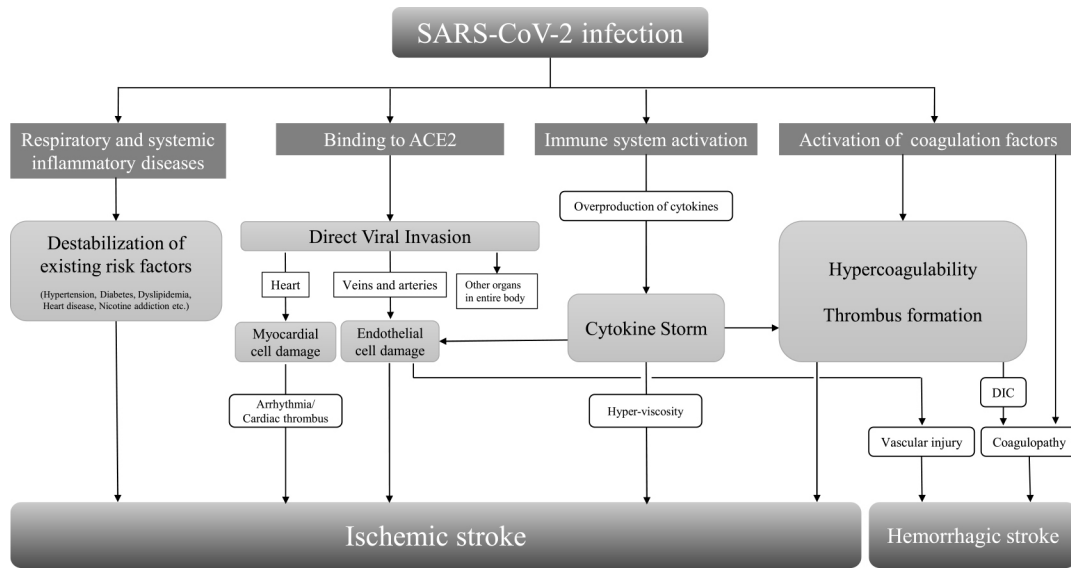


Fig. 1 Assumed pathophysiology of stroke in corona virus disease 2019 (COVID-19).

SARS-CoV-2: severe acute respiratory syndrome coronavirus 2, ACE2: angiotensin-converting enzyme 2, DIC: disseminated intravascular coagulation.

(0.2%)が脳梗塞を発症しており、COVID-19患者の脳梗塞発症率は、インフルエンザ患者の約7.5倍だった。

Shahjoueiらは、11か国65地域の99の三次医療センターのCOVID-19入院患者17,799例を検討して脳卒中発症は0.5%と報告し、そのうち虚血性脳卒中が79%だった<sup>79)</sup>。彼らは、インフルエンザなどの従来の流行性呼吸器感染症でも脳卒中発症率は増すといわれ、COVID-19がそれらを大きく上回るものではない可能性を指摘している。同様の日本の施設を含んだ研究も進行中である<sup>80)</sup>。

## 7. 脳卒中の発症機序

SARS-CoV-2感染が脳卒中発症の病態に与える影響は明確にはなっていないが、複合的なものと考えられている。SARS-CoV-2は、ACE2(angiotensin-converting enzyme 2)を介して細胞内に侵入する<sup>81)</sup>。ACE2は、肺、心臓、腎臓、血管内皮で発現しており、これらの臓器が直接ウイルスの標的となる<sup>82)</sup>。心臓へのダメージは、塞栓症のリスクをはらんでおり、血管内皮の損傷が脳卒中を含む血管疾患を引き起こすことにもなる。重症COVID-19では免疫システムが制御不能となりサイトカインストームが起こる場合がある<sup>83)</sup>。これに伴い、D-ダイマー高値などとして現れる凝固亢進も発症機序として注目される(Fig. 1)。

ニューヨークのBelaniらは、パンデミック期に緊急画像診断で脳梗塞が確認された患者41例を同時期に脳卒中を疑われて受診したものの画像診断で所見がなかった患者82例と比較している<sup>84)</sup>。脳梗塞のうち46.3%はCOVID-19患者で、対照の18.3%と比較して有意に高率( $P = .001$ )で、年齢、性別、リスク要因の調整後もCOVID-19であることは脳梗塞

