Chapter 13
Ischemic Stroke

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Clinical Scenario

An 86-year-old, right-handed Caucasian woman is brought into the Emergency Department (ED) by ambulance as a stroke alert. Her daughter accompanies her and states that she was last seen to be neurologically normal at 11:00 PM the night before when she went to bed. This morning, at 7:30 AM, her daughter found her unable to get out of bed. EMS reported that she had right gaze preference, slurred speech, left facial droop, and left hemiparesis. Immediately upon arrival, she undergoes neurologic evaluation by the vascular neurologist and is found to have a National Institutes of Health Stroke Scale (NIHSS) score of 10. The past medical history includes hypertension and diabetes. Her only home medications are amlodipine and aspirin. Her vital signs and blood pressure are within normal limits.

13.1 History and Neurologic Examination

For this patient who woke with new neurologic deficits, there is concern that she suffered an ischemic stroke during sleep. Acute ischemic stroke (AIS) is a neurologic emergency. It is important that clinicians are able to immediately recognize the signs of acute ischemic stroke and act expeditiously. Each minute brain tissue is deprived of oxygen, an estimated 1.9 million neurons are lost [1]. The mainstays of treatment of acute ischemic stroke are intravenous alteplase (IV-tPA) and

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mechanical thrombectomy; therefore, much of the initial evaluation centers around establishing whether the patient is appropriate for these interventions.

Current guidelines dictate the administration of IV-tPA for adult patients (over age 18) with an ischemic stroke who present within 3 h of symptom onset [2]. Recent studies suggest that tenecteplase (another fibrinolytic agent) may be superior to alteplase for vessel recanalization and non-inferior at 3 months with respect to disability outcome; however, alteplase is the only FDA-approved agent at this time [3]. IV-tPA is also indicated for selecting patients presenting between 3 and 4.5 h after symptom onset who meet certain criteria (age <80, without a history of diabetes mellitus or prior stroke, with NIHSS score <25, not taking oral anticoagulants, and without evidence of ischemia involving greater than 1/3 the territory of the middle cerebral artery) [2, 4]. A series of recent randomized controlled trials have proven definitively the benefit of mechanical thrombectomy for the treatment of this disease (Table 13.1) [5–12]. As few as three patients are needed to undergo this intervention in order to see benefit [13].

All patients who present with signs of acute ischemic stroke should undergo a quick, yet thorough history and neurologic examination that includes the following information:

- *Timing*: It is important to ascertain when the patient was last observed to be at neurologic baseline. For patients who awaken from sleep with new neurologic deficit, the timing of stroke is unclear. In these scenarios, magnetic resonance imaging (MRI) of the brain helps to identify patients who are likely to have had a stroke within 4.5 h and are candidates for fibrinolytic therapy. Diffusion weighted imaging that demonstrates a region of restriction (bright spot) that is not hyperintense (bright) in the same area on fluid attenuated inversion recovery (FLAIR) sequence suggests stroke within the past 4.5 h [14]. Current guidelines, based on a moderate quality of evidence, indicate that MRI can be useful in guiding treatment with IV-tPA [2]. For patients with symptom onset less than 6 h from presentation, noninvasive computed tomography angiography (CTA) or magnetic resonance angiography (MRA) should be performed to identify large vessel occlusions and characterize vascular anatomy prior to mechanical thrombectomy. Patients who present 6–24 h after symptom onset are recommended to undergo perfusion imaging to help quantify the volume of reversible brain tissue injury [2].
- *Neurologic symptoms*: Patients suffering an acute ischemic stroke present with sudden onset of neurologic deficits. Inquire about unilateral weakness or numbness (face, arm, or leg); confusion, difficulty speaking, or understanding; visual changes; gait instability, dizziness, imbalance, or loss of coordination; severe headache, nausea, or vomiting; and changes in level of consciousness. The presence of severe headache, nausea, and emesis suggests the presence of a space-occupying lesion or hydrocephalus, which can often mimic an ischemic event. Stroke scales accurately quantify the extent of neurologic deficit, facilitate communication, and identify patients who are candidates for mechanical thrombectomy and fibrinolytic therapy [2]. The NIHSS is a validated, reliable clinical

