Title: **Rescue extracranial-intracranial bypass for ischemic stroke secondary to progressive human immunodeficiency virus-associated vasculopathy**

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Abstract

Background: Human immunodeficiency virus (HIV)-associated vasculopathy can cause ischemic cerebral stroke; however, there is limited evidence on optimal management. Herein, we report a case of acute ischemic stroke due to progressive internal carotid artery (ICA) stenosis in an HIV-positive patient. Superficial temporal artery to middle cerebral artery (STA-MCA) bypass, in addition to the best medical treatments, prevented stroke progression.

Clinical Description: A 39-year-old man with HIV infection presented with a sudden onset of aphasia and right hemiparesis. Magnetic resonance imaging revealed an ischemic lesion in the left basal ganglia and concentric thickening of the vessel wall in the terminal portion of the bilateral ICAs. Despite maximal medical treatments for HIV-associated vasculopathy and possible opportunistic infections, bilateral ICA stenoses progressed, leading to a second hemodynamic stroke event. Because tissue plasminogen activator treatment failed, we performed STA-MCA bypass. A significant improvement in neurological symptoms and cerebral blood flow was observed after surgery. No further stroke events occurred during the continuation of medical treatments.

Conclusion: This is the first case of STA-MCA bypass performed in a patient with recurrent ischemic stroke caused by HIV-associated vasculopathy. Although further evidence is needed, such treatment options can shed new light on the management of progressive HIV-associated vasculopathy, which is refractory to maximal medical treatment.

Keywords: acquired immunodeficiency syndrome; AIDS; EC-IC bypass; STA-MCA bypass; Vessel wall magnetic resonance imaging

Introduction

Human immunodeficiency virus (HIV) infection is an important risk factor for cerebral stroke.[1,2] Atherogenic metabolic syndromes are frequently seen in HIV-infected patients, possibly due to inflammation and/or the side effects of antiretroviral therapy (ART). Additionally, HIV infection can cause pathological changes in the cerebral arteries directly or indirectly (e.g., opportunistic infection-related vasculitis). HIV-associated vasculopathy, encompassing HIV-associated vasculitis and nonatherosclerotic vasculopathy, can cause aneurysmal dilation or occlusive disease of the cerebral arteries through inflammation-induced vessel wall remodeling.

Although recent studies have shown that intravenous tissue plasminogen activator (t-PA) can be administered safely for acute ischemic stroke in HIV-infected patients,[3,4] knowledge regarding the optimal treatment of HIV-related stroke is limited. Herein, we report a case of repeat ischemic stroke due to progressive internal carotid artery (ICA) stenosis in an HIV-positive patient. Superficial temporal artery (STA) to middle cerebral artery (MCA) bypass as a rescue treatment, along with other medical treatments, successfully prevented further stroke progression.

Case description

A 39-year-old man with a history of pneumocystis pneumonia, tertiary syphilis, and non-Hodgkin lymphoma who was diagnosed with HIV infection and acquired immunodeficiency syndrome four years prior was studied. He was started on ART (abacavir, lamivudine, and dolutegravir) post-diagnosis; however, he had ceased ART voluntarily two years before admission.

He presented with mild aphasia and right hemiparesis and was admitted to our hospital seven days after onset. Laboratory test results were as follows: white blood cell count, 3400/μL; hemoglobin, 13.0 g/dL; platelets, 13.9×10^4 /μL; CD4-positive cell count, 22/μL; and HIV-RNA, 551000 copies/mL. Serum rapid plasma reagin (RPR), *T. pallidum* hemagglutination (TPLA) tests were positive (serum RPR, 3764.9 RU; serum TPLA, 3921.8 RU). Cerebrospinal fluid (CSF) examination showed

lymphocytic pleocytosis (20/μL, 90% lymphocytes), an increased protein level (163 g/dL), and a decreased glucose level (33 mg/dL). CSF RPR and TPLA were positive (CSF PRP, 213.6 RU; CSF TPLA, 243.12 COI). Polymerase chain reaction (PCR) assays of CSF were positive for varicella zoster virus (VZV) and cytomegalovirus (CMV). Magnetic resonance imaging (MRI) revealed an acute ischemic lesion in the left basal ganglia. MR angiography revealed stenotic changes in the bilateral terminal portion of the ICAs. Vessel wall MRI (VW-MRI) revealed gadolinium-enhanced concentric thickening of the vessel wall in the left terminal portion of the ICA (**Figure 1**).

