

COVID-19 Associated Wake-Up Stroke Treated With DWI/FLAIR Mismatch Guided Intravenous Alteplase

A Case Report

Earl Biag, MD, Krystian Solis, MD, Ahmed Abd Elazim, MD,
and Omar Hussein, MD

Introduction: Wake-up strokes are challenging to manage due to unknown time of onset. Recently, the wake-up trial demonstrated that recombinant tissue plasminogen activator (rtPA) could be administered based on the magnetic resonance imaging (MRI)-diffusion weighted imaging/fluid attenuated inversion recovery mismatch. Many still doubt the safety results due to the higher rate of hemorrhagic conversion reported. Although it was statistically insignificant, the study was terminated early. Furthermore, Corona virus disease-19 is associated with coagulopathy and a higher risk of hemorrhagic conversion.

Case Report: A 46-year-old fully functioning male presented with a wake-up right hemiparesis, right facial droop, and expressive aphasia. His National Institute of Health Stroke Scale was 4 upon arrival. Last known well state was >4.5 hours. He tested positive for SARS-CoV-2 viral infection. He had left distal-M2 occlusion. He was deemed not a candidate for rtPA. Hyperacute-MRI protocol showed diffusion weighted imaging/fluid attenuated inversion recovery mismatch. The patient received rtPA at 6.5 hours from the last known well state. Follow-up MRI-susceptibility weighted imaging revealed fragmented clot. The stroke burden was less than that shown on the initial computed tomography-perfusion scans implying saved penumbra. There was no hemorrhagic conversion despite low fibrinogen levels.

Conclusion: The hyperacute-MRI protocol for wake-up COVID-19 associated strokes might be a safe option.

Key Words: COVID-19, SARS-CoV-2, wake-up stroke, DWI/FLAIR mismatch, thrombolysis, intravenous alteplase

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Magnetic resonance imaging (MRI)-diffusion weighted imaging (DWI)/fluid attenuated inversion recovery (FLAIR) mismatch is currently an imaging modality accepted by many neurologists to guide intravenous alteplase administration for wake-up strokes. However, reports from the original trial showed increased symptomatic intracranial bleeding

rate and mortality rate among the alteplase group versus the placebo group. While these were statistically insignificant ($P=0.15$ and 0.07 , respectively), it was concerning enough for some as the study was terminated early. These concerns are legitimate because the increased bleeding risk and mortality rate might have been significant if recruitment of the predetermined sample size was completed.¹ In contrast, coagulopathy is a well-recognized problem in Corona virus disease-19 (COVID-19) patients. To that extent, both ischemic and hemorrhagic strokes were reported.² Furthermore, there are increased incidences of hemorrhagic conversion of ischemic strokes as well.³ That makes decisions to give intravenous alteplase more challenging especially if the symptom-onset was unclear. That is because intravenous alteplase beyond 4.5 hours from symptom-onset has a higher bleeding risk in non-COVID-19 patients.⁴ With COVID-19 patients, the risk might be higher.^{3,5}

CASE PRESENTATION

A 46-year-old fully functioning male with a history of hyperlipidemia developed acute-onset right hemiparesis, right facial droop, and expressive aphasia. He was well before going to sleep at 23:00 the night before. He was found down at around 03:30 and got transferred to the emergency department at 04:15. During transfer, there was noticeable improvement of his weakness. On arrival, the patient had a blood pressure of 161/98 mm Hg and a serum glucose-level of 120 mg/dL. His neurological examination was significant for severe expressive aphasia, mild dysarthria, and right pronator drift giving him a National Institute of Health Stroke Scale (NIHSS) of 4. The initial laboratories were significant for positive SARS-CoV-2 viral infection, thrombocytosis (417,000 to 470,000/ μ L), low fibrinogen (105 mg/dL), and elevated low density lipoprotein (146 mg/dL). The patient had normal D-dimers (<215 ng/mL), normal white blood cell count (5800/ μ L), normal C-reactive protein (<0.3 mg/dL), and normal erythrocyte sedimentation rate (4 mm/h). Computed tomography (CT)/head was unremarkable for acute abnormalities. Computed tomographic angiography/head and neck demonstrated a left-middle cerebral artery distal superior division occlusion (distal-M2). Computed tomographic perfusion scan (RAPID-software) showed an infarct core volume (cerebral blood flow <30%) of 0 mL and a penumbra volume at ($T_{max} > 6.0$ s) of 47 mL (Fig. 1A). The vessel occlusion was deemed unreachable by the endovascular interventionist. A hyperacute-MRI showed a DWI/FLAIR mismatched lesion (ie, restricted diffusion on the diffusion-sequences and no signal on the FLAIR-sequence) in the middle cerebral artery territory (Figs. 1B–E). The findings were consistent with salvageable hyperacute cerebral ischemia. Thus, a standard dose of recombinant tissue plasminogen activator (rtPA) (0.9 mg/kg) was administered at 05:30 due to persistent aphasia despite improved motor function. 24-hour post-rtPA MRI/diffusion-scans showed a small evolving ischemic infarct measuring 6.9 mL (Figs. 2C, D). There was no evidence of hemorrhagic transformation on the susceptibility weighted imaging (Fig. 2B). All the patient's symptoms resolved. Transthoracic echocardiography showed normal left ventricular size and function without evidence of clots or intracardiac-shunts. The patient was started on aspirin, clopidogrel, and