Table 13.1 Summary of the major randomized clinical trials that have demonstrated the superiority of mechanical thrombectomy over medical management for ischemic stroke

Trial	Year	Principal finding	Primary outcome measure(s)	Imaging modality for infarct volume
DAWN	2018	Endovascular thrombectomy and standard medical therapy 6–24 h after acute ischemic stroke resulted in better outcomes than medical therapy alone	Score on utility-weighted mRS at 90 days	DW-MRI, CT perfusion
DEFUSE 3	2017	Endovascular thrombectomy and standard medical therapy 6–16 h after acute ischemic stroke resulted in better outcomes than standard medical therapy alone	Score on mRS at 90 days	DW-MRI, CT perfusion
ESCAPE	2015	Endovascular therapy and medical therapy improved outcomes compared to medical therapy alone	Score on mRS at 90 days	CTA, non-contrast CT
MR CLEAN	2015	Intraarterial treatment and standard medical therapy within 6 h of acute ischemic stroke improved outcomes compared to medical therapy alone	Score on mRS at 90 days	CTA, MRA, non-contrast CT
EXTEND IA	2015	After administration of alteplase, endovascular thrombectomy, less than 4.5 after acute ischemic stroke, improved outcomes compared to continued administration of alteplase alone	Reperfusion at 24 h; early neurological improvement (≥8-point reduction on the NIHSS or a score of 0 or 1 on day 3)	CT perfusion
REVASCAT	2015	Endovascular thrombectomy and standard medical therapy within 8 h after acute ischemic stroke improved outcomes compared to standard medical therapy alone	Score on mRS at 90 days	DW-MRI, non-contrast CT
SWIFT PRIME	2015	Endovascular thrombectomy and standard medical therapy within 6 h after acute ischemic stroke improved outcomes compared to standard medical therapy alone	Score on mRS at 90 days	CTA, MRA

Source: Nogueira et al. [5], Albers et al. [6], Goyal et al. [7], Berkhemer et al. [8], Goyal et al. [9], Jovin et al. [10], Saver et al. [11], Campbell et al. [12]

assessment to evaluate stroke patients that helps to determine appropriate treatment and prognosticates [15–19]. Furthermore, the NIHSS is the best predictor of future independence and mortality in ischemic stroke patients [20–23].

- *Laboratory analysis*: Hypoglycemia (<50 mg/dL) is the only laboratory finding that should delay the administration of IV-tPA [2]. Hypoglycemia may cause altered mental status that can mimic stroke. Fortunately, glucose levels are

readily obtained via point of care testing in the emergency setting. Baseline troponins should be measured, and a coagulopathy workup should be obtained. In the absence of suspected coagulopathy, one should not await the results of these tests to administer treatment. However, thrombocytopenia (platelet count <100,000 mm^3), elevated International Normalized Ratio (INR >1.7), prolonged activated partial thromboplastin time (aPTT >40 s), and prolonged prothrombin (PT >15 s) are contraindications to IV-tPA [2, 4].

- *Vital signs*: Vital signs should be measured as part of any evaluation in the emergency setting. Patients who are candidates for fibrinolytic should have blood pressure lowered to a target of 185/110 mmHg prior to administering IV-tPA [2]. Blood pressure goals are more liberal for patients not receiving fibrinolytic therapy when there are no comorbid conditions requiring urgent treatment of hypertension (such as an intracranial hemorrhage). It may be reasonable to lower blood pressure by 15% in the first 24 h for patients presenting with a blood pressure greater than 220/120 mmHg. For patients who present with a blood pressure less than 220/120, treatment of hypertension within the first 48–72 h does not improve outcomes [2].
- *Medical history*: IV-tPA should not be administered to patients who have had a stroke within the past 3 months, severe traumatic brain injury within the past 3 months, intracranial or intraspinal injury within the past 3 months, prior history of intracranial hemorrhage, or gastrointestinal hemorrhage or malignancy within the past 3 months [2, 4].
- *Medications*: Patients who have received therapeutic doses of low molecular weight heparin (LMWH) within 24 h should not receive IV-tPA. Patients receiving direct thrombin inhibitors (IIa) or factor Xa inhibitors should not receive IV-tPA unless coagulopathy has been excluded or the patient is confirmed not to have received the drug for at least 48 h and has normal renal function [2, 4].