Opportunistic infection-related vasculitis and/or HIV-associated vasculopathy were suspected to cause ICA lesions. ART; antiviral, antibacterial, and antifungal agents; and aspirin (100 mg/day) were started (details are summarized in **Figure 2**). Although CSF PCR was negative for VZV and CMV in two weeks, follow-up MRI showed progressive stenosis of the bilateral ICA with vessel wall thickening, leading to cerebral blood flow (CBF) reduction in the left MCA territory (**Figure 3**). Steroid pulse therapy (methylprednisolone 1 g/day) was administered; however, on the 56th day of admission, aphasia and right hemiparesis (National Institutes of Health Stroke Scale [NIHSS] score of 7) were noted. Although diffusion-weighted imaging (DWI) did not show a new hyperintense lesion, the left ICA was nearly occluded (**Figure 3 F, G**). Intravenous t-PA (0.6 mg/kg) was administered, and symptoms slightly improved 12 hours after t-PA therapy; however, symptoms exacerbated (NIHSS score of 9) during the following eight hours. DWI showed new scattered lesions in the watershed territory of the MCA with a reduction in CBF on the arterial spin labeling sequence. Computed tomography angiography confirmed severe left ICA stenosis (**Figure 4 A-C**).

The patient was offered the option of surgery and consented. Therefore, we performed STA-MCA bypass 24 hours after onset (**Figure 4 D-H**). Pre- and intra-operatively, we maintained a systolic blood pressure >120 mmHg until the anastomosis was completed to avoid stroke progression. No abnormal findings in either the recipient or donor arteries were observed, and craniotomy site CSF was also normal. Postoperatively, the systolic blood pressure was maintained at <120 mmHg to prevent

hyperperfusion syndrome. Antiplatelet therapy (aspirin was changed to cilostazol 200 mg/day) was re-started 24 hours after the surgery. The patient recovered with no neurological deficit (NIHSS score of zero) three days post-surgery. Although follow-up VW-MRI revealed further progression of the bilateral stenotic lesion until the 75th day, no new ischemic lesions or neurological symptoms had occurred (**Figure 5**). Medical treatments, including second steroid pulse therapy, were continued. He was discharged on the 98th day because stenotic lesion progression had stopped. His clinical status remained stable in the subsequent 17-month period (**Figure 5**).

Discussion

We, for the first time, described a successful experience of STA-MCA bypass in a patient with acute stroke secondary to progressive ICA stenosis caused by HIV-associated vasculopathy. Little evidence is available regarding its management. Although immunosuppression with corticosteroids,[5] ART,[6] and t-PA therapy[3,4,7,8] have been conducted previously, the effectiveness of these therapies in acute stroke remains unknown.

Endovascular revascularization is a possible treatment option. Almandoz et al. reported successful endovascular therapy for HIV-associated vasculopathy. Their three cases were all aneurysmal dilation rather than stenotic lesions.[9] Pillay et al. reported their experience with endovascular therapy for large-vessel HIV-related vasculopathy.[10] They found that aneurysmal and occlusive disease were associated with good and poor outcomes, respectively. They speculated that diffuse arterial wall disease, immune status, and coagulopathies under an HIV-infection background were possible explanations for these poor outcomes. Considering the vulnerable histological structure of the intracranial artery, endovascular treatment should be considered. Endovascular means are generally not recommended in moyamoya vasculopathy, which also causes stenosis in the terminal portion of the ICA.[11]

Contrastingly, an extracranial-intracranial bypass procedure can be performed without direct

manipulation of the inflammatory site if the stenotic site is in the proximal arteries, such as moyamoya vasculopathy, as anastomosis can be performed at the distal MCA. Our operative findings suggest no abnormal findings in either the recipient or donor arteries. Although open surgery is disadvantageous in its invasiveness, a recent study showed an excellent result of coronary artery bypass grafting even in HIV-infected patients.[12] Adequate management of the immunosuppressive state might be mandatory before open surgical procedures.

Regarding extracranial-intracranial bypass in acute or progressive stroke, excellent results were shown with carefully chosen surgical candidates.[13,14] A recent pooled analysis of 117 patients showed that transient complication (including hyperperfusion syndrome), minor complication (including asymptomatic infarction growth and minor hemorrhage), and major complication (including graft occlusion and major hemorrhage) were occurred only in five (4.3%), four (3.4%), and three (2.6%) patients, respectively.[15] Although further evidence is needed, extracranial-intracranial bypass can be an effective option if all the following conditions are met: 1) in-progress stroke despite maximal medical treatment, 2) moderate-to-severe neurological severity, 3) small infarcted core area, and 4) proven low perfusion area.