の独立したリスクだった(odds ratio, 3.9; 95% CI, 1.7–8.9;  $P = .001$ )。

## 8. COVID-19蔓延期の脳卒中診療

3月11日のWHOパンデミック宣言から間もないイタリアから、混乱を極める病院で脳卒中患者がほとんど見られないという「不可解」な事象が起こっていることが報告された<sup>85)</sup>。過去5年の月平均患者数から実に88%減少していた。

その後、ヨーロッパ、アメリカ大陸へとCOVID-19が拡大するにつれ、自国の実情に応じた都市封鎖(ロックダウン)が行われ、それを経験した各国から同様の報告が続いていく。

Table 3に報告された順に、脳卒中診療が行われた国や地域、都市とともに、対象期間(主にロックダウン期)、脳卒中患者やその治療件数の増減や急性期脳卒中診療の遅れに関する記述を示す<sup>85)~113)</sup>。対象は、脳卒中全体、脳梗塞やTIA、脳出血やくも膜下出血で、やはり緊急疾患である急性冠症候群(acute coronary syndrome, 以下ACSと略記)、MI、ST上昇型MI(ST-segment elevation MI, 以下STEMIと略記)などの虚血性心疾患にも同時に着目した研究もあった。

入院・受診患者を観察した報告が多いが、救急車の搬送数や画像解析ソフトRAPIDの解析件数で研究したものもある<sup>87)91)103)</sup>。報告された国や地域、都市では、Table 3に見られるように、程度の差はあるが脳卒中患者の受診数は、ロックダウン期には減少傾向を示していた。また、受診患者の減少に伴って、再灌流療法(IVT, MT)の施行数も減少している。ただ、Tejada Mezaら(2報告)、Kerlerouxら、Paliwalらのように、再灌流療法の施行率は非流行期と不変であることを強調している報告もある<sup>92)93)104)113)</sup>。また、発症から来院ま

Table 3 Situation of stroke medical care during corona virus disease 2019 (COVID-19) pandemic period in each country and region.