Other parts of the history may further help guide treatment. These are largely unique scenarios but can provide invaluable information if recognized and communicated to the neurologic team. For example, patients with a history of peripheral vascular disease may have known arterial occlusions that may necessitate alternative access sites during endovascular thrombectomy. In addition, stroke is a recognized complication of coronary angiography [24]. Onset of neurologic deficit may be recognized before completion of the cardiac catheterization. The presence of an arterial sheath obviates a step for thrombectomy, and may shorten the time to clot removal by the neurointerventionalist.

13.2 Differential Diagnosis

This particular patient is an elderly woman who presents with acute onset of left-sided neurologic symptoms that would be referrable to the right cerebral hemisphere. Right gaze preference suggests dysfunction of the right frontal eye fields.

The left hemiparesis, facial droop, and dysarthria localize to the right primary motor cortex. The left hemibody numbness localizes to the right primary somatosensory cortex. Based on this constellation of findings, she is suspected to have a right middle cerebral artery stroke.

A patient who presents with an atraumatic, rapid-onset neurologic deficit is presumed to have an AIS until proven otherwise. AIS is increasingly common in older patients—the incidence doubling every decade after age 55 [25, 26]. Elderly patients presenting with new onset seizure should also be suspected to have had a stroke, as cerebrovascular disease represents the most common cause of newly acquired epilepsy in this population [27, 28]. When a patient's initial presentation is accompanied by severe headache, nausea, or emesis, one should suspect a hemorrhagic stroke, a space-occupying lesion, or hydrocephalus. Hemorrhagic stroke includes intracerebral hemorrhage (ICH) and subarachnoid hemorrhage (SAH). Primary and secondary brain tumors can present with both neurologic deficits and seizure and should remain on the differential [29].

In the pediatric population, sickle cell anemia is the most common etiology of AIS [30]. Rarely, AIS may have a viral association. There are multiple reports of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)—the virus responsible for the COVID-19 outbreak—in association with acute ischemic stroke [31–34]. Non-structural causes of acute neurologic deficit that may present similarly in the elderly include psychosis, hypoglycemia, migraine headache, meningitis, encephalitis, pneumonia, and urinary tract infection [35–37].

AIS represents 87% of all strokes, whereas ICH and SAH account for 10% and 3%, respectively [25, 26]. It is important to discriminate among AIS, ICH, and SAH as the management varies drastically for these three stroke types. The diagnosis will become apparent on initial cranial imaging.

13.3 Diagnostic Evaluation

The patient in this case scenario underwent a focused history and neurologic examination with documentation of an NIHSS score. A non-contrast CT head was performed, demonstrating no acute intracranial hemorrhage (Fig. 13.1a). Furthermore, the Alberta Stroke Program Early CT Score (ASPECTS) was calculated and found to be greater than six. CTA of the head and neck was performed with advanced imaging. She was found to have right MCA stroke with ischemic penumbra (Fig. 13.1b, c).

Patients suspected of AIS are immediately evaluated by a multidisciplinary team comprised of vascular neurologists, specialized nursing staff, and other personnel. The physician will perform a focused history and physical examination to establish a baseline NIHSS. Labs will be drawn, and the patient will undergo dedicated cranial imaging with subtle variation depending on hospital capabilities and institutional practice patterns.

