Intracranial Aneurysms and Vasospasm: Evidence-Based Diagnosis and Treatment

14

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Contents

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Key Points

- DSA remains the most accurate method of intracranial aneurysm diagnosis, although recent technological advances in CTA have led to almost equivalent diagnostic performance (strong evidence).
- If a patient has a classic clinical presentation and CT pattern of perimesencephalic hemorrhage, DSA may not be indicated if the initial CT angiogram is negative for aneurysm (limited evidence).
- Regarding ruptured cerebral aneurysms that can be treated by both endovascular and surgical techniques, endovascular coiling results in lower morbidity at 1 year and lower mortality at 5 years after treatment, despite a slightly higher re-hemorrhage rate (strong evidence).
- Regarding unruptured cerebral aneurysms, there is insufficient evidence to recommend a standard method of management. Such aneurysms should be managed on a case-by-case basis with the estimated risks of treatment carefully weighed against the risk of rupture (insufficient evidence).
- Compared to DSA, TCD is an accurate method for diagnosis of MCA vasospasm with a diagnostic performance of approximately 80 %. CTA is more accurate than TCD, with a diagnostic performance of 98 % (moderate evidence).
- There is insufficient evidence regarding the diagnostic accuracy of MRA, MRP, and CTP for vasospasm diagnosis, although preliminary studies have shown some promising results (insufficient evidence).
- Nimodipine and magnesium are beneficial for preventing delayed cerebral ischemia when used prophylactically in aneurysmal subarachnoid hemorrhage (A-SAH) patients, although there are conflicting reports about the benefits of treatment with hydroxymethylglutaryl coenzyme A reductase inhibitors (statins) (strong evidence).
- There is insufficient evidence that "Triple H" therapy improves patient outcomes, although there is limited evidence that the hypertension component of the "Triple H" treatment increases cerebral blood flow (CBF) (insufficient evidence).
- Papaverine infusion and balloon angioplasty are effective treatments for vasospasm and have been shown to result in clinical improvement, although there are no prospective randomized clinical trials to show an effect on patient outcomes (moderate evidence).
- Intra-arterial infusion of vasodilatory medications, such as verapamil and other calcium channel blockers, appears to be effective for the treatment of vasospasm, although their utility is not established in randomized controlled studies (insufficient evidence).

Definition and Pathophysiology

An aneurysm is an abnormal dilatation of an artery that can be saccular or fusiform in shape. Although the pathophysiology of cerebral aneurysm formation is incompletely understood, aneurysm formation is thought to be the result of a complex cascade involving hemodynamic stress, abnormal vascular remodeling, and inflammation [1, 2]. Risk factors for aneurysms include a personal or family history of aneurysms and/or subarachnoid hemorrhage (SAH), autosomal dominant polycystic kidney disease, type IV Ehlers-Danlos syndrome, Marfan syndrome, fibromuscular dysplasia, alpha-1-antitrypsin deficiency, the presence of an arteriovenous malformation, abdominal aortic aneurysms, atherosclerosis, and sickle cell disease. Risk factors for subarachnoid hemorrhage include family history, cigarette smoking, hypertension, alcohol consumption (>2 drinks per day), non-white ethnicity, cocaine use, and/or the use of sympathomimetic drugs [3, 4].

Patients with A-SAH who survive the initial hemorrhage should be treated by endovascular coiling or surgical clipping of the ruptured aneurysm in order to prevent re-bleeding. In the post-hemorrhage period, A-SAH patients are prone to developing both cerebral vasospasm and delayed cerebral ischemia (DCI), the pathophysiology of

which is also not completely understood. The term "cerebral vasospasm" is commonly used to refer to both the clinical findings of delayed onset of neurologic deficits and the narrowing of cerebral vessels documented by imaging studies. However, such a definition does not account for the fact that many patients do not necessarily exhibit both clinical and imaging findings of vasospasm. Recently, an expert opinion recommended that the term vasospasm be reserved for the presence of anatomic arterial narrowing documented on imaging studies [5]. In addition, DCI has been shown to be best defined as the delayed onset of neurological deterioration or the presence of cerebral infarction documented on imaging studies, which is not explained by other causes. Others suggest the diagnosis of DCI be reserved for cases of delayed neurological deterioration or infarction when the cause was felt to be attributable to vasospasm [6].

Epidemiology

The overall prevalence of cerebral aneurysms in the general population is estimated at 2.3 %. Prevalence tends to increase with age, and aneurysms are associated with the risk factors delineated above [7]. A-SAH accounts for 5 % of all strokes in the United States and affects as many as 30,000 Americans each year. The annual incidence of A-SAH varies by country, from 2.0 per 100,000 population in China to 22.5 per 100,000 in Finland [3]. A-SAH has a poor prognosis, with mortality rates as high as 45 % from the initial hemorrhage and significant morbidity among survivors [3]. In patients with A-SAH, cerebral vasospasm, defined as arterial narrowing on DSA, is seen in up to 70 % of patients, although DCI affects approximately 20–30 % of the A-SAH population [6, 8, 9].

Overall Cost to Society

There are few studies that analyze the cost to society of cerebral aneurysms and A-SAH. A German study calculated the total first-year costs of treating and caring for a patient with A-SAH at EUR 38,300 (approximately 54,000 USD) [10]. This amount includes both direct and indirect costs (productivity losses). A British cost of illness analysis estimates health-care costs from aneurysmal SAH to be 23,294 lb sterling 2005 (approximately 41,000 2010 USD), with additional informal care costs of 5800 (approximately 10,300 USD) per patient, and loss of future earnings of 38,600 per patient (men and women, approximately 68,300 USD) [11]. An analysis of cost data from the International Subarachnoid Aneurysm Trial (ISAT) reported that mean total health-care costs for A-SAH patients at 24 months after the initial hemorrhage were approximately pound sterling 28,175 (approximately 45,000 USD) in patients with delayed ischemic neurological deficit and pound sterling 18,805 (approximately 30,000 USD) in patients without delayed ischemic neurological deficit [12]. A recent study on the cost of vasospasm in A-SAH patients concluded that the total inpatient cost was 27 % higher for patients with symptomatic vasospasm ($143,201) compared to those without symptomatic vasospasm ($113,092) [13].

One potentially important variable in the cost of SAH treatment is how critically ill the patient is on arrival. An analysis of poor WFNS grade SAH patients (grades 4 and 5) in the UK in 2001 reported the acute-care cost (including aneurysm evaluation and treatment if performed as well as intensive care costs) for this cohort was approximately 23,000 2010 USD and the cost per life saved was approximately 77,000 USD. Of this cohort, 15 % of patients achieved a favorable outcome, but only 53 % of the patients included in this study underwent treatment of their aneurysm. The rest were managed supportively and all died [14].

Another potentially important variable in the cost of treating SAH is how experienced the health-care providers are in providing care for these critically ill patients. A cost-utility analysis of patients receiving SAH treatment at low-volume (<20 admissions per year) versus high-volume (≥ 20 admissions per year) hospitals found that while costs associated with treatment

were higher at high-volume centers, the gain in QALYs achieved in patients treated at high-volume centers was cost-effective ($10, 548/QALY) [15].

Goals of Imaging

In the setting of a suspected cerebral aneurysm, the first goal of imaging is to diagnose or to confidently exclude the presence of an aneurysm. If an aneurysm is present, the goals of imaging are the precise determination of the aneurysm location, orientation, and size, including neck and dome measurements. It is of critical importance to define the relationship of the aneurysm to the parent vessel and to accurately depict any arterial branches that may arise from the aneurysm. In cases where no aneurysm is detected, other vascular causes of the patient's symptoms must also be excluded, such as arteriovenous malformations, dural arteriovenous fistulae, vasculitis, dissections, or venous obstruction, among others. For A-SAH patients who are suspected of having cerebral vasospasm, the goal of imaging is to accurately, confidently, and quickly diagnose or exclude vasospasm so that proper treatment may be administered without delay.