No.	Epub Date	Author	City/ Country/ Region	Diseases of interest	Number of facilities	Observation target	Observation period	Control period	Increase/decrease in the number of patients/treatments, etc.	Delay in acute stroke treatment
1	2020/4/14	Morelli N <sup>(8)</sup>	Alessandria, Italy	Ischemic Stroke	Multicenter research	Admitted patients	2020/2/21-3/25 (first month of lockdown)	monthly average of the past 5 years (2015-2019)	Monthly average decreased from 51 cases to 6 cases per month: 88% decrease	NR
2	2020/5/6	Naccarato M <sup>(9)</sup>	Trieste, Italy	Stroke	Single-center research	Admitted patients	2020/3/9-4/9 (first month of lockdown)	the same period in 2019	29: 16 Patients 45% ↓ (No change in severe patients)	NR
3	2020/5/8	Kansagra AP <sup>(7)</sup>	United States	Ischemic Stroke	Multicenter research	Cases processed with RAPID	2020/3/26-4/8 early-pandemic epochs	prepandemic epochs	Imaging processed with RAPID decreased by 39% No regional difference	NR
4	2020/5/11	de Havenon A <sup>(8)</sup>	United States	Stroke, ACS	Multicenter research, 65 facilities	Admitted patients	2020/2/1-3/31	the same period in 2018 and 2019	Stroke 18.5% ↓, Ischemic 19.9% ↓, Hemorrhagic 11.5% ↓, ACS 7.5% ↓, MT18.8% ↑, IVT3.3% ↓, PCI 14.7% ↓	NR
5	2020/5/12	Pop K <sup>(9)</sup>	Strasbourg, France	Stroke	Multicenter research, 3 facilities	Code strokes, IVT, MT	2020/3/1-3/31	the same period in 2019	Code strokes 39.6% ↓ IVT 40.9% ↓, MT27.6% ↓	No differences in time delays or severity of clinical symptoms for patients treated by IVT or MT
6	2020/5/14	Siegler JE <sup>(8)</sup>	Camden, NJ, United States	Ischemic Stroke	Single-center research	Patients, Telesroke- consultations	6 weeks following 2020/3/1 (COVID-19 period)	5 months prior to 2020/3/1 (pre-COVID-19)	Stroke diagnoses 38% ↓ Daily transfers from referral centers 59% ↓ Telesroke consultations 25% ↓ Patients presenting directly by private vehicle 55% ↓ Patients through emergency services 29% ↓	NR
7	2020/5/14	Holmes JL <sup>(3)</sup>	Edgobaston, United Kingdom	MI, Stroke	—	Emergency ambulance services	2020/3/23-4/19 (lockdown period of United Kingdom)	2018/1/10-3/23	STEMI 9.1 ↓ (not significant) Stroke 21.7 ↓ (not significant)	NR
8	2020/5/16	Tejada Meza H <sup>(2)</sup>	Zaragoza, Spain	Ischemic Stroke	Multicenter research	Admitted patients	2020/3/9-4/19 (lockdown period)	2019/12/30-2020/3/8 (pre-lockdown period)	Patients 27.5week → 12/week No differences in the proportion of IVT or MT	ODT median 102 vs. 183 (min.), delayed, DNT median 50 vs. 64 (min.), not delayed, DPT median 59.5 vs. 68 (min.), not delayed, pre-pandemic vs. pandemic
9	2020/5/20	Kerleroux B <sup>(6)</sup>	France	Ischemic Stroke	Multicenter research	MT	2020/2/15-3/30 (15 days prior the epidemic containment measures initiation, to 15 days after mitigation measures were instituted)	the same period in 2019	MT 21% ↓, Rate of reperfusion 82.3% vs. 82%, similar. In-hospital mortality 12.9% vs. 17.3%, similar	IPT mean 144.9 vs. 126.2 (min.), delayed (overall), IPT mean 138 vs. 144.6 (min.), not delayed (at the stroke center of initial presentation (i.e. mothership subgroup))
10	2020/5/20	Teo KC <sup>(4)</sup>	Hong Kong	Stroke, TIA	Single-center research	ODT	2020/1/25-3/24 (during the first 60 days since the first diagnosed COVID-19 case in Hong Kong)	the same period in 2019	NR	ODT median 154 vs. 95 (min.), delayed, proportion of ODT within 4.5 hours 55% vs. 72%, lower; TIA presented to the hospital 4% vs. 16%, lower
11	2020/5/20	Zhao J <sup>(5)</sup>	China	Stroke	Multicenter research	Hospital admissions related to stroke IVT, MT	2020/2/1-2/29	the same period in 2019	Hospital admissions related to stroke 40% ↓ IVT 26.7% ↓ MT 25.3% ↓	NR
12	2020/5/22	Rudilosso S <sup>(6)</sup>	Barcelona, Spain	Stroke	Multicenter research	Emergency calls, Code strokes, Admitted patients, MT	2020/3/1-3/31	the same period in 2019	emergency calls 330% ↑ (679,569 vs. 158,005) Code strokes 18% ↓ (426 vs. 517) admitted patients 23% ↓ (83 vs. 108) MT 24% ↓ (16 vs. 21)	No differences in prehospital or in-hospital workflow metrics
13	2020/5/26	Bres Bullrich M <sup>(7)</sup>	London, ON, Canada	Stroke	Single-center research	Code strokes, Stroke admissions, Clinic referrals	2020/2/3-3/15 2020/2/16-4/26 (lockdown period)	the same period in 2019	Code strokes 20% ↓ Stroke admissions no changes Clinic referrals 22% ↓	NR