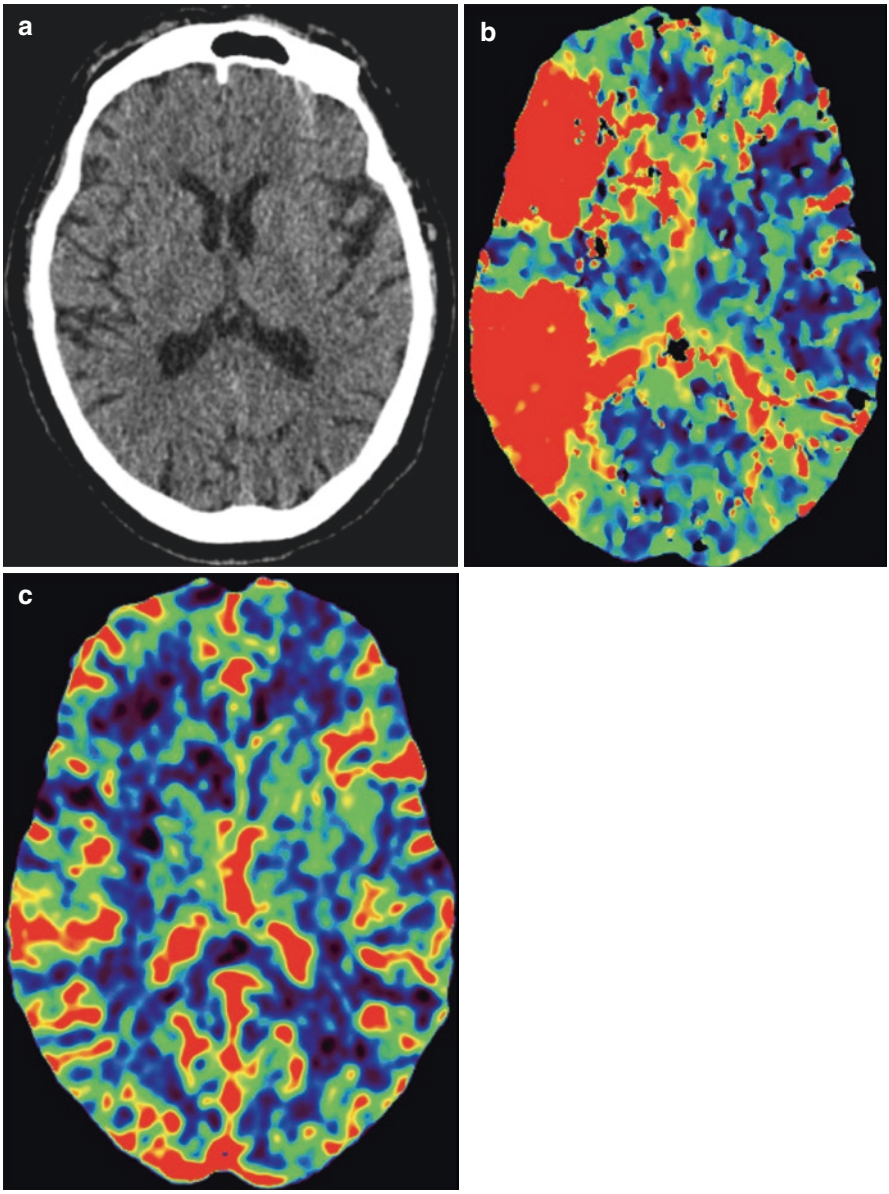

Fig. 13.1 (**a**) Non-contrast CT head demonstrates no evidence of intracranial hemorrhage. (**b**) CT head perfusion sequence demonstrates an increase time to peak in the distribution of the right middle cerebral artery. This is represented as red in the distribution of the right middle cerebral artery. (**c**) CT head perfusion demonstrates preserved blood volume in the right middle cerebral artery. Low blood flow would be represented as dark blue, as is seen in the subcortical white matter under normal physiologic conditions. The finding of increased time to peak in the setting of preserved cerebral blood volume suggests the presence of an ischemic penumbra

A non-contrast CT head is mandatory. This will indicate the presence of an intracranial hemorrhage—which is a direct contraindication for IV-tPA. Furthermore, large volume parenchymal hypodensity is consistent with completed stroke. Fibrinolytic therapy is not indicated in these patients as outcomes are poor, irrespective of treatment. A hyperdense blood vessel noted on CT head often represents the site of vascular occlusion. The non-contrast CT head also allows for calculation of the ASPECTS—a ten-point quantitative score to determine the extent of irreversibly damaged brain in stroke due to middle cerebral artery occlusion (Table 13.2) [38]. The middle cerebral artery territory is divided into ten brain regions, with a point deducted for each region of brain affected by stroke on non-contrast CT head. Current American Heart Association and American Stroke Association guidelines only recommend mechanical thrombectomy for patients with ASPECTS of 6–10 [2]. ASPECTS has high inter-observer reliability, and lower scores predict an increased likelihood of hemorrhagic conversion of infarct, future functional dependence, and mortality [38–41].