Methodology

Several MEDLINE searches were performed using PubMed (National Library of Medicine, Bethesda, Maryland) for original research publications discussing (1) the diagnostic performance of CTA compared to DSA for aneurysm diagnosis, (2) the use of CTA in cerebral aneurysm treatment planning, (3) the treatment of ruptured and unruptured cerebral aneurysms, (4) the diagnostic accuracy of noninvasive imaging modalities for vasospasm diagnosis, and (5) the effectiveness of vasospasm treatments. The search covered the dates up to March 2011 and was limited to human studies and the English language literature. The search strategy employed different combinations of the following terms: (1) digital subtraction angiography, (2) CT angiography, (3) MR angiography, (4) cerebral aneurysm, (5) vasospasm, (6) treatment, and (7) accuracy. Additional articles were identified by reviewing the reference lists of the relevant papers. The author performed an initial review of the titles and abstracts of the identified articles followed by review of the full text in articles that were relevant.

Discussion of Issues

Intracranial Aneurysms

Intracranial Aneurysm Diagnosis and Treatment Planning

Summary

DSA continues to remain the most accurate imaging tool in the workup of a suspected intracranial aneurysm, although CTA has nearly equivalent diagnostic performance according to the most recent data. The benefit of the additional information obtained by DSA must be weighed against its risks and costs, as compared with CTA. MRA has the advantages of lack of exposure to ionizing radiation and iodinated contrast material, but its reported diagnostic accuracy is lower than CTA or DSA. CTA or DSA may serve as primary tools in the diagnostic workup of patients suspected of harboring cerebral aneurysms, but it is important for radiologists and clinicians to fully understand the strengths and weaknesses inherent in each modality in order to realize their full potential. In SAH patients with a classic perimesencephalic hemorrhage pattern, there is some initial evidence that DSA may not be indicated if the initial CT angiogram is negative for aneurysm.

Supporting Evidence

Aneurysm Diagnosis DSA and CTA are regarded as the two most accurate methods for cerebral aneurysm diagnosis. Four meta-analyses have been published which compared the accuracy of CTA and DSA in the detection of intracranial aneurysms, and all four have shown that DSA is superior to CTA. A meta-analysis performed by White et al. in 2000 demonstrated

a per-patient sensitivity of 92 % and a per-patient specificity of 94 % of CTA for the detection of both ruptured and unruptured aneurysms compared with cerebral angiography in patients with SAH or symptoms suggesting an aneurysm. CTA had a greater sensitivity of 96 % for detection of aneurysms larger than 3 mm compared to detection of aneurysms 3 mm or smaller (61 % sensitivity) [16]. A meta-analysis by van Gelder et al. in 2003 further studied the accuracy of CT angiography, with the majority of studies performed between 1993 and 1998. Similarly, the articles comprising this meta-analysis used single-detector CT scanners. The per-aneurysm sensitivity of CT angiography in patients with SAH or symptoms suggesting an aneurysm ranged from 53 % for 2-mm aneurysms to 95 % for 7-mm aneurysms compared with DSA or surgery as the reference standards. The overall specificity of CTA was 99 % [17]. A meta-analysis by Chappell et al. in 2003 showed CTA to have a per-patient sensitivity of 93 % and a specificity of 88 % compared to DSA in depicting aneurysms in patients presenting with SAH or symptoms suggesting a cerebral aneurysm [18]. Again, all the studies in this meta-analysis used single-detector row CT scanners. The most recent meta-analysis assessing the diagnostic performance of CTA represents an advance as most of the studies included in the analysis (30 out of 50) used 4 detector scanners and the remainder of the studies utilized 16 or 64 detector CT scanners. This meta-analysis demonstrated a per-patient sensitivity of 98 % and a specificity of 100 % of CTA for the diagnosis of cerebral aneurysms in patients presenting with acute SAH [19]. The reference standard in this study was DSA, surgery, endovascular treatment, or autopsy, a more robust reference standard than DSA alone. Seventy-one patients out of 4,097 total patients had ruptured aneurysms that were not diagnosed by CTA. The majority of these patients harbored small aneurysms of the internal carotid and posterior communicating arteries located near the central skull base, adjacent to bony structures that may interfere with accurate CTA interpretation.

When considering the results of these meta-analyses, it is important to acknowledge their limitations. The studies comprising the meta-analyses were performed on patients with a high prevalence of cerebral aneurysms, a factor that may result in artificially high estimations of sensitivity and specificity. Furthermore, there is the very real potential for publication bias in all four of these meta-analyses, given that smaller studies, and studies with less favorable results, are less likely to be published compared to larger studies which show positive results. Additionally, authors who are publishing studies comparing CTA and DSA likely have significant experience with these modalities, which may not reflect the reality at all sites where these modalities are utilized.

Newer DSA and CTA techniques have the potential to further improve the diagnostic accuracy of both modalities, although there is not yet enough evidence to determine their impact. 3-D rotational angiography has been shown to improve the diagnostic accuracy of DSA in small series of patients [20–22]. Bone subtraction techniques for CTA such as “matched mask bone elimination” and “dual energy methods” have been designed to improve the accuracy of aneurysm detection adjacent to bony structures. Although there have been some relatively small studies which have shown promising results, currently, there is insufficient data to determine the utility of such techniques [23, 24].

MR angiography is a third modality that can be used to diagnose cerebral aneurysms with high diagnostic accuracy. Given the lack of exposure to ionizing radiation and iodinated contrast material, MRA has definite advantages over both DSA and CTA. There is only one systematic review comparing MRA to DSA for cerebral aneurysm diagnosis. That study compiled the results of 38 studies and reported a per-patient sensitivity of 87 % and specificity of 92 % for cerebral aneurysm diagnosis [16]. A prospective, blinded study published after that systematic review compared MRA to DSA for cerebral aneurysm detection and reported a per-patient sensitivity of 74 % and specificity of 94 %, with lower sensitivity and specificity when calculations were made on a per-aneurysm basis as well as for small aneurysms (<5 mm) [25].

MRA has also been used to screen asymptomatic patients for incidental aneurysms. A cost-effectiveness analysis based on a Markov (mathematical) model found screening for asymptomatic aneurysms with MRA to be cost-effective if the annual rate of aneurysm rupture was 2 % but not if the rupture rate was 0.5 % [26]. Sensitivity analysis found the incidence of asymptomatic aneurysm had some impact on the cost-effectiveness ratios, but this was overwhelmed by other factors. A 2010 cost-effectiveness analysis examined this further, modeling screening patients with two first-degree relatives with aneurysm using MRA [27]. This model found screening to be effective and suggested an optimal screening strategy of obtaining MRA every 7 years from ages 20–80.

Treatment Planning As detailed above, there is strong evidence supporting the superior diagnostic performance of DSA compared to CTA for detecting cerebral aneurysms. However, the high diagnostic accuracy of CTA, coupled with its non-invasiveness, has led many to question whether it could potentially serve as a first-line diagnostic modality for A-SAH patients. When considering the use of CTA as a first-line diagnostic modality, it is important to balance the added information obtained from a DSA examination against the risks and costs associated with DSA. Such added information includes detection of additional, unruptured cerebral aneurysms in addition to the culprit aneurysm, as well as better delineation of vessels emanating from the parent vessel or from the aneurysm itself [28]. The most recent meta-analysis on the diagnostic performance of CTA by Westerlaan et al. calculated the sensitivity and specificity of CTA on a per-patient basis, as opposed to a per-aneurysm basis. The authors acknowledge this limitation and state that there is probably value in detecting as many incidental aneurysms as possible, both for treatment planning in the acute setting as well as for follow-up.

Despite the advantages of DSA, several studies have shown that many patients can be triaged for treatment based solely on CTA results, although this remains a subject of controversy, and no strong evidence exists to support a single approach. A few relatively small studies showed that 64- and 16-detector row CTA are useful in the triage of most patients for interventional or surgical treatment of ruptured intracranial aneurysms but that there is a considerable amount of variability and subjectivity among the physicians making these determinations [29–31]. One study showed that in 133/224 patients with acute symptoms of a cerebral aneurysm, CTA was successfully used as a first-line test in treatment planning, with neurosurgical ($n = 55$) or endovascular treatment ($n = 78$) following the CTA examination alone [32]. However, there is no long-term follow-up on these patients, and therefore, the implications of using CTA as a sole first-line method of triage for A-SAH patients are unknown.

In SAH patients with a classic perimesencephalic hemorrhage pattern of hemorrhage, there is some initial evidence that DSA may not be indicated if the initial CTA is negative for an aneurysm. In a retrospective study of 93 patients with a perimesencephalic pattern of hemorrhage, all had negative findings on CTA which were confirmed on DSA [31]. The same study showed that in patients with an aneurysmal pattern of SAH and a negative CTA, DSA is able to diagnose aneurysms and other causes of SAH, such as vasculitis, arterial dissection, or dural arteriovenous malformations not seen on CTA [31]. In SAH patients with an aneurysmal pattern of hemorrhage and no aneurysm seen on the initial CTA and/or DSA, repeat delayed DSA is currently recommended, although there is insufficient evidence to fully support this practice [33–35].