From the Department of Neurology, University of New Mexico Hospitals, Albuquerque, NM.

E.B. and K.S. contributed equally and are first authors.

O.H.: Conceptualized, executed, and supervised the case report also he obtained written consent from the patient. K.S., E.B., A.A.E., and O.H.: conceived the case report. E.B. and K.S.: cowrote the first draft. A.A.E. and O.H. sourced and reported high-quality images for this study. O.H., E.B., K.S., and A.A.E.: revised the manuscript for important intellectual content. All authors have read and approve the final version of the manuscript.

The authors declare no conflict of interest.

Correspondence to: Omar Hussein, MD, Department of Neurology, University of New Mexico Hospitals, MSC10 5620, 1 UNM, Albuquerque, NM 87131. E-mails: ohussein@salud.unm.edu; oyhussein@yahoo.com.

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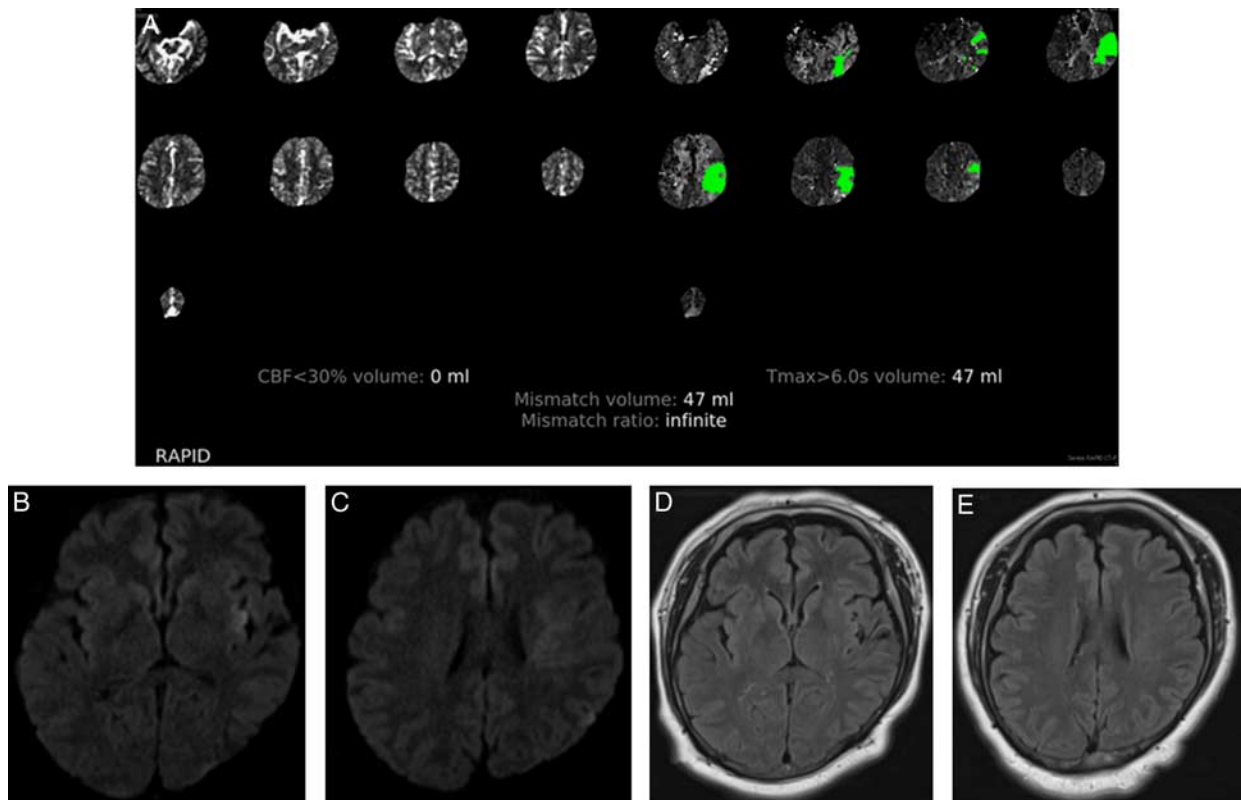