Table 13.2 ASPECTS allows for determination of the extent of irreversibly damaged brain tissue in the setting of a middle cerebral artery stroke. The scoring system is based on ten anatomic territories that might be impacted by such a stroke, as documented by the initial non-contrast CT head. Current guidelines recommend mechanical thrombectomy for a score ≥6

Alberta Stroke Program Early CT Score (ASPECTS)		
Structure	Ischemic change (score)	
Caudate	Yes (**−1**)	No (**0**)
Internal capsule	Yes (**−1**)	No (**0**)
Lentiform nucleus	Yes (**−1**)	No (**0**)
Insular ribbon	Yes (**−1**)	No (**0**)
Anterior MCA cortex (M1)	Yes (**−1**)	No (**0**)
MCA cortex lateral to insular ribbon (M2)	Yes (**−1**)	No (**0**)
Posterior MCA cortex (M3)	Yes (**−1**)	No (**0**)
Anterior cortex (M4)	Yes (**−1**)	No (**0**)
Lateral cortex (M5)	Yes (**−1**)	No (**0**)
Posterior cortex (M6)	Yes (**−1**)	No (**0**)

From an initial score of 10, calculate ASPECTS score; scores of ≤7 predict worse functional outcomes at 3 months, based on mRS

Source: Barber et al. [38], https://www.sciencedirect.com/science/article/pii/S0140673600022376?via%3Dihub

Patients should also undergo baseline neurovascular imaging to identify the patency of intracranial and cervical extracranial vessels. CTA can be completed at the time of the initial CT head. If a large vessel occlusion (LVO) is identified, and the patient has salvageable ischemic penumbra, the patient should be expeditiously transported to the angiography suite for mechanical thrombectomy. The decision to proceed to thrombectomy may be based on ASPECTS alone, but advanced perfusion imaging can further delineate the extent of ischemic penumbra. There is significant equipoise among stroke specialists about the utility of advanced imaging, as some physicians feel it may lead to unnecessary delay in vessel recanalization [42]. If a hospital has the capacity to rapidly process imaging to produce a perfusion scan, we feel that this provides excellent information with negligible harm to the patient. However, for patients presenting late—that is, greater than 6 h from last known normal—advanced imaging is recommended; perfusion imaging was obtained per protocol in randomized clinical trials demonstrating the benefit of delayed mechanical thrombectomy [2, 5, 6]. MRA brain, with accompanying DWI sequences, is a reasonable alternative at centers where MRI can be obtained expeditiously.

It is important to image the extracranial circulation as well. Patients may have extracranial cervical or carotid artery occlusions, tandem occlusions, or critical vessel stenosis that would warrant angioplasty or stenting at the time of intervention. Furthermore, imaging of the aortic arch to identify anatomical variants such as bovine arch, arteria lusoria (aberrant origin of the right subclavian artery distal to the left subclavian artery), or an anomalous origin of the vertebral artery can be helpful if identified prior to catheter angiography [43–45]. This allows for the interventionalist to best plan the operative approach to maximize the likelihood of successful, quick recanalization.

13.4 Clinical Decision-Making and Next Steps

In the present case, the patient was noted to have a right gaze preference. Right gaze preference with left hemibody deficits should cue the examiner to a large vessel occlusion. Specifically, such a constellation of neurologic deficits must encompass a sufficiently large vascular territory to affect the frontal eye fields (gaze preference), motor cortex or its fibers (motor deficits and dysarthric speech), and somatosensory cortex or its fibers (hemibody numbness or neglect). She was found to have an MCA stroke with ischemic penumbra on CTA perfusion (Fig. 13.1b, c). Her blood pressure was within normal limits; however, as a “wake up” stroke with uncertain timing of symptom onset, she was not a candidate for intravenous fibrinolytic therapy. The patient was immediately brought to the angiography suite for mechanical thrombectomy. We did not pursue MR imaging to assess candidacy for IV-tPA, as this would result in delay of mechanical thrombectomy. The America Heart Association and American Stroke Association provide guidelines to help with clinical decision-making in this setting (Table 13.3).