No.	Epub Date	Author	City, Country/Region	Diseases of interest	Number of facilities	Observation target	Observation period	Control period	Increase/decrease in the number of patients/treatments, etc.	Delay in acute stroke treatment
14	2020/5/28	Schirmer CM <sup>(8)</sup>	Danville, PA, United States	Ischemic Stroke	Multicenter research, 12 facilities	Stroke admissions, ODT	2020/2/1-2/29 (the pre-COVID period) 2020/3/1-3/31 (the COVID period)	the same period in 2019 (the baseline period)	Stroke admissions per week decreased during the COVID period. (No description of reduction rate)	ODT mean 603 vs. 442 (min), delayed
15	2020/5/29	Montaner J <sup>(9)</sup>	Seville, Spain	Stroke	Multicenter research, 2 facilities	Stroke Unit admissions, Code strokes, Consultations through telestroke, ODT, DNT	2020/3/16-3/31 (lockdown period)	2020/1/16-3/15 (pre-lockdown period)	Stroke Unit admissions, 25% ↓ (44 vs. 58 cases/15 days) Consultations through telestroke ↓ (7 vs. 25 cases/15 days) Code Strokes dispatched to hospitals ↓ (78% vs. 57%)	ODT >30 minutes delayed DNT 16 minutes delayed
16	2020/6/4	Pasnikowski CR <sup>(10)</sup>	Toronto, Ontario, Canada	Stroke	Single-center research	Code Strokes	2020/3/17-5/8	2019/3/1-2020/3/16 (pre-lockdown period)	Code Strokes ↓ (No indication of reduction rate, shown as approximately 2/3 reduction in the figure). The ratio of patient arrival methods remained unchanged (via EMS, transfers from another hospital, emergency room walk-in, and inpatients)	NR
17	2020/6/4	Pandey AS <sup>(11)</sup>	Ann Arbor, MI, United States	Ischemic Stroke, ICH, SAH	Multicenter research, 12 facilities	Admitted patients	2020/3/1-3/31	2020/2/1-2/29 (Last month of the same year) 2019/3/1-3/31 (Same month of the last year)	Ischemic Stroke 18% ↓, 15% ↓, MT 39% ↓, 43% ↓, IYV similar, similar, ICH 39% ↓, similar, SAH similar, similar. (The former is compared with last year and the latter with last month, respectively)	No significant difference in ODT or DPT compared to last month in MT
18	2020/6/9	Hoyer C <sup>(12)</sup>	Mannheim, Germany	Ischemic Stroke, TIA	Multicenter research, 4 facilities	Admitted patients	2020/1/1-4/12 (weeks 1-15)	2019/1/1-4/14 (weeks 1-15)	In 3/4 facilities TIA ↓ (85% ↓, 46% ↓, 42% ↓), in 2/4 facilities Stroke admission rate ↓ (40% ↓, 46% ↓) after 2020/3/16. In 1/4 facilities IYV 60% ↓ MT 61% ↓. (The pandemic began to impact public life in Germany after 2020/3/16.)	NR
19	2020/6/11	Khot UN <sup>(13)</sup>	Cleveland, OH, United States	STEMI, Stroke, AAE	—	Emergency transfers	2020/3/9-5/6	2019/3/9-5/6	STEMI 48% ↓ Stroke 39% ↓ AAE 21% ↓	NR
20	2020/6/11	Tejada Meza H <sup>(14)</sup>	Zaragoza, Spain	Ischemic Stroke	Multicenter research	Admitted patients	2020/3/14-5/3 (after the state of emergency in Spain)	2019/12/30-2020/3/13 (before the state of emergency in Spain)	The weekly mean admitted patients ↓ (124 vs. 173) In-hospital mortality of stroke patients ↑ (9.9% vs. 6.5%) The proportion of IYV no differences (17.3% vs. 16.1%) The proportion of MT no differences (22% vs. 23%)	NR
21	2020/6/12	Diegoli H <sup>(15)</sup>	Joinville, Brazil	Stroke, TIA	Single-center research	Admitted patients	2020/3/17-4/15	the same period in 2019	Stroke admissions 36.4% ↓ (6.3 vs. 12.9/100,000) Severe stroke (NIHSS score >8), ICH, SAH no difference	NR
22	2020/6/13	Sweid A <sup>(16)</sup>	Philadelphia, PA, United States	Ischemic Stroke	Single-center research	Admitted patients, Telestroke	2020/3/15-4/30	the last three years	Telestroke 48% ↓ MT 50% ↑	Diagnosis to intervention 493 vs. 544 (min), not delayed (6 of all MT (24) cases were SARS-CoV-2 positive, constituting 25% of all MT.)
23	2020/6/16	Fiebler J <sup>(17)</sup>	61 countries	Stroke	Multicenter research	475 doctors of stroke centers in 61 countries	conducted mid-March 2020	—	A decrease in emergency procedures was reported by 69% of participants (52% in ischemic and hemorrhagic stroke, 11% ischemic, and 6% hemorrhagic stroke alone). Only 4% reported an increase in emergency cases.	NR
24	2020/6/25	Lange SJ <sup>(18)</sup>	47 States, United States	MI, Stroke, Hyperglycemic crisis	Multicenter research	Use of Emergency Departments	2020/3/15-5/23	2020/1/5-3/14	MI 23% ↓ Stroke 20% ↓ Hyperglycemic crisis 10% ↓	NR
25	2020/6/29	Perry R <sup>(19)</sup>	London, United Kingdom	Stroke	Single-center research	Admitted patients	2020/4/1-5/11 (40 days)	2020/2/1-3/12 (40 days)	The decline in the number of patients admitted with mild strokes (NIHSS ≤ 5) was far more dramatic than was seen for moderate or severe strokes (NIHSS > 5).	NR