Treatment of Intracranial Aneurysms: Coiling Versus Clipping

Summary

Surgical clipping and endovascular coiling are both viable options for treatment of ruptured and/or unruptured cerebral aneurysms. For ruptured aneurysms that can be treated by endovascular or surgical techniques, endovascular coiling results in lower morbidity at 1-year follow-up and lower mortality at 5-year follow-up, despite a slightly higher re-hemorrhage rate. There is insufficient evidence to recommend a standard method of management for unruptured cerebral

aneurysms. Such aneurysms should be managed on a case-by-case basis with the estimated risks of treatment weighed against the estimated risk of rupture.

Supporting Evidence

In the case of ruptured cerebral aneurysms, the options for treatment include surgical clipping or endovascular coiling, and there is an abundance of strong evidence that both treatments improve patient outcomes by reducing the risk of aneurysm re-bleeding. Several reports have shown favorable results for endovascular coiling [9, 36, 37], although the only large, prospective, randomized trial comparing surgery and endovascular techniques is the International Subarachnoid Aneurysm Trial (ISAT) [38, 39]. In that study, 2143 patients with ruptured intracranial aneurysms were enrolled between 1994 and 2002 at 43 neurosurgical centers and randomly assigned to clipping or coiling. The 1-year rate of death and dependency was significantly lower in the endovascular group compared to the surgical group (23.5 % vs. 30.9 %) [38]. Long-term follow-up (6–14 years) of the ISAT study patients showed that there was a significantly increased risk of re-bleeding from a coiled aneurysm compared with a clipped aneurysm but that the overall risk of death at 5 years was still significantly lower in the coiled group than in the clipped group [39].

There is much controversy in the interpretation of the results of the ISAT trial [40, 41]. Some common criticisms include the fact that 78 % of the eligible participants were excluded from randomization because of their clinical status or their aneurysm angioanatomy, which did not allow for both endovascular coiling and surgical clipping. The increased time to treatment in the surgical group (1.7 days) compared to endovascular group (1.1 day) has also been raised as a potential bias against clipping, as some patients in the surgical group re-bled in the pretreatment period, which contributed to increased morbidity and mortality in that group. Concerns have also been raised regarding the skill of both the surgeons and neurointerventionalists who participated in the ISAT trial and the accuracy of the postal questionnaire to adequately assess clinical status. Since the majority of the ISAT patients were treated in the United Kingdom, questions have been raised regarding the generalizability of the results. Given the increased re-bleeding rate in the coiling group, concerns have also been raised that the benefits of coiling may eventually be diminished over the very long term.

Regarding the treatment of unruptured aneurysms, there have been no randomized comparisons of coiling and clipping, although a large, statewide, retrospective study in California from 1990 to 1998 reported that endovascular treatment was associated with better patient outcomes than surgery. In the context of that study, adverse outcomes were defined as in-hospital death or discharge to a nursing home, and such adverse outcomes were more frequently seen among the 1,699 patients treated with surgery (25 %) compared to the 370 patients treated by endovascular techniques (10 %) [42]. Regardless of treatment method, when considering the treatment of an unruptured cerebral aneurysm, the estimated risk of bleeding must be weighed against the risk of treatment on a case-by-case basis. However, the annual risk of bleeding from an unruptured aneurysm is a controversial topic. Many series and meta-analyses have reported a rate of rupture of between 0.05 % and 2 % per year [43], with more than half of such patients suffering major morbidity or death following rupture [44, 45].

The International Study of Unruptured Intracranial Aneurysms (ISUIA) is the largest and highest-quality study of the natural history of unruptured intracranial aneurysms, involving multiple centers and a total of 4,060 patients throughout the United States, Canada, and Europe [45]. That study showed that aneurysm size and location were reliable predictors of aneurysm rupture, with larger aneurysms and posterior circulation aneurysms associated with increased rates of rupture. Of the patients managed conservatively in this study, 3 % had SAH over the 5-year follow-up. Aneurysms in the anterior circulation measuring less than 7 mm in patients without a personal history of SAH had an extremely low annual rate of rupture

(approximately 0.1 % per year). Aneurysms of similar size and location in patients with a personal history of SAH had a higher rate of rupture (approximately 0.3 % per year). Rupture rates did not differ significantly between patients with and without a personal history of SAH for aneurysms greater than 7 mm in size for any location.

The reported very low rate of rupture of anterior circulation aneurysms <7 mm (0.1 % per year) is a result which has caused much controversy as many claim that such a low value does not seem to be supported by actual practice. Such critics hypothesize that the selection and intervention biases of the ISUIA study may have led to artificially low estimates of rupture rates. Patients in the study who were managed conservatively were evaluated and counseled by neurosurgeons, and a determination was ultimately made that those patients could be managed conservatively, since they were considered to be at low risk for aneurysm rupture. Furthermore, these patients may have been able to modify their risk factors for rupture, thereby decreasing the rupture rate and leading to a falsely low rate of rupture. Such biases raise the possibility that the reported probability of aneurysm rupture in the ISUIA study may indeed be artificially low and not generalizable to all patients.

Given that there is no randomized controlled study comparing conservative management of unruptured aneurysms to interventional or surgical treatments, there is insufficient evidence to recommend a standardized course of action in a given patient. Management decisions for patients with unruptured aneurysms need to be made on a case-by-case basis, with the following considerations taken into account: size and location of the aneurysm, any specific risk factors for rupture, the patient's life expectancy, and the estimated risks associated with treatment [46].

Applicability to Children

The incidence of cerebral aneurysms and subarachnoid hemorrhage in the pediatric age group is extremely low, accounting for 1–2 % of all aneurysm cases with approximately 700 cases described in the literature [47]. Pediatric aneurysms are most commonly located at the internal carotid artery bifurcation (26 %), anterior communicating artery (19 %), middle cerebral artery bifurcation (17 %), and posterior circulation (17 %) [47]. SAH is the most common presentation of pediatric aneurysms, but mortality after SAH is lower than in adults, ranging from 10 % to 20 % [48]. Most children with intracranial aneurysms can be successfully treated with low morbidity and mortality using either surgical or endovascular techniques [49].

Cost-Effectiveness Analysis

Most of the available data shows that coiling is associated with lower total costs and shorter hospital stays when compared with clipping. The largest study performed in the United States to date on this topic is from the University of Florida, where researchers conducted a national analysis using data from the Nationwide Inpatient Sample (NIS) from the Healthcare Cost and Utilization Project for all cases of clipping or coiling of both unruptured and ruptured aneurysms between 2002 and 2006 [50]. A total of 19,034 hospitalizations were included, with approximately half representing ruptured aneurysms and the other half unruptured. For both groups, clipping compared to coiling was associated with a significantly longer hospital stay and significantly higher total hospital charges [50]. An Australian study showed a similar result, with clipping associated with higher total costs compared to coiling [51]. However, a study from the UK examined costs associated with the ISAT patients and showed no significant difference in costs between either treatment modality at 12 and 24 months [52].

Vasospasm

What Are the Respective Diagnostic Performances of TCD, CTA, CTP, MRA, and MRP Compared to DSA for Vasospasm Diagnosis?

Summary

Noninvasive methods of vasospasm diagnosis include clinical examination, TCD, CTA, CTP, MRA, and MRP. Although there is no perfect

method of vasospasm diagnosis, DSA is widely regarded as the current gold standard. At best, there is moderately strong evidence regarding the diagnostic accuracy of the noninvasive modalities mentioned above. According to a meta-analysis of CTA and CTP, the sensitivities and specificities are approximately 80 % and 93 % for CTA and 74 % and 93 % for CTP, respectively [53]. TCD sensitivity and specificity for detection of MCA vasospasm are approximately 67 % and 99 % [54]. There is insufficient data regarding the diagnostic performance of MRA or MRP for vasospasm diagnosis. Regarding vasospasm treatment, there is strong evidence supporting the use of nimodipine in A-SAH patients, although its effects are thought to be related to neuroprotection and not the prevention of angiographic vasospasm. There is preliminary evidence that induced hypertension is effective in increasing CBF, although this is insufficient. There is moderate evidence that papaverine infusion results in short-lived clinical improvement in approximately 40 % of patients treated for vasospasm [55]. However, there is still insufficient evidence regarding the utility of other vasodilatory medications such as verapamil, which are being used more frequently given their lower incidence of adverse reactions compared to papaverine. Balloon angioplasty has been shown to result in clinical improvement in approximately 60 % of patients, although no prospective randomized clinical trials have been performed to show that it ultimately improves patient outcomes [55].

