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MR angiography of the carotid arteries and intracranial circulation: advantage of a high relaxivity contrast agent

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Abstract Several studies have shown the usefulness of contrast-enhanced MR angiography (CE-MRA) for imaging the supraortic vessels, and, as a consequence, it has rapidly become a routine imaging modality. The main advantage over unenhanced techniques is the possibility to acquire larger volumes, allowing demonstration of the carotid artery from its origin to the intracranial portion. Most published studies on CE-MRA of the carotid arteries have been performed with standard Gd-based chelates whose T1 relaxivity values are similar. Recently new gadolinium chelates such as gadobenate dimeglumine (Gd-BOPTA, MultiHance; Bracco Imaging, Milan, Italy) have been developed which have markedly higher intravascular T1 relaxivity values. When administered at an equivalent dose to that of a standard agent, these newer contrast agents produce significantly greater intravascular signal enhancement. The availability of an appropriate high-relaxivity contrast agent might also help to overcome some of the intrinsic technical problems (e.g. those related to flow) that affect time-of-flight (TOF) and phase contrast (PC) MR angiography of the intracranial vasculature. To avoid the problem of superimposition of veins, ultrafast gradient echo MRA techniques with very short TR and TE have been developed. Although the precise sequence parameters vary between manufacturers, they are basically similar. The choice between performing a time-resolved or high spatial resolution CE-MRA examination depends upon the precise clinical application. The most common applications include the study of cerebral aneurysms, arteriovenous malformations, dural arteriovenous fistulas and dural venous diseases.

Keywords CE-MR angiography · Carotid arteries · Intracranial circulation · Cerebral aneurysms ·Arteriovenous malformations · Gadobenate dimeglumine

Introduction

The advent of magnetic resonance angiography (MRA) in the mid-1990s opened new possibilities for diagnostic imaging of the vasculature. However, until the availability of contrast-enhanced rapid acquisition sequences, MRA was not considered a valid diagnostic alternative to digital subtraction angiography (DSA