Conclusion

We report the first successful case of STA-MCA bypass in a patient with stroke secondary to HIV-associated vasculopathy. Such treatment options shed new light on the management of progressive HIV-associated vasculopathy that is refractory to medical treatment.

Abbreviations: HIV = human immunodeficiency virus; STA = superficial temporal artery; MCA = middle cerebral artery; AIDS = acquired immunodeficiency syndrome; ART = antiretroviral therapy; RPR = rapid plasma reagin; TPLA = T. pallidum hemagglutination; CSF = cerebrospinal fluid; CBF = cerebral blood flow; PCR = polymerase chain reaction; VZV = varicella zoster virus; MRI = magnetic

resonance imaging; DWI = diffusion-weighted imaging; FLAIR = fluid-attenuated inversion recovery; magnetic resonance angiography = MRA; internal carotid artery = ICA; vessel wall magnetic resonance imaging = VW-MRI; National Institutes of Health Stroke Scale = NIHSS; combination antiretroviral therapy = cART; arterial spin labeling = ASL; incidence rate ratio = IRR; tissue plasminogen activator = tPA; endovascular treatment = EVT; N-isopropyl-p-[(123)I]-iodoamphetamine single photon emission computed tomography = ^{123}I-IMP SPECT

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Informed consent: Informed consent was obtained from the patient included in the study.

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Figure Captions

Fig. 1

Diffusion-weighted imaging (DWI, **A**) and fluid-attenuated inversion recovery (FLAIR, **B**) on admission show a high-intensity lesion in the left basal ganglia. Magnetic resonance angiography (MRA, **C**) reveals bilateral stenoses of the terminal portion of the internal carotid artery (ICA). Gadolinium-enhanced vessel wall magnetic resonance imaging (VW-MRI, **D**) shows concentric vascular wall enhancement of the left intracranial ICA.

Fig. 2

Time course of medication and laboratory data. The day of admission is set to day zero.

Abbreviations in Fig. 2

3TC, lamivudine; ABC, abacavir; ACV, acyclovir; AZM, azithromycin; BIC, bictegravir; CTRX, ceftriaxone; DTG, dolutegravir; EMB, ethambutol; FLCZ, fluconazole; FTC, emtricitabine; GCV, ganciclovir; HIV, human immunodeficiency virus; INH, isoniazid; MCA, middle cerebral artery; mPSL, methylprednisolone; PCG, penicillin G; PZA, pyrazinamide; RMP, rifabutin; SMZ, sulfamethoxazole; STA, superficial temporal artery; TAF, tenofovir; TMP, trimethoprim; t-PA, tissue plasminogen activator; VGCV, valganciclovir

Fig. 3

Follow-up images until the second stroke event. MRA and VW-MRI on day 8 (**A**, **B**) and 42 (**C**, **D**) show progressive stenoses of bilateral ICAs with Gadolinium-enhanced vessel wall thickening. N-isopropyl-p-[(123)I]-iodoamphetamine single photon emission computed tomography (^{123}I-IMP SPECT, **E**) shows cerebral blood flow (CBF) reduction on left middle cerebral artery (MCA)

territory. MRA and DWI on day 56 (**F**, **G**) show further worsening of left ICA stenosis despite no new hyperintensity lesion.

Fig. 4

Preoperative (day 57) CT angiography (CTA, **A**), DWI-MRI (**B**), and arterial spin labeling MRI (**C**) show severe stenosis of left ICA, increased scattered DWI high intensity spots, and reduced perfusion on left MCA territory.

Intraoperative photograph (**D**) and indocyanine green video angiography (**E**) show the superficial temporal arteries (STA) anastomosed to both the frontal and temporal sides of the MCA branches. No abnormal findings in either recipient or donor arteries are observed intraoperatively.

Postoperative CTA (**F**) and DWI-MRI (**G**) show the patency of the STA-MCA bypass without an increase in ischemic stroke. Postoperative ^{123}I-IMP SPECT (**H**) shows normalized CBF in the left MCA territory.

Fig. 5

Follow-up MRI after STA-MCA bypass surgery. Although MRA and VW-MRI on day 75 (**A**, **B**) shows further worsening of bilateral ICA stenoses with vessel wall enhancement, those on day 97 (**A**, **B**) and 224 (**E**, **F**) show alleviation of vessel wall enhancement.