No.	Epub Date	Author	City, Country/Region	Diseases of interest	Number of facilities	Observation target	Observation period	Control period	Increase/decrease in the number of patients/treatments, etc.	Delay in acute stroke treatment
26	2020/7/3	Kristoffersen ES <sup>106</sup>	Lørenskog, Norway	Stroke, TIA	Single-center research	Admitted patients	2020/3/13-4/30 during lockdown	2020/1/3-3/12 before lockdown	Admissions/week ↓ (15.0 vs. 21.8) NIHSS average ↑ (5.9 vs. 4.2)	OR was 2.05 (95% CI 1.0-3.83, p = 0.024) for not reaching hospital within 4.5 hours during the lockdown as compared to the period before the lockdown.  ODT median 387 vs. 161 (min.), delayed DPT median 120 vs. 93 (min.), delayed
27	2020/7/6	Frisullo G <sup>110</sup>	Rome, Italy	Stroke, TIA	Single-center research	Admitted patients	2020/3/11-4/11	the same period of 2019	Admitted patients, no difference IVT ↓ (7 vs. 13) MT ↑ (15 vs.9) not significant	
28	2020/7/8	Hsiao J <sup>121</sup>	Ohio, Kentucky, and Indiana, United States	Stroke	Multicenter research, 30 facilities	Admitted patients	2020 Week 11-15 (after the announcement of measures to mitigate COVID-19)	2020 Week 1-10 (before the announcement) 2019 Week 11-15 (the same period of 2019)	Stroke consultations 39% ↓ compare to 2020 Week 1-10, Reperfusion treatments 31% ↓ compare to 2019 Week 11-15 (specifically IVT 33% ↓)	NR
29	2020/7/13	Paliwal PR <sup>119</sup>	Singapore	Stroke	Single-center research	Code strokes	2020/2/7-2020/4/30 (during DORSCON Orange)	2019/1/1-2020/2/7 (pre-DORSCON Orange)	Code strokes 41.1% ↓ The proportion of recanalization therapy 32.6% vs. 28.6%, similar. IVT only 16.6% vs. 12.1%, similar, bridging IVT with MT 11.1% vs. 11.7%, similar. EVT only 4.9% vs. 4.9%, similar	The procedure of recanalization therapy (IVT, MT), not delayed

ACS: acute coronary syndrome, MI: myocardial infarction, TIA: transient ischemic attack, ICH: nontraumatic intracerebral hemorrhage, SAH: subarachnoid hemorrhage, STEMI: ST-segment elevated myocardial infarction, AAE: acute aortic emergencies, RAPID: the name of software platform, IVT: intravenous thrombolysis, MT: mechanical thrombectomy, PCI: percutaneous coronary intervention, EMS: emergency medical service, NR: not reported, NIHSS: National Institutes of Health Stroke Scale, ODT: onset-to-door time, DNT: door-to-needle time, DPT: door-to-puncture time, IPT: imaging-to-puncture time, SARS-CoV-2: severe acute respiratory syndrome coronavirus 2.

での時間 (onset-to-door time) は、ほとんどの報告でロックダウン期に延長している<sup>92/94/98/99/111</sup>。ただ、来院後の door-to-needle time, door-to-puncture time, imaging-to-puncture time などについては、延長したとするものと不変だったとするものが混在する<sup>92/101/111</sup>。

ロックダウン期の脳卒中患者受診数減少について、Kristoffersen らは、入院時の NIHSS の平均がロックダウン期には高くなっている (5.9 対 4.2) ことを示し、Perry らは軽症脳卒中 (NIHSS ≤ 5) の減少が中等症-重症脳卒中 (NIHSS > 5) の減少より顕著であることを示して、軽症患者の受診控えが脳卒中患者減少の一因であるとしている<sup>109/110</sup>。

また、Rai らは、COVID-19 の neuroendovascular clinical trials への影響も指摘している<sup>114</sup>。全米 101 研究機関中 65 機関 (64%) が回答し、COVID-19 蔓延後に臨床研究登録は 51 機関 (78%) で停止、49 機関 (75%) では新試験保留となっており、混乱が生じている。

## 9. 脳卒中に関するわが国の対応

わが国でも、4月7日に7都府県に緊急事態宣言が発令され、16日に全都道府県に拡大した。そのような状況下で、「入院中の COVID-19 患者の脳卒中発症時対策」「COVID-19 が否定できない患者 (patient under investigation: PUI) の救急受診時対策 (再灌流療法・外科治療対策も含む)」が喫緊の課題となった。