Supporting Evidence

Several diagnostic modalities are commonly utilized in clinical practice for the diagnosis of vasospasm in A-SAH patients. To date, DSA is the most widely accepted gold standard for vasospasm, and other diagnostic modalities such as TCD, CTA, CTP, MRA, and MRP have been compared to it in order to determine their relative diagnostic performances. Regarding the evidence behind CTA and CTP, there is a single meta-analysis published comparing CTA and CTP to DSA for the diagnosis of vasospasm in A-SAH patients [53]. This meta-analysis was limited by the number of relevant studies available for statistical analysis, incomplete data reporting in many of the studies, the high variability in methodology between studies, and the overall high level of heterogeneity of the data. Despite these limitations, this meta-analysis provides the best current estimate of the diagnostic accuracy of CTA and CTP, although the results should be considered preliminary. The estimated pooled sensitivity and specificity of CTA were 79.6 % (95 % CI, 74.9–83.8 %) and 93.1 % (95 % CI, 91.7–94.3 %), respectively, and the estimated pooled sensitivity and specificity of CTP were 74.1 % (95 % CI, 58.7–86.2 %) and 93.0 % (95 % CI, 79.6–98.7 %), respectively [53]. The area under the summary receiver operating characteristic (SROC) curve was 98 $\pm$ 2.0 % for CTA and 97 $\pm$ 3.0 % for CTP [53].

Regarding TCD, a meta-analysis comparing TCD with DSA showed that for the middle cerebral artery (5 trials, 317 tests) and using a velocity threshold of 120 cm/s, the sensitivity was 67 % (95 % CI, 48–87 %), and the specificity was 99 % (95 % CI, 98–100 %). For the anterior cerebral artery (3 trials, 171 tests), sensitivity was 42 % (95 % CI, 11–72 %), and specificity was 76 % (95 %, CI 53–100 %). Data for the meta-analysis was only available from 7 trials, and the authors indicate that most of these data were of low methodological quality [54]. Since that meta-analysis, a number of studies have been performed to further assess the diagnostic performance of TCD compared to DSA for vasospasm diagnosis. A prospective study on TCD diagnosis of MCA vasospasm using DSA as the gold standard demonstrated that the diagnostic accuracy of TCD for moderate-to-severe MCA vasospasm using peak systolic velocity and Lindegaard index was 0.93 and 0.95, respectively. For the diagnosis of mild MCA vasospasm, diagnostic accuracy based on these two parameters was 0.90 and 0.91, respectively [56]. A second prospective study compared TCD and transcranial color sonography (TCCS) using DSA as the reference standard for the diagnosis of MCA vasospasm. The authors of that study reported that the TCD and TCCS accuracy ranged from 76 % to 82 % [57]. A retrospective study of TCCS accuracy compared to DSA concluded that the overall

diagnostic accuracy of TCCS for the diagnosis of MCA vasospasms was 0.8, with ROC analysis indicating that the optimal tradeoff between sensitivity and specificity in diagnosing vasospasm was at a threshold peak systolic velocity of 182 cm/s [58]. Another retrospective study evaluating the accuracy of TCD compared to DSA in predicting angiographic vasospasm demonstrated that in patients with TCD findings positive for vasospasm, the diagnostic odds ratio of detecting vasospasm on angiography was 27 for the ACA territory and 17 for the MCA territory [59].

MRA and MRP have also been studied for their potential role in vasospasm diagnosis. In a small series of 21 patients, Blasel et al. evaluated the accuracy of time-of-flight MR angiography (TOF-MRA) for the diagnosis of vasospasm in A-SAH patients. They report that 44.2 % of maximum intensity projection (MIP) images overestimated the vascular narrowing seen on DSA and therefore conclude that TOF-MRA may not be an appropriate test for vasospasm diagnosis [60]. Another study comparing MRA and DSA for vasospasm diagnosis reported MRA to have a 92 % sensitivity and a 97 % specificity for vasospasm diagnosis, but those results are based upon a definition of vasospasm as >25 % vessel narrowing, thus combining moderate and severe vasospasm patients into a single group [61]. Regarding MRP imaging and vasospasm diagnosis, there are a limited number of small studies in the literature, most of which involve few patients and are retrospective analyses. One prospective study correlating DSA findings with MRP time-to-peak (TTP) values reported significant delays in cerebral circulation time as measured by MRP in patients with vasospasm seen on DSA [62]. A second prospective study in which MRP and DSA were performed about 5 days after onset of SAH reported decreased rCBF and rCBV in patients with SAH and vasospasm, with the decrease in rCBF proportional to the degree of vasospasm [63]. MRP has been shown to be useful for determining the hemodynamic effects of balloon angioplasty in the treatment of vasospasm. A prospective study of 10 patients by Beck et al. reported improvement in MRP parameters after balloon angioplasty treatment for vasospasm [64].

Efficacious Vasospasm Treatments

All A-SAH patients should undergo prophylactic measures to prevent vasospasm and delayed cerebral ischemia. There is strong evidence supporting the use of nimodipine in A-SAH patients, although its effects are thought to be related to neuroprotection and not to the prevention of angiographic vasospasm. Nimodipine antagonizes voltage-gated calcium channels and reduces the entry of calcium into smooth muscle cells and neurons. Several randomized trials have shown that nimodipine has a statistically significant positive effect on outcome in patients with A-SAH [65–71]. A Cochrane database systematic review of calcium antagonists in the setting of A-SAH concluded that calcium antagonists reduce the risk of poor outcome and secondary ischemia after A-SAH and are therefore indicated in these patients [72].

The use of hydroxymethylglutaryl coenzyme A reductase inhibitors (statins) has been shown in some studies to prevent vasospasm in A-SAH patients [73–75]. The randomized controlled studies currently available show that statins do indeed reduce the incidence of delayed cerebral ischemia in A-SAH patients, with a trend toward lower mortality also reported [76]. However, when observational studies are included in the analysis, statins have no statistically significant effect on the incidence of delayed cerebral ischemia in this patient population [76].

Magnesium administration has been shown to have some benefit for preventing vasospasm in A-SAH patients. The largest randomized controlled trial to date showed a 34 % reduction in the risk of delayed ischemic injury in patients receiving magnesium, and a smaller randomized controlled study reported a 29 % decreased risk [77, 78]. A meta-analysis demonstrated that although administration of magnesium reduced the likelihood of a poor

outcome after SAH (death, vegetative state, or dependency), patient mortality was not improved [79].

A systematic review analyzing the potential benefit of prophylactic "Triple H" (hypertension, hypervolemia, and hemodilution) or "hyperdynamic" therapy in A-SAH patients reported an overall paucity of data as well as significant limitations in the design of the available studies which precluded an accurate assessment of the potential benefit of this treatment [80].

A multicenter, randomized clinical trial performed to evaluate the utility of prophylactic balloon angioplasty on cerebral vasospasm and outcome in patients with Fisher grade III SAH showed that balloon angioplasty does not result in improvement in outcome of Fisher grade III A-SAH patients [81].

Patients with vasospasm are typically treated with "Triple H" therapy, intra-arterial infusion of vasodilators, and/or balloon angioplasty. Regarding "Triple H" therapy, there are no randomized clinical trials on the effect of such therapy on patient outcome. A Cochrane systematic review found no sound evidence for the use of volume expansion (hypervolemia) in patients with A-SAH [82]. Likewise, there is no data to support hemodilution in the setting of A-SAH. A systematic review on the effect of "Triple H" therapy on CBF in A-SAH patients concluded that there is no good evidence that such therapy results in an increase in CBF, although induced hypertension is considered the most promising component of "Triple H" therapy [83]. The conclusions of this study are only preliminary given the small sample sizes (4–51 patients per study), the heterogeneity of the interventions and the study populations, and the fact that only 1 of 11 studies was a randomized trial. Despite the lack of strong evidence regarding "Triple H" therapy, one prospective study demonstrated a significantly decreased rate of delayed cerebral ischemia as well as improved patient outcomes for those patients treated after the adoption of hypervolemic hemodilution strategies when compared with A-SAH patients treated prior to the incorporation of such strategies [84].