Table 13.3 Current guideline recommendations from the 2019 American Heart Association/American Stroke Association for mechanical thrombectomy in ischemic stroke

American Heart Association and American Stroke Association guidelines for mechanical thrombectomy for patients 0–6 h after acute ischemic stroke		
Recommendation	**SOR**	**SOE**
1. Patients should undergo mechanical thrombectomy with a stent retriever if they meet all the following criteria: (A) patient has a prestroke mRS score of ≤1; (B) the causative occlusion is of the ICA or MCA segment 1; (C) the patient is ≥18 years; (D) NIHSS score of ≥6; (E) ASPECTS of ≥6; and (F) treatment can be initiated ≤6 h of symptom onset.	Strong	Meta-analyses of high-quality RCTs
2. Although the benefits are uncertain, the use of mechanical thrombectomy with stent retrievers may be reasonable for select patients with acute ischemic stroke caused by occlusion of the MCA segment 2 or MCA segment 3 if treatment can be initiated ≤6 h of symptom onset.	Weak	Randomized
3. Although the benefits are uncertain, the use of mechanical thrombectomy with stent retrievers may be reasonable for patients with acute ischemic stroke caused by occlusion of the ICA or MCA segment 1 and have a prestroke mRS score >1, NIHSS score <6, or ASPECTS <6 if treatment can be initiated ≤6 h of symptom onset.	Weak	Randomized
4. Although the benefits are uncertain, the use of mechanical thrombectomy with stent retrievers may be reasonable for select patients with acute ischemic stroke caused by occlusion of the vertebral arteries, basilar artery, PCA, or ACA.	Weak	Limited data
American Heart Association and American Stroke Association guidelines for mechanical thrombectomy for patients 6–24 h after acute ischemic stroke		
Recommendation	**COR**	**LOE of QOE**
1. In patients with acute ischemic stroke who are 6–16 h from last known normal and have a large vessel occlusion in the anterior circulation and meet other DAWN or DEFUSE 3 eligibility criteria, mechanical thrombectomy is recommended.	Strong	Meta-analyses of high-quality RCTs
2. In select patients with acute ischemic stroke who are 16–24 h from last known normal and have a large vessel occlusion in the anterior circulation and meet other DAWN eligibility criteria, mechanical thrombectomy is reasonable.	Moderate	Randomized

SOR strength of recommendation, *SOE* strength of evidence, *mRS* modified Rankin Scale, *ICA* internal carotid artery, *MCA* middle cerebral artery, *NIHSS* National Institute of Health Stroke Scale, *ASPECTS* Alberta Stroke Program Early Computed Tomography Score, *PCA* posterior cerebral artery, *ACA* anterior cerebral artery, *COR* class of recommendation, *LOE of QOE* levels of evidence vs. quality of evidence
Source: Powers et al. [2]

Once in the angiography suite, the neurointerventionalist must first determine the optimal site for arterial access. The femoral artery is most common, but transradial access for ischemic stroke is becoming increasingly popular [46–48]. For a basilar occlusion with a dominant right vertebral artery, a right transradial approach may be ideal. In addition, a right transradial approach may be preferable for patients with a bovine arch and a left anterior circulation stroke. A basilar

occlusion with a dominant left vertebral artery can be approached through a left transradial or a transfemoral approach. An arteria lusoria represents a contraindication for a right transradial approach. The use of ultrasound for radial artery catheterization has been demonstrated to increase the catheterization success rate in randomized controlled trials and is recommended as an adjunct for all transradial interventions [49]. Ultrasound also allows the surgeon to identify patients in which the ulnar artery provides the dominant perfusion of the distal extremity. In these patients, ulnar access is preferable and is a safe alternative to radial access [50].

Next, it is important to identify the presence of any tandem lesions on preoperative vascular imaging. When confronted with both an intracranial occlusion and an extracranial high-grade stenosis or occlusion, one must decide which lesion to address first. Tandem lesions are estimated to occur in 10–20% of LVOs [51]. No definitive data exist extolling the comparative benefit of treating intracranial or extracranial disease first [52–56]. The first priority is revascularization of the intracranial circulation to save brain tissue at risk. Therefore, we favor addressing the intracranial pathology first whenever possible. Once the patient has confirmed revascularization, we aim to increase cerebral perfusion by addressing flow-limiting extracranial stenosis and reduce the risk of future atheroembolic events by performing balloon angioplasty—with or without stenting. Prior to placing an extracranial stent, consideration should be given to administering dual antiplatelet therapy.