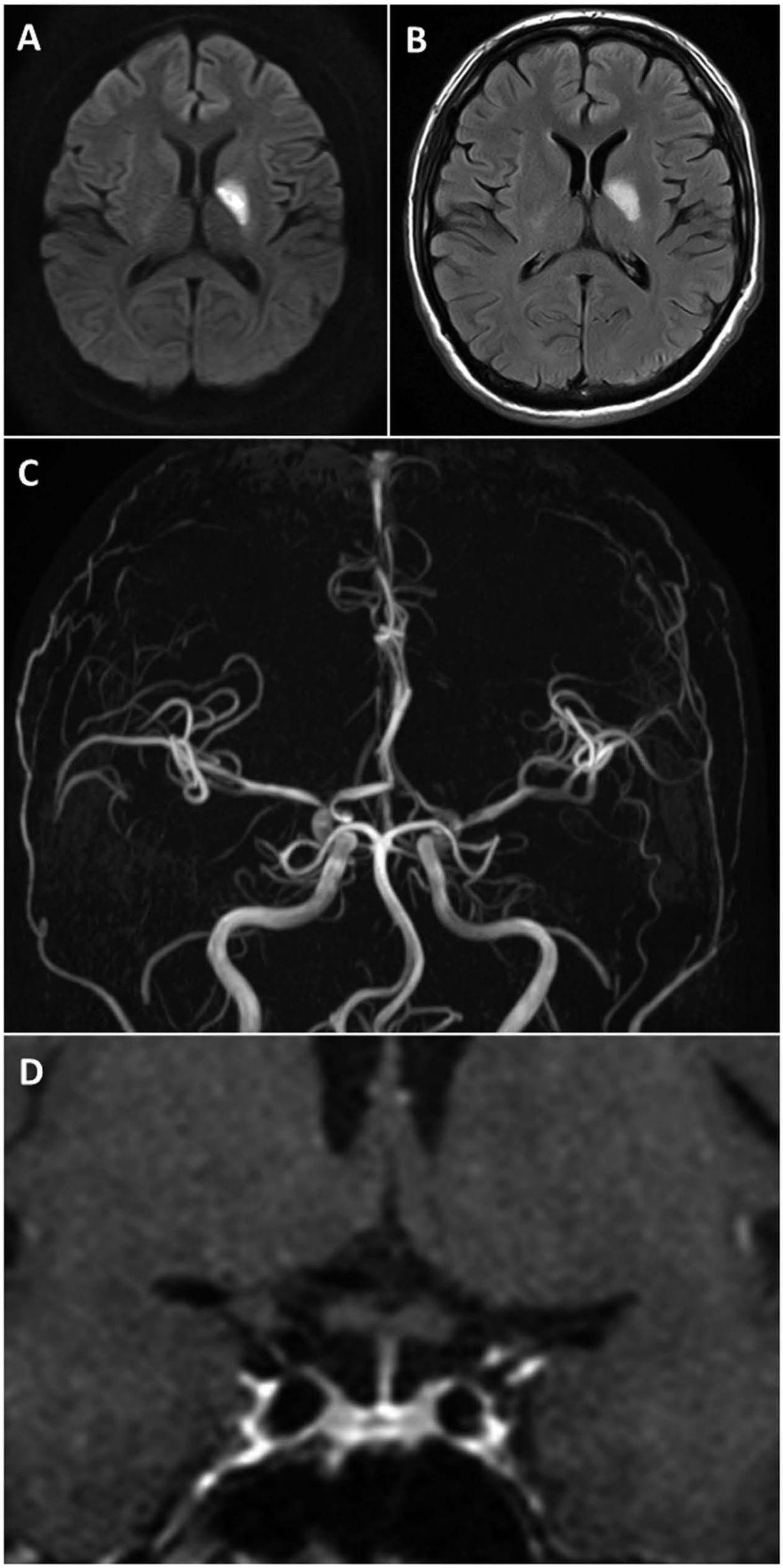
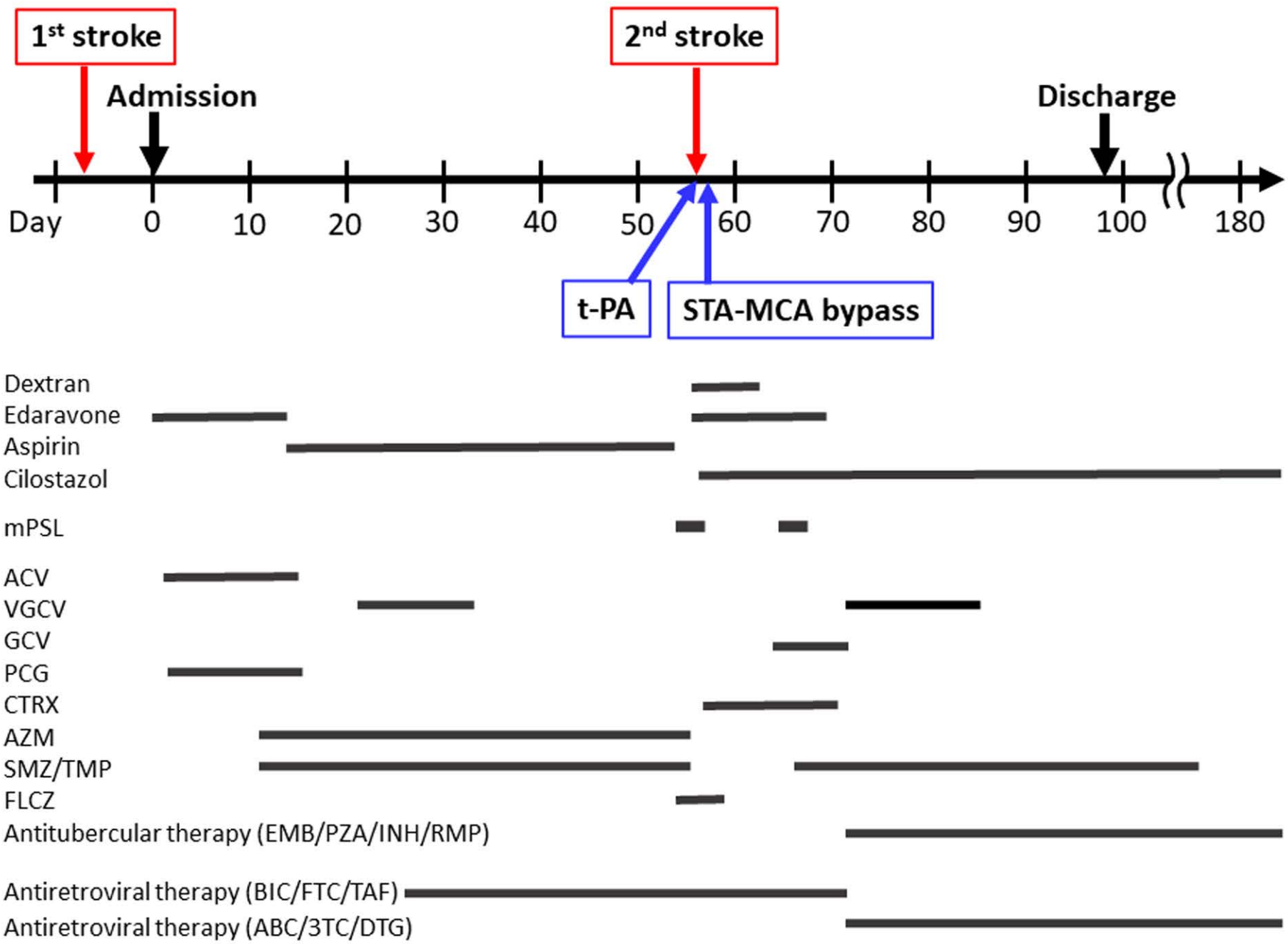