Selective intra-arterial infusion of vasodilatory medications is also used in the treatment of vasospasm. Papaverine hydrochloride, a derivative of opium, is known to cause arterial dilatation, probably by a phosphodiesterase inhibitory mechanism. The reported success rates of intra-arterial papaverine infusion range widely in the literature. However, a systematic review performed by Hoh et al. in 2005 found that there was overall clinical improvement in 43 % of patients (148/346) [55]. Important limitations of papaverine infusion include its short-lived effect as well as its tendency to increase intracranial pressure. Given these limitations, other intra-arterial vasodilating agents have come into favor more recently, such as verapamil and other calcium channel blockers [85–87]. Although these agents appear to be safer than papaverine, their utility is not established.

An initial study of balloon angioplasty in 33 A-SAH patients with vasospasm reported successful treatment of angiographic vasospasm and improved clinical symptoms [88]. Subsequent retrospective studies supported these initial findings, showing improvement rates in clinical symptoms from 31 % to 92 % [89]. However, no prospective randomized clinical trial has been performed regarding balloon angioplasty to show that it ultimately improves patient outcomes. A systematic review performed by Hoh et al. in 2005 analyzed the benefit of balloon angioplasty and infusion of intra-arterial vasodilators. The authors reported overall clinical improvement in 62 % of patients (328/530) after balloon angioplasty [55]. There is some evidence that clinical improvement may be related to the timing of the angioplasty procedure, with significantly better results reported with angioplasty done within 24 h and within 2 h of the neurological change [90, 91]. However, a study by Eskridge et al. showed that patients treated within 12 h from the onset of symptoms did not differ significantly from patients treated within 18 h [92].

Take-Home Tables

Tables 14.1 and 14.2 highlight aneurysm detection and vasospasm diagnosis, respectively.

Imaging Case Studies

Case 1: 65-Year-Old Female with No Past Medical History Presented with "the Most Painful Headache of My Life" (Fig. 14.1a–g)

Case 2: 59-Year-Old Female Presented with "the Most Painful Headache of My Life" (Fig. 14.2a–e)

Case 3: 51-Year-Old Female with a Family History of Aneurysms and Subarachnoid Hemorrhage Presented with Frequent Headaches (Fig. 14.3a–c)

Case 4: 52-Year-Old Woman with Right-Hand Clumsiness (Fig. 14.4a–d)

Case 5: Patient Developed Increased Lethargy 14 Days Post Hemorrhage (Fig. 14.5a–c)

Case 6: 48-Year-Old Male Presented to the ED with Headache in the Setting of Cocaine Use (Fig. 14.6a–d)

Suggested Imaging Protocol: Nontraumatic SAH

The following imaging protocol (Fig. 14.7) was adapted from Agid et al. [31]. An important caveat of this imaging protocol is that patients treated solely on the basis of CTA findings may rarely harbor additional aneurysms, or other vascular lesions, not detected by that modality, and the impact of this is not certain.

Table 14.1 Aneurysm detection

Modality	Sensitivity	Specificity	AUC (ROC)	Limitations	Costs
DSA	NA	NA	NA	Invasive procedure, contrast, and radiation	$$$$
CTA, per patient. Westerlaan et al.	98.0 %	100 %	1.00	Contrast and radiation	$$
MRA, per patient. White et al.	87.0 %	92.0 %	0.89	No significant risks	$$$

Table 14.2 Vasospasm diagnosis

TCD (MCA vasospasm, 120 cm/s velocity threshold)	67.0 %	99.0 %	NA	Operator dependence and lack of adequate sonographic windows to evaluate all vessels	$
CTA	79.6 %	93.1 %	0.98	Contrast and radiation	$$
CTP	74.1 %	93.0 %	0.97	Contrast and radiation	$$
MRA (42 patients, Grandin et al.)	92.0 %	97.0 %	NA	No significant risks	$$$
MRP	NA	NA	NA	Contrast material reaction and NSF	$$$

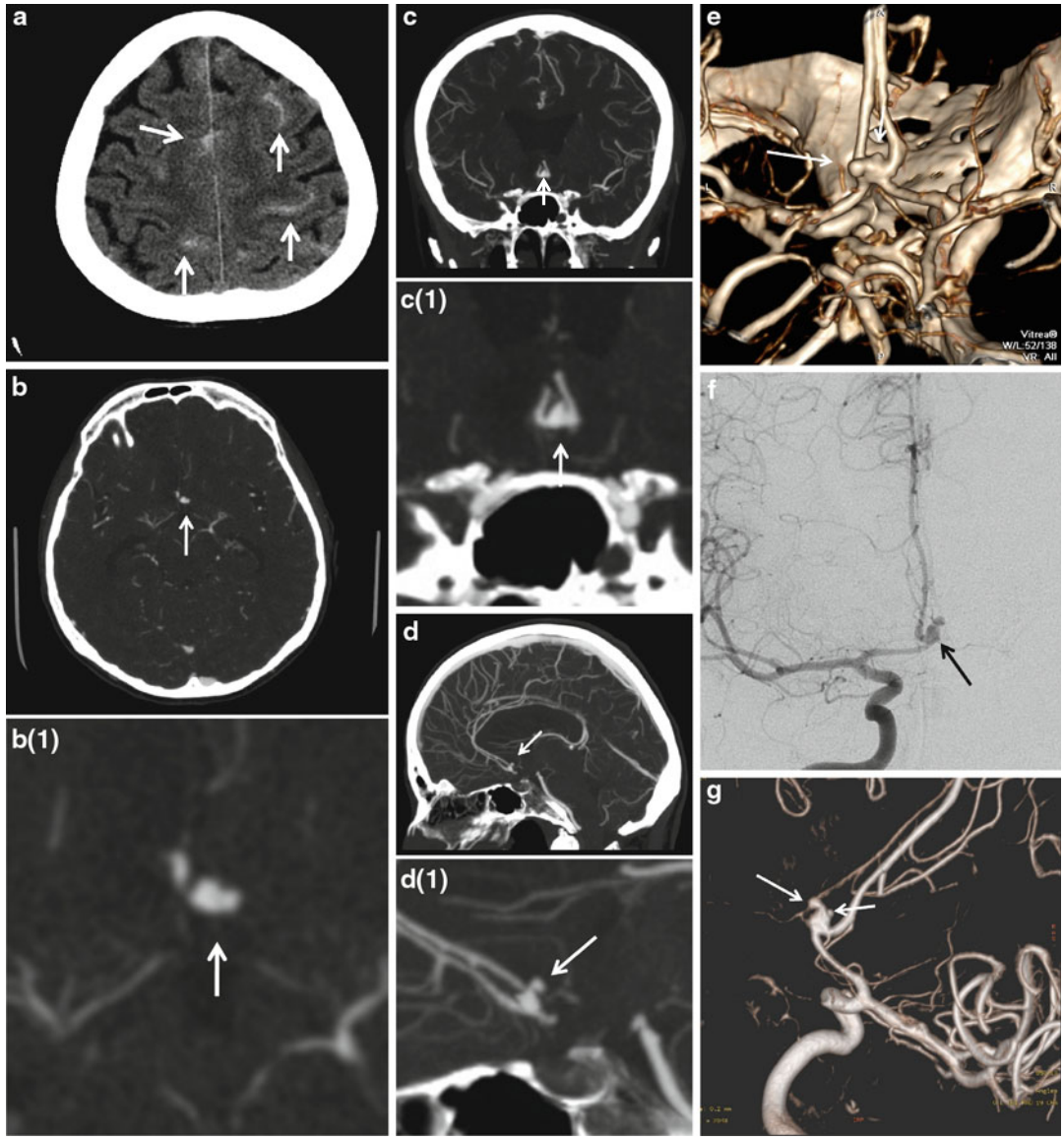

Fig. 14.1 (**a**–**g**) A 65-year-old female with no past medical history presented with "the most painful headache of my life." (**a**) Non-contrast-enhanced CT(NECT) of the head shows SAH (*white arrows*). (**b**) Subsequent CTA shows a multilobulated aneurysm of the anterior communicating artery. Axial source images demonstrate the aneurysm (*white arrow*), which extended over several slices above and below the displayed image. The magnification (**b**(1)) view shows the aneurysm to better advantage (*white arrow*). (**c**) Coronal maximum intensity projection (MIP) reformats show both **a**2 segments of the anterior cerebral arteries arise from the aneurysm (*white arrow*); **c**(1) is the magnification. (**d**) Sagittal maximum intensity projection (MIP) reformats reveal the superiorly and posteriorly oriented daughter sac (*white arrow*); **d**(1) is the magnification. (**e**) 3-D surface-rendered reformatted image again shows the orientation of the aneurysm and its relationship to the parent vessel, and clearly shows the two lobulations, or daughter sacs (*white arrows*). Both **a**2 segments of the anterior cerebral arteries arise from the aneurysm. (**f**) Right ICA injection from DSA confirms the CTA findings (*black arrow*). (**g**) 3-D rotational angiography was performed via a right internal carotid artery injection. The reconstructed images nicely illustrate the lobular contour of the aneurysm, as well as the *right* **a**2 segment arising from the aneurysm (the *left* **a**2 segment is not seen on this injection)