For this patient, CTA of the neck demonstrated occlusion of the right subclavian artery. She did not have any tandem lesions. She underwent right transfemoral angiography for her planned thrombectomy. Angiography confirmed occlusion of the right middle cerebral artery (Fig. 13.2a, b). She underwent mechanical thrombectomy with complete revascularization (Fig. 13.2c, d). Postoperatively, she was transferred to the neuromedicine intensive care unit. On postoperative examination, her NIHSS score was 0. She was discharged home on postoperative day 2, neurologically intact.

13.5 Clinical Pearls

- Any patient who presents with sudden onset of atraumatic neurologic deficit should be suspected of having an acute ischemic stroke until proven otherwise.
- Non-contrast CT head should be performed on all patients suspected of acute ischemic stroke to rule out the presence of intracranial hemorrhage.
- Mechanical thrombectomy has revolutionized stroke care with a number needed to treat as low as three patients.
- Time is brain! Stroke triage must be quick and efficient to minimize time to revascularization.

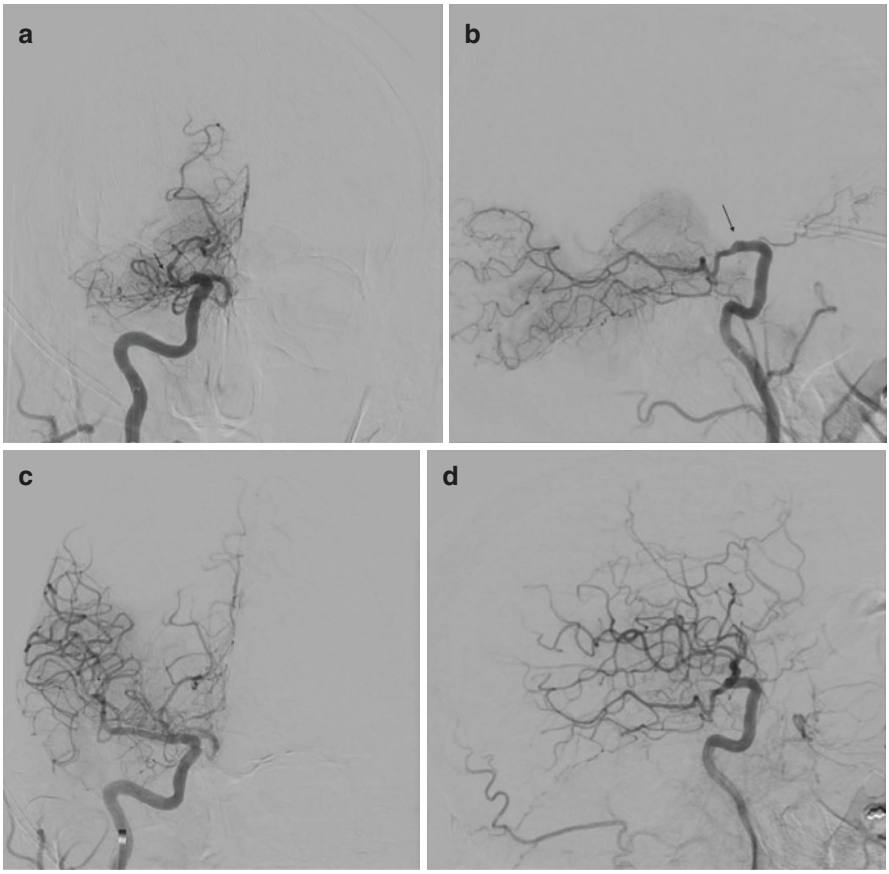

Fig. 13.2 (**a**, **b**) Right internal carotid artery anteroposterior (**a**) and lateral (**b**) injections demonstrate occlusion (arrows) of the right middle cerebral artery. (**c**, **d**) After mechanical thrombectomy is performed, repeat anteroposterior (**c**) and lateral (**d**) right internal carotid artery injections demonstrate revascularization of the occluded middle cerebral artery

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