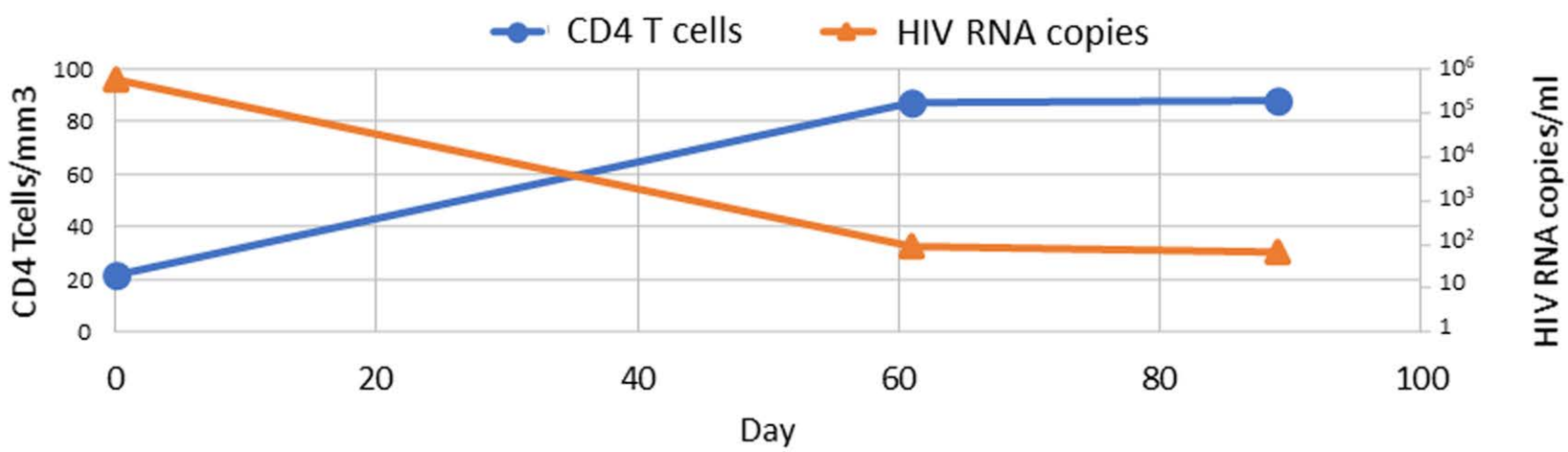