4月9日に「COVID-19 に関する日本脳卒中学会・日本循環器学会 合同声明」が出された<sup>115</sup>。

4月15日に日本神経学会と日本神経救急学会は「脳神経内科当直医のための、新型コロナウイルス感染を配慮した意識障害等の神経症候を呈する患者への救急外来対応マニュアル (ver. 1)」を発表した<sup>116</sup>。

4月24日に日本脳卒中学会は、「専門性」と「時間との戦い」に加えて「医療従事者の感染防御 (安全性の担保)」も図りつつ脳卒中急性期に対応する「COVID-19 対応 脳卒中プロトコル (日本脳卒中学会版 PCS: JSS-PCS)」を発表した<sup>117</sup>。

## 10. PCS

COVID-19 流行で問題に直面した各国で、従来の安全で有効かつ迅速な治療を完全な感染対策下で行う努力がはじめられた。その対応策として、カナダから PCS が提案され、注目された<sup>11</sup>。日本でも平野らによって、上記の JSS-PCS が示された<sup>117</sup>。PCS とは、医療従事者の感染防御を第一に考慮した脳卒中急性期治療指針で、医療従事者自身やその家族の健康を守ることにつながる。濃厚接触者の連鎖による就業制限や病院機能縮小による医療崩壊を防ぐことも目指し、それによって、本来救われるべき、脳卒中患者を守ることが可能となる。

JSS-PCS では、PCS を適用する患者の判断基準を明確にしている。既に COVID-19 と診断されていて脳卒中を発症した

患者に加えて、COVID-19 疑似症患者、さらには脳卒中特有の意識障害や失語で病歴不明の患者も適用対象としている。そして、患者受け入れ体制、個人用防護具 (personal protective equipment: PPE)、画像診断、家族対応、治療時の注意点、患者搬送方法などに言及している。なお、各国の事情に合わせた PCS が構築されているが、医療従事者の感染防御の大原則と適用患者はほぼ同様で、それ以降も類似しているが、病院の前にモバイル CT を設置して、院外で CT までは済ませてしまうという現状の日本では実現困難な方法を組み込んだものも見られた<sup>118</sup>。

## 11. おわりに

COVID-19 患者の脳卒中の特徴としては、①脳梗塞が多く、脳出血は稀で、脳静脈血栓症もある、②ACS・MI よりも脳卒中発症が多い、③高血圧、糖尿病、脳卒中の既往歴を含む心血管危険因子を持つ患者は脳卒中を発症する可能性が高い、④若年者での脳梗塞発症が増える可能性もあるが、極端に多いとはいえない。若年で発症した場合でも転帰不良である、⑤大血管病変の症例が増える可能性がある、⑥潜性脳梗塞が多い、⑦COVID-19 軽症例で発症する場合も、重症例で発症する場合もある、⑧D-ダイマー高値例が多い、⑨ループスアンチコアグラント陽性例、抗リン脂質抗体陽性例が多い可能性もある、⑩転帰不良例が多い、ということがあげられる。

COVID-19 流行下における脳卒中診療の問題点が明らかにされ始めている。COVID-19 のさらなる感染拡大期の到来によっても、わが国の脳卒中の救急医療が揺るがないことを願っている。

※著者全員に本論文に関連し、開示すべき COI 状態にある企業、組織、団体はいずれもありません。

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**Abstract****COVID-19 and stroke**

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Due to the pandemic of corona virus disease 2019 (COVID-19), the stroke medical care system is unavoidably undergoing major changes such as a decrease in the number of stroke patients receiving consultation, delay in consultation, and a decrease in the number of intravenous thrombolysis and mechanical thrombectomy procedures. Stroke incidence in COVID-19 patients is approximately 1.1%. The features of stroke with COVID-19 have been elucidated: higher incidence in ischemic stroke than hemorrhagic stroke, increasing number of young patients, high D-dimer levels, and higher risk in elderly patients with cardiovascular risk factors such as hypertension and diabetes. In patients with COVID-19, venous thromboembolism is more common than arterial thromboembolism, and stroke is more common than acute coronary syndrome. Protected code stroke (PCS) has been proposed which provides safe, effective and prompt treatment under complete infection control.

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**Key words:** COVID-19, stroke, large vessel occlusion, cryptogenic stroke, protected code stroke

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