FIGURE 1. CTP shows a core-infarct volume of 0 mL and a penumbra volume of 47 mL in the left-MCA territory (A). Initial hyperacute-MRI shows DWI/FLAIR mismatch; DWI shows restricted diffusion in the left basal ganglia and insular cortex (B, C), whereas FLAIR shows no signal changes in the corresponding areas (D, E). CTP indicates computed tomographic perfusion scan; DWI, diffusion weighted imaging; FLAIR, fluid attenuated inversion recovery; MCA, middle cerebral artery; MRI, magnetic resonance imaging.

a statin for stroke prevention as well as a course of dexamethasone and remdesivir for COVID-19 pneumonia. He required minimal oxygen during hospitalization.

DISCUSSION

Traditionally, large-vessel-occlusion (LVO) strokes are treated via intravenous rtPA and/or mechanical thrombectomy if presented within a certain time-window and had eligible CT-imaging criteria. The time onset of the window is evaluated based on a last-known-well state. Patients presenting with wake-up strokes are often outside that window especially if they have no LVO or have unreachable occlusion (like distal-M2 occlusion). However, according to the 2018 Wake-up trial,¹ they might still be eligible for chemical thrombolysis if they had DWI/FLAIR mismatch on MRI. If such protocol is followed, you rely on the imaging, and arguably pathologic, window rather than the time-window. However, it still makes some neurologists nervous because the study was early terminated due to funding problems. The study recruited 503 patients out of 800 planned enrollments. While the results of the study showed that the technique was efficient in reducing the modified ranking score, the safety measures did not show clear-cut evidence. There was increased mortality rate (4.1% in rtPA-group vs. 1.2% in placebo-group, $P=0.07$) and increased rate of symptomatic intracranial hemorrhage (2% in rtPA-group vs. 0.4% in placebo-group, $P=0.15$) among the treatment group.¹ However, these differences did not reach statistical significance but many argued that it might have been the case if the targeted number of patient enrollment was met. Furthermore, in the

COVID-19 positive status, the bleeding risk might be even increased.^{3,5}

Our case demonstrates such a scenario. The patient had unreachable distal-M2 occlusion and thus was not a candidate for mechanical thrombectomy. The patient's last-known-well state was >4.5 hours (about 5 h) upon presentation and therefore was deemed outside the CT-protocol time-window for intravenous alteplase. However, there was a diffusion/FLAIR mismatch according to the hyperacute-MRI-protocol indicating the pathology was recent and, therefore, intravenous rtPA was given.

This patient was a newly diagnosed COVID-19 patient. His core-infarct size post-rtPA on a repeat-MRI was remarkably less than the penumbra demonstrated on the initial CT-perfusion scans (Figs. 2C–F). In addition, the susceptibility images on that repeat-MRI showed that the thrombus was fragmented and partially moved distally (Figs. 2A, B). There was no associated hemorrhagic conversion.

While intervening for patients with mildly symptomatic LVO strokes (≤ 6) has long been debated, most neurologists do so. A decline in the admission-to-discharge NIHSS was suggested as a marker of good outcomes. Worse outcomes were associated with unchanged-NIHSS.⁶ Our case improved after the intervention. It might not have been the case if such intervention was not administered, especially; in the setting of a fragmented clot.

Our patient had normal D-dimers as well as other coagulation profile. Elevated D-dimer at presentation was predictive of coagulopathy-associated complications during COVID-19. It