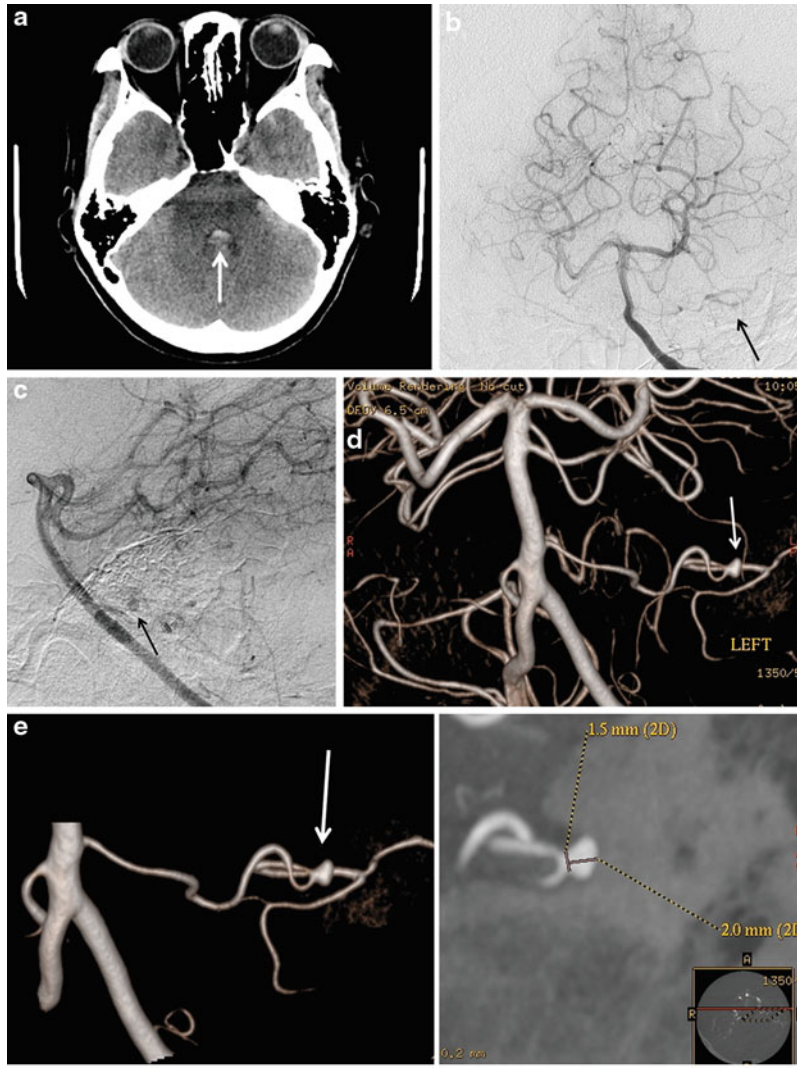

Fig. 14.2 (**a**–**e**) A 59-year-old female presented with "the most painful headache of my life." (**a**) NECT shows fourth ventricular hemorrhage (*white arrow*). No aneurysm was detected by CTA. (**b**, **c**) Left vertebral injection of DSA showed questionable prominence of vessels in the region of the distal left anterior inferior cerebellar artery (AICA) (*black arrows*). (**d**, **e**) Surface-rendered reformats from 3-D rotational clearly demonstrate an aneurysm of the left AICA measuring 2.0 × 1.5 mm (*white arrows*). The patient underwent endovascular embolization of the aneurysm and parent artery with NBCA glue, with excellent result

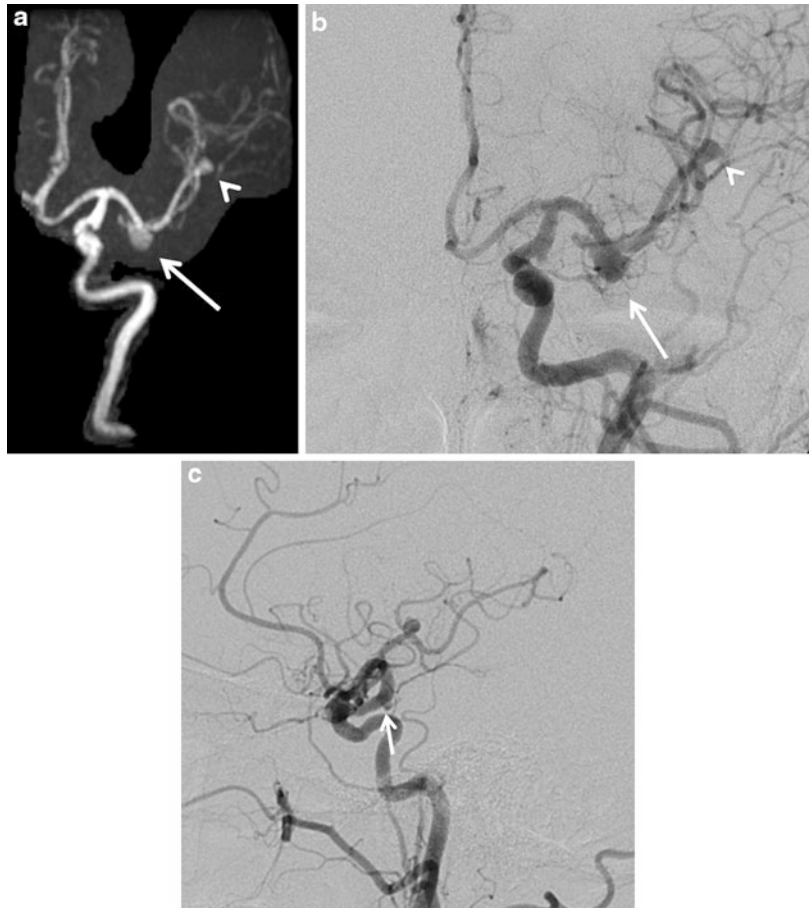

Fig. 14.3 (**a**–**c**) A 51-year-old female with a family history of aneurysms and subarachnoid hemorrhage presented with frequent headaches. (**a**) 3-D TOF MRA detected two left MCA aneurysms, one at the bifurcation directed inferiorly (*white arrow*) and a second more distal aneurysm directed superolaterally (*white arrowhead*). In addition, a possible anterior choroidal aneurysm or infundibulum was noted. (**b**, **c**) Frontal and lateral projections from a left common carotid injection redemonstrate the two MCA aneurysms (*white arrow and white arrowhead*, respectively). However, on the lateral projection of this DSA, there is clearly an infundibulum of the left anterior choroidal artery, not an aneurysm (*white arrow*)