Figure 1


1st stroke
Admission
2nd stroke
Discharge
Day
0
10
20
30
40
50
60
70
80
90
100
180
t-PA
STA-MCA bypass
Dextran
Edaravone
Aspirin
Cilostazol
mPSL
ACV
VGCV
GCV
PCG
CTRX
AZM
SMZ/TMP
FLCZ
Antitubercular therapy (EMB/PZA/INH/RMP)
Antiretroviral therapy (BIC/FTC/TAF)
Antiretroviral therapy (ABC/3TC/DTG)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HIV RNA copies
CD4 Tcells/mm3
HIV RNA copies/ml
Day
0
20
40
60
80
100

Figure 2

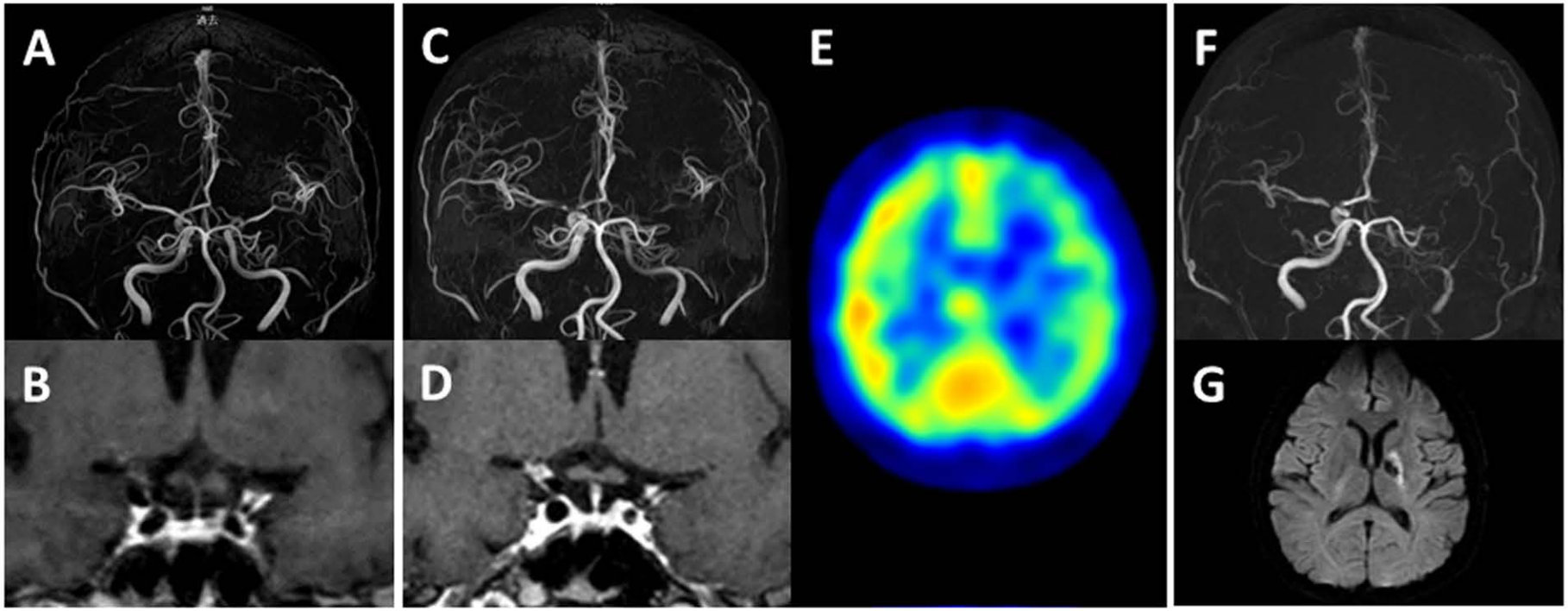

Figure 3

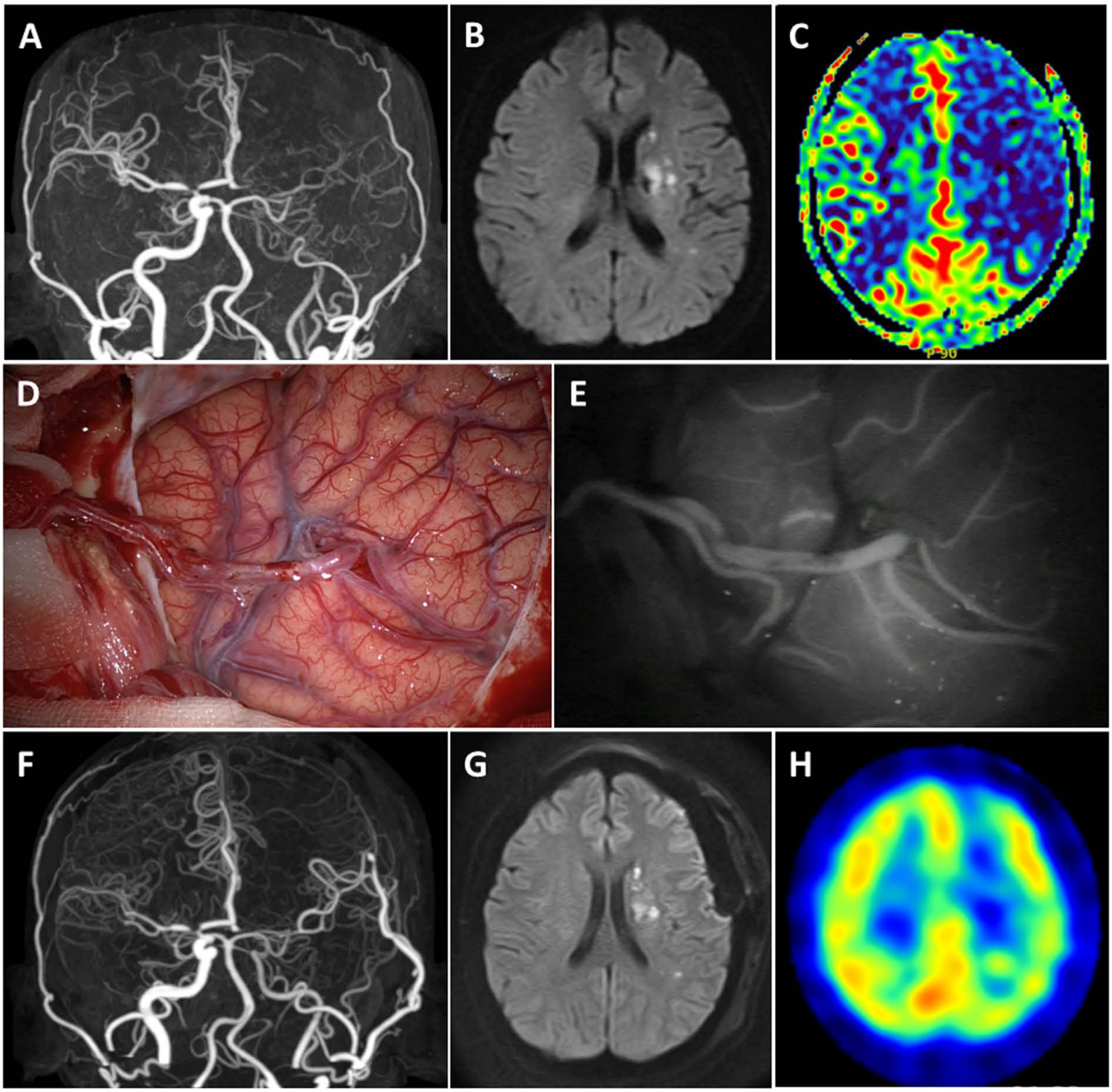

Figure 4

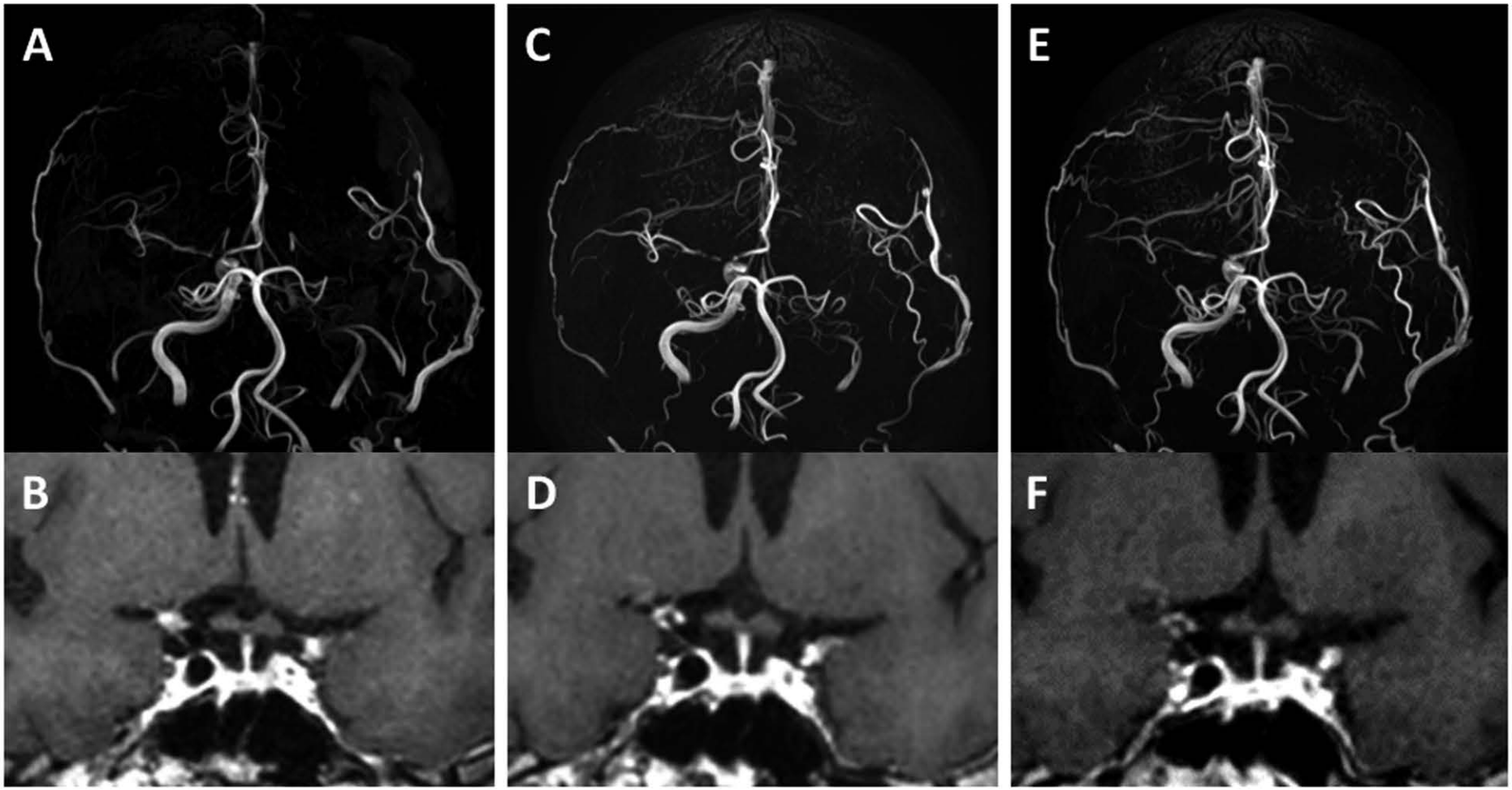

Figure 5