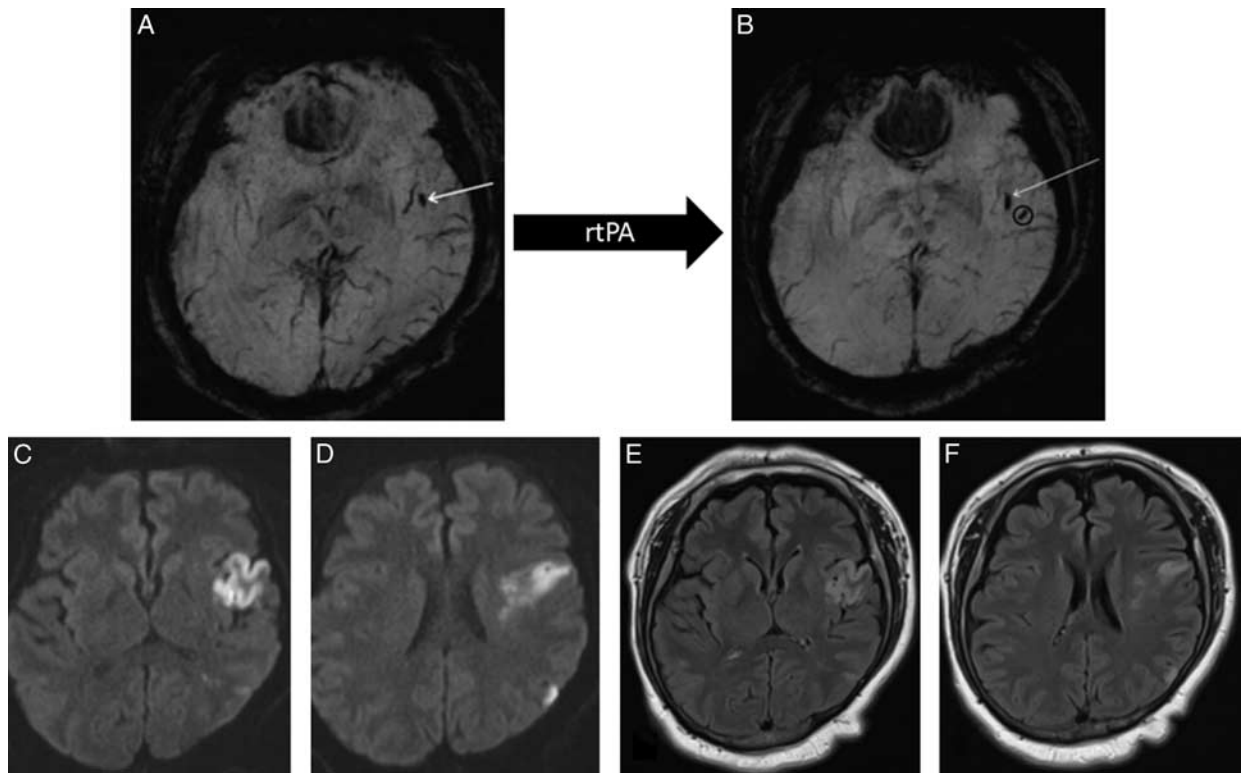


FIGURE 2. (A) Initial SWI shows a clot in the distal-M2 superior division branch (white arrow). (B) Post-recombinant tissue plasminogen activator (rtPA) SWI shows a fragmented (white arrow) and partially displaced clot distally (black circle). (C–F) Follow-up 24-hour post-rtPA MRI shows a DWI/FLAIR matched infarct of 6.9 mL in the left-MCA territory. DWI indicates diffusion weighted imaging; FLAIR, fluid attenuated inversion recovery; MCA, middle cerebral artery; MRI, magnetic resonance imaging; SWI, susceptibility weighted imaging.

had an average odds ratio of 6.79 for thrombosis and an adjusted odds ratio of 3.56 for bleeding. However, coagulopathic events have occurred with normal D-dimers (26% of thrombotic events and 42% of bleeding events). Other markers for thrombosis include elevated platelet count $\geq 450,000/\mu\text{L}$, elevated C-reactive protein $\geq 100 \text{ mg/L}$, elevated erythrocyte sedimentation rate $\geq 40 \text{ mm/h}$ (adjusted OR, 3.56, 2.71, and 2.64, respectively). Our patient had an elevated platelet count. It is important to note that platelets are inflammatory markers and might not be specific. Other markers associated with bleeding included those of disseminated intravascular coagulopathy, thrombocytopenia, and reduced fibrinogen levels.² Our patient had low fibrinogen levels (105 mg/dL). However, the fibrinogen level was checked 74 hours after administering rtPA. rtPA is known to lower the fibrinogen levels, however; that effect usually lasts no longer than 24-hours. Furthermore, there is evidence in the literature that there are increased incidence of bleeding when fibrinogen is $< 200 \text{ mg/dL}$ after administering rtPA.⁷ Our patient did not bleed despite the low fibrinogen level.

Limitations

Several factors should be considered as bleeding risk factors when administering intravenous rtPA that were not present in our case. These include older patients, having thrombocytopenia, liver disease, other coexisting cause of

coagulopathy, or being on dual antiplatelet therapy. Therefore, we encourage neurologists to evaluate each clinical scenario on case by case basis until a formal study in that regard is conducted.

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