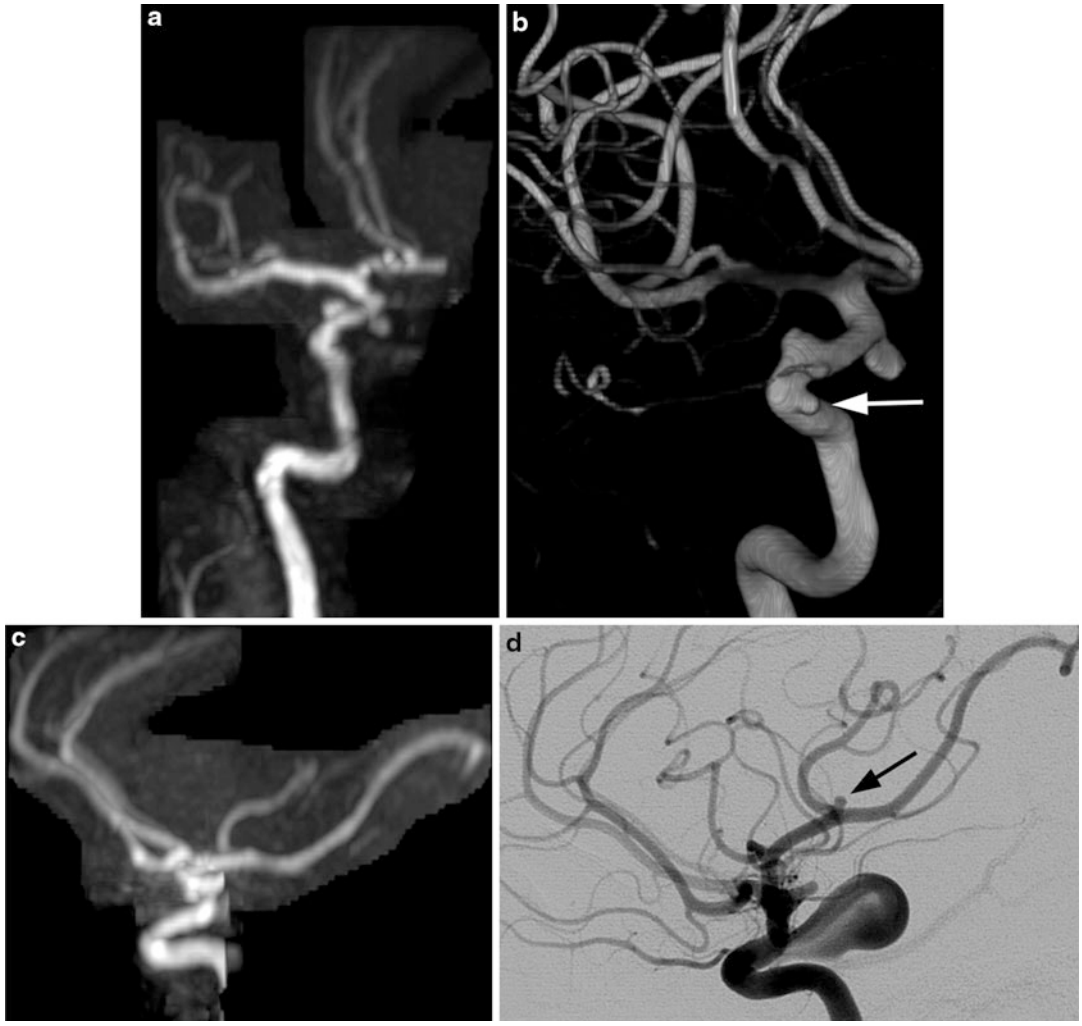

Fig. 14.4 (**a**–**d**) 52-year-old woman with right-hand clumsiness. MRA was obtained as part of evaluation for stroke, and multiple aneurysms were found. (**a**) 3-D volume-rendered reformat of the right ICA shows a posterior communicating artery and supraclinoid carotid artery aneurysm. (**b**) Subsequent DSA demonstrates an additional cavernous ICA aneurysm, occult by MRA (*white arrow*). (**c**, **d**) DSA also demonstrates an occult left MCA bifurcation aneurysm (*black arrow* in **d**)

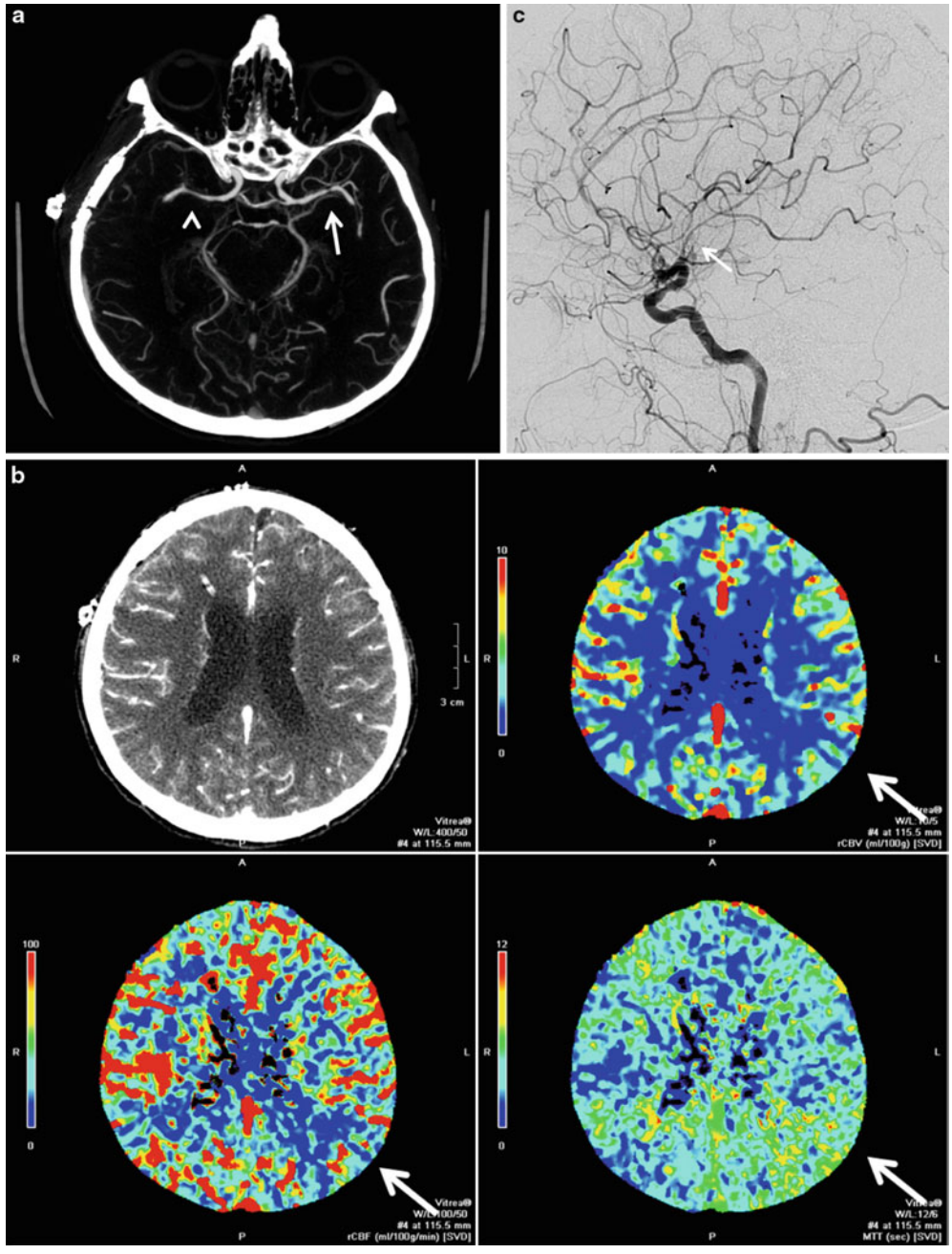

Fig. 14.5 (**a**–**c**) On day 14 post hemorrhage, the patient whose initial imaging is depicted in Fig. 14.1 developed increased lethargy. CTA and CT perfusion (CTP) performed to evaluate for vasospasm. (**a**) CTA demonstrates severe focal narrowing of the left distal M1 segment of the MCA, consistent with vasospasm (*white arrow*). There is also moderate narrowing of the right M1 (*white arrowhead*). (**b**) CTP demonstrates elevated mean transit time (MTT) in the left parietal lobe (*bottom right*) with corresponding decreased cerebral blood flow (CBF, *bottom left*) and preserved cerebral blood volume (CBV, *top right*) (*white arrows*). These findings suggest cerebral hypoperfusion secondary to vasospasm. (**c**) On the basis of these clinical and imaging findings, the patient was taken DSA. A lateral projection of a left common carotid injection confirms the presence of vasospasm, with multiple areas of arterial narrowing involving left MCA (*white arrow*)

