

Asymptomatic Cerebral Aneurysm in Stroke Patients Eligible for Intravenous Thrombolytic Therapy

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Abstract-

Purpose: To report two cases of acute ischemic stroke with anterior communicating artery aneurysm presented to emergency room within 3 hours after onset, and to review the literature.

Case Report: Two cases of previously unreported anterior communicating artery aneurysm were candidates for intravenous thrombolysis for their acute stroke. Recombinant tissue plasminogen activator was eventually withdrawn by other reasons. The aneurysms presented as nodular lesions with slightly increased density just above sellae turcica on non-contrasted computed tomography and were later diagnosed by magnetic resonance angiography.

Conclusion: Asymptomatic cerebral aneurysm could be undiagnosed by non-contrasted computed tomography. Careful reading at selected regions can reduce pitfalls. Computed tomographic angiography and magnetic resonance angiography are alternative screening tools for thrombolysis if available in ER. The composite effect of r-tPA on cerebral aneurysms is still uncertain. A more inclusive definition of cerebral aneurysms and miscellaneous vascular anomalies in current criteria of thrombolysis is recommended.

Key Words: aneurysm, computed tomographic angiography, magnetic resonance angiography, acute stroke, recombinant tissue plasminogen activator, thrombolysis.

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INTRODUCTION

In the limited time window, emergency physicians and neurologists have to decide whether patients of acute ischemic stroke are eligible for intravenous thrombolysis. Current protocols in Taiwan mainly depend on the non-contrast computed tomography (NCCT) to rule out intracranial hemorrhage or anomaly associated with

increased bleeding risk. We report two cases of acute ischemic stroke with anterior communicating artery aneurysm presented to emergency room within 3 hours after ictus.

CASE REPORT

Case 1 is a 78 years old man who was well before

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this event. He had received colectomy for colon cancer 7 years ago. He suddenly became aphasic and right hemiplegic while walking in some day morning in December 2011 and visited the first institution shortly after onset. NCCT showed no hemorrhage. Neurology consultant was not available that day so he was transferred to our hospital. We completed necessary evaluation at 130 minutes. National Institutes of Health Stroke Scale (NIHSS) was 17 points. However, the neurological deficits were improving. The colon cancer was not properly followed and disease activity was not clear. Finally Alteplase was not given, and aspirin 300mg stat with 100mg daily was prescribed. Brain MRI performed next day denoted a wedged parietal cortical infarction, left MCA recanalization, and a previously unreported 8mm aneurysm at anterior communicating artery (Figure 1A). Reread the outside brain CT we found the nodular lesion in the section just above sellae turcica (Figure 1B). The patient became independent and received a successful surgical clipping with oral anticoagulation in the third hospital. Unfortunately he suffered another major embolic stroke at right proximal MCA two weeks after surgery.

Case 2 is a 56 years old woman lived at mountain-side with regular follow up for hypertension, diabetes mellitus and hyperthyroidism. She experienced several

events of atrial flutter, angina, as well as shortness of breath and intolerance to exercise in recent months. In an evening in June 2012, she was found aphasic and right hemiplegic at home and was rapidly brought to the first hospital. Initial brain CT study showed no intracranial hemorrhage. Due to shortage of neurological intensive care she was transferred. The score of NIHSS was 21 at our ER. After gathering all the biochemistry data required and checking the routine list for exclusion, she received Alteplase within 150minutes of stroke onset. However, she suddenly suffered respiratory distress and became cyanotic soon after the injection of 5mg bolus dose, and was intubated immediately. Blood pressure and heart rate showed no obvious change. Bronchodilator and intravenous hydrocortisone were administered, and the Alteplase infusion was withdrawn. Follow-up chest X-ray showed mild pulmonary edema with increased interstitial infiltration. Under ventilator support she became stable and NIHSS score did not change. In intensive care unit, another brain CT performed two days later showed hemorrhagic transformation with midline shift. Antiplatelets and anticoagulants were not prescribed. Brain MRI performed 19 days after onset confirmed the extensive area of infarction and left MCA recanalization. Agenesis of A1 segment of right