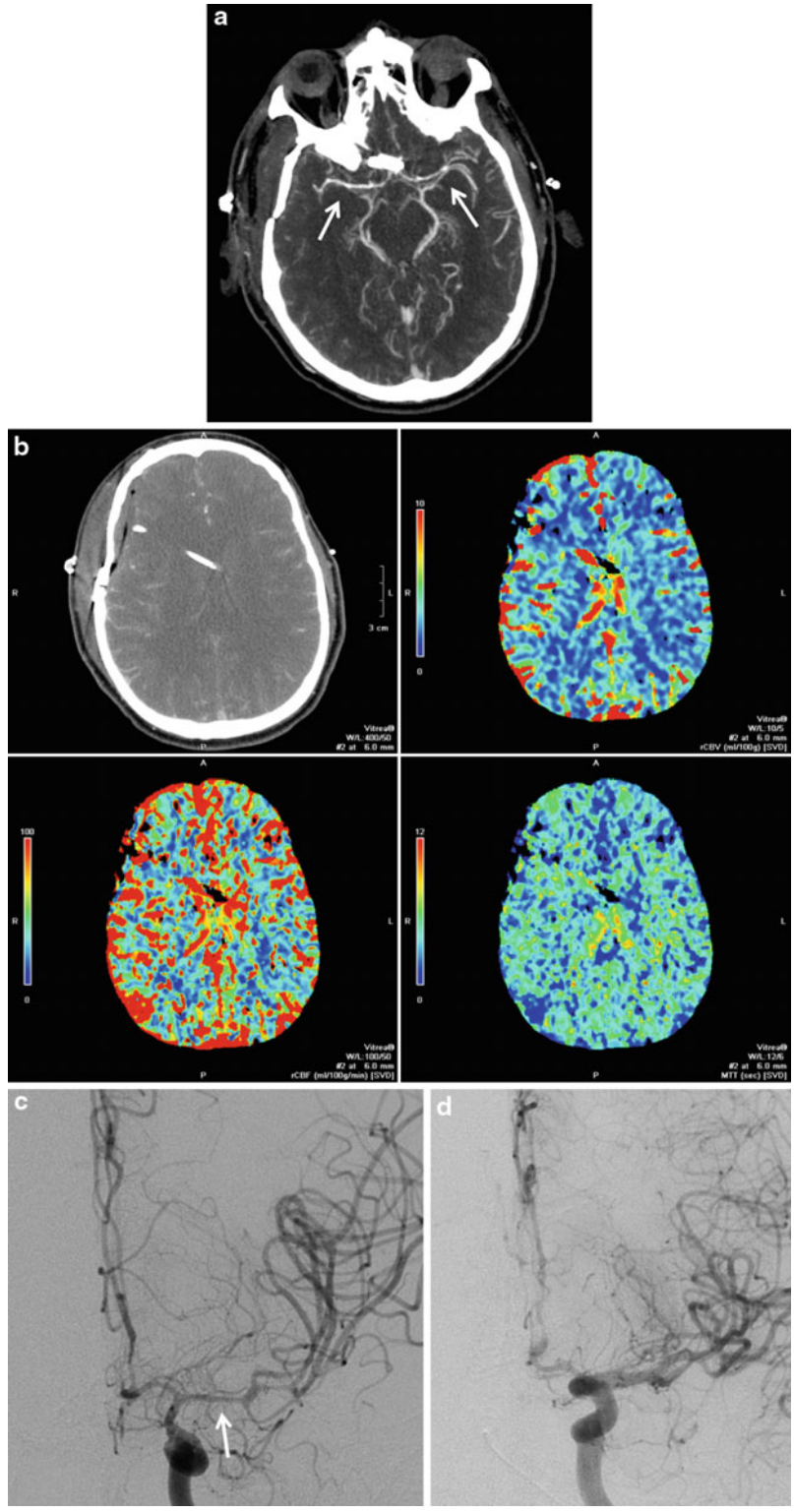

Fig. 14.6 (continued)

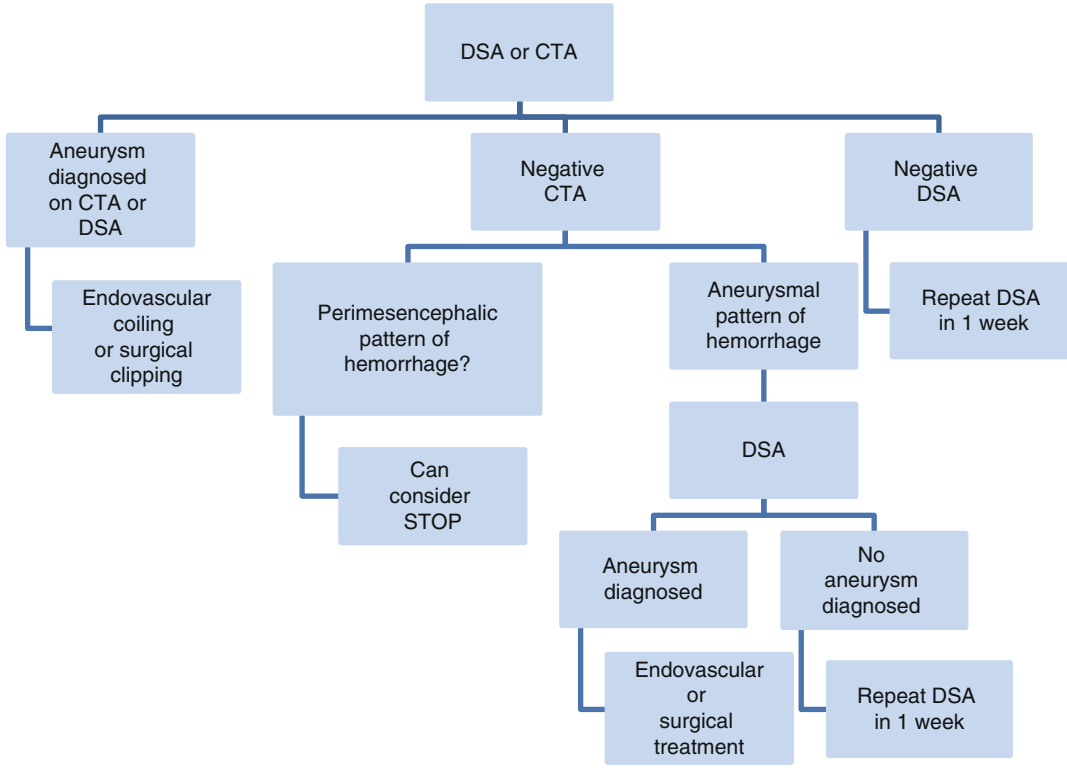

Fig. 14.7 Suggested imaging protocol for nontraumatic SAH

Fig. 14.6 (**a**–**d**) A 48-year-old male presented to the ED with headache in the setting of cocaine use. Diagnostic workup revealed a ruptured right MCA aneurysm which was surgically clipped. Ten days after hemorrhage, the patient presented with nonspecific personality changes. CTA and CTP was performed. (**a**) Axial MIP image from CTA shows moderate to severe bilateral MCA narrowing consistent with vasospasm (*white arrows*). (**b**) CTP demonstrates symmetric perfusion, with no definite focal perfusion deficit noted. (**c**) Based on the clinical and CTA findings, the patient underwent DSA. PA projection of left internal carotid artery injections demonstrates moderate to severe vasospasm of the proximal left MCA, with involvement of the **a**1 and **a**2 segments of the left ACA as well (*white arrows*). (**d**) The patient was treated with a combination of intra-arterial verapamil and balloon angioplasty of the left MCA. Posttreatment PA projection demonstrates marked improvement in caliber of the M1 and M2 segments, in the regions where angioplasty was performed (*white arrow*)

Future Research

- Improving the diagnostic performance of CTA and MRA, with the goal of acquiring diagnostic information similar to DSA without having to perform an invasive procedure
- Assessing the risk of aneurysm rupture as well as predictors of aneurysm rupture in order to better stratify patients for treatment
- Assessing long-term outcomes for patients who have undergone surgical or interventional treatment for an intracranial aneurysm(s)
- Assessing the diagnostic performance of perfusion studies (CTP and MRP) for vasospasm diagnosis
- Understanding the underlying pathophysiology of cerebral vasospasm in an attempt to improve diagnostic and treatment approaches
- Performing randomized trials of the various medical and interventional treatments for vasospasm

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