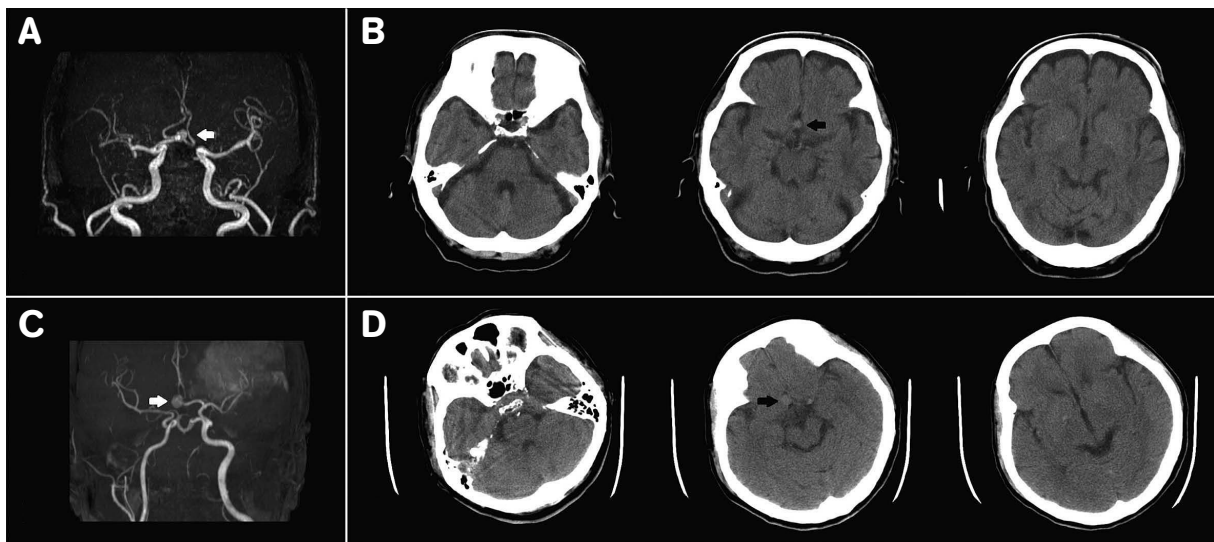


Figure 1. A and C: cerebral magnetic resonance angiography of case 1 and case 2, respectively. B and D: initial outside non-contrasted cerebral computed tomography of case 1 and case 2, respectively. White arrows: anterior communicating artery aneurysms, black arrows: suprasellar nodules with increased density.

anterior cerebral artery, and dysplasia of basilar and bilateral vertebral arteries with the compensating trigeminal artery supplied from left internal carotid artery were depicted on MR angiography (MRA) (Figure 1C). At the same time, a 9mm aneurysm of anterior communicating artery was found. Reappraised the images of two CT series we identified a nodule of slightly increased density at medial base of right frontal lobe (Figure 1D). Her family refused further management for the aneurysm. Her neurological status gradually improved and was successfully discharged. Her modified Rankin scale was 4 during outpatient follow-up 2 months later.

DISCUSSION

Patients with cerebral aneurysm share similar risk factors of atherosclerosis. From 2011 July to 2012 Jun, 64 patients of acute ischemic stroke visited our facility within 3 hours and activated our stroke team. Two of them had cerebral aneurysms (2/64, 3%). Asymptomatic cerebral aneurysms are found in about 3.2% to 6.6% of cases with internal carotid artery stenosis or acute stroke (1,2,24-26).

The presence of cerebral aneurysm is considered contraindicated to intravenous thrombolysis according to current treatment guidelines of acute ischemic stroke (17,28). However, cerebral aneurysms could be overlooked by NCCT if they are clinically silent. An institutional reading paradigm of selected regions, e.g. suprasella, frontal base, peritectum, supracollicus, falx, and sylvian fissure, may reduce pitfalls. Contrast CT scan might surpass plain brain scan in identifying large aneurysms as well as other vascular or neoplastic lesions but is still not recommended for its low test-yield at the expense of delay. On the other hand, multi-slice computed tomographic angiography (CTA) and MRA have a good sensitivity for diagnosing cerebral aneurysms (3,5,6) although the time needed by these studies in emergency room is a major concern. Actually in several studies, multi-model CTA/CTP/CTASI and MRI/MRA have successfully helped to screen eligibility of thrombolysis, with or without joint treatment of intra-arterial (IA) thrombolysis, in patients who visited ER within 3 or 3-6 hours (7-10).

CTA and MRA, with dual advantages, thus have potential for diagnosing aneurysms and stratifying patients with hyperacute ischemic stroke and increasing safety for thrombolysis.

Many protocols, including that of Taiwan Stroke Society (TSS), do not clearly define the contraindication related to cerebral aneurysms. In early safety reports of IV r-tPA treatment (11), the participants were carefully screened by traditional angiography. Later on, the well-known NINDS (12) and ECASS (13) study in 1995 did not clearly include aneurysms or vascular anomalies in the exclusion criteria. ECASS II (14) in 1999 excluded cases with aneurysmal bleeding history but did not mention un-ruptured aneurysm in the exclusion criteria. The STARS study (15) in 2000 used the same criteria of NINDS. PROACT II (16) study in 1999 excluded all intracranial tumors except small meningioma. ATLANTIS (17) study in 1999 was the first study and was followed by SITS-MOST (18) study in 2002-2006 that clearly listed "history of aneurysm, AVM, and neoplasm" in the exclusion criteria. ECASS III (19) study in 2008 listed "other major disorders associated with an increased risk of bleeding" but not strictly "aneurysm and vascular neoplasm" in the exclusion criteria.

The discrepancy of exclusion criteria in different studies makes defining protocol violation difficult. Cerebral aneurysms could be previously diagnosed but untreated; previously diagnosed and treated by clipping or endovascular embolization (20); diagnosed-in-time at ER; or undiagnosed at ER and later found by other imaging modality or ruptured with subarachnoid hemorrhage. Not all the aforementioned situations were properly described in the protocols of major trials and TSS. Different situations may bear different risk of hemorrhage after administration of thrombolytic agents. Strict universal exclusion of all these patients with cerebral aneurysm might prohibit some patients from the benefit of thrombolytic therapy.

We searched PubMed with keywords "cerebral aneurysm" and "thrombolysis". Retrospective cohorts, reviews and case reports were collected. There were limited reports of intravenous (IV) rtPA-related aneurysmal hemorrhage in literature to date (21-24). Lagares et. al.

reported cerebral aneurysm rupture in a case of acute myocardial infarction treated IV r-tPA⁽²¹⁾. Rammos et. al. reported a patient with A-com aneurysm rupture after IV thrombolysis for acute MCA thromboembolism⁽²²⁾. On the other hand, there were several reports describing successful off-label thrombolysis in intracranial aneurysms. In Aleu's review⁽²³⁾, 31 patients of cerebral aneurysm

treated with off-label IV and IA thrombolysis were collected and only 3 of them had subarachnoid hemorrhage. In Mittal's, Kim's and Sheth's retrospective studies (24-26), the hemorrhages in cases received thrombolysis were located at infarct zones and were not caused by rupture of cerebral aneurysms. By summarizing Mittal's, Kim's, and Sheth's cohorts, Rammos' case report, and 9

Table 1. Summary of Mittal's, Kim's, and Sheth's cohorts, Rammos' case report, and 9 articles reviewed in Aleu's review.

| Authors | Case No. | No. of aneus. Hemorrhage | Clinical diagnosis and characteristics | IV or IA/ urokinase or r-tPA | Type of hemorrhage and outcome |
|----------------------------|----------|--------------------------|---|--|--|
| 1 Cronqvist M, 1998. | 19 | 2 | During endovascular treatment of cerebral aneurysm | IA urokinase when fully heparinized, 9 cases also had mechanical clot fragmentation. | Aneurysm rupture in 2 cases, 1 with good recovery. |
| 2 Pelz DM, 1998. | 1 | 0 | During GDC embolization of cerebral aneurysms | IA r-tPA 10 mg 6 hour after embolization. | No. |
| 3 Matsumaru, 1998. | 3 | 1 | Angiographically invisible aneurysms found after attempted fibrinolytic therapy for acute stroke | IV urokinase | 1 aneurysm bled during the procedure with a tragic result. |
| 4 Sahito N, 2000. | 1 | 0 | ICA aneurysm visualized during endovascular treatment of carotid embolism | IA urokinase infusion just aside the large ICA aneurysm. | No. |
| 5 D'Olhaberriague, 2000. | 2 | 0 | Acute ischemic stroke | IV r-tPA | No. |
| 6 Nomura H, 2002. | 1 | 0 | Incidentally detected during thrombolysis for acute stroke | IV urokinase | No. |
| 7 Ritter MA, 2003. | 1 | 1 | Complication of a thrombosed intracranial aneurysm | IA r-tPA | Aneurysm rupture and mortality |
| 8 Fiorella D, 2004. | 2 | 1 | During endovascular treatment of aneurysms | IA | 1 died, 1 with good outcome. |
| 9 Yukihiro, 2009. | 1 | 0 | For acute ischemic stroke | IV r-tPA. | No aneurysmal bleeding |
| 10 Rammos, 2012. | 1 | 1 | For acute ischemic stroke | IV rt-PA | Aneurysm rupture and mortality |
| 11 Mittal, 2012. | 10 | 0 | For acute ischemic stroke (retrospective cohort) | IV rt-PA | No aneurysmal bleeding |
| 12 Kim, 2012. | 8 | 0 | For acute ischemic stroke (retrospective cohort) | IV r-tPA | 3 had ICH at site of infarction. |
| 13 Sheth, 2012. | 8 | 0 | For acute ischemic stroke (retrospective cohort) | IV r-tPA | 1 sICH, no aneurysmal bleed |
| Subtotal: | 58 | 6 | For primary strokes: 35 / for endovascular treatment: 23 | Bleeding in IV tx (2/34); bleeding in IA tx (4/24) | Totally 6 bleeding (6/ 58) |
| Historical risk estimation | | | Aneurysmal bleeding risk in IV or IA thrombolysis for acute ischemic infarction with cerebral aneurysms was 2/35 (5.7%). (Note: A. the 2 bled cases both received IV thrombolysis. B. the outcome of aneurysmal bleeding was poor.) | | |

articles reviewed in Aleu's review, we had the historical risk estimation, that aneurysmal bleeding risk in IV or IA thrombolysis for acute ischemic infarction with cerebral aneurysms was 2/35 (5.7%). The two bled cases both received IV thrombolysis and the outcome was poor with aneurysmal bleeding. (Table 1)

At present, recanalization therapy by mechanical intra-arterial technologies⁽²⁷⁾ may theoretically be an ideal choice for this subgroup of patients. However, it is not universally available. For a cerebral aneurysm identified beforehand, together with extended time window offered by the CTA/MRA study, the pros and cons of IA or IV thrombolytic therapy for an acute proximal occlusion of MCA in the dominant hemisphere warrants attention and further discussion.

Asymptomatic cerebral aneurysm could be undiagnosed by NCCT in acute stroke patients eligible for thrombolytic therapy. Careful reading at selected regions can reduce pitfalls. Non-invasive angiographic studies like multi-model CTA and MRA are alternative tools for screening thrombolysis in ER if they are incorporated well into the flowchart. These studies may at the same time help for detecting silent cerebral aneurysm, guide timely assessment, and increase patient safety. The effect of r-tPA on asymptomatic cerebral aneurysms is still uncertain based on reviewed literatures. A more inclusive and descriptive definition of cerebral aneurysms and miscellaneous vascular anomalies in current criteria of thrombolysis is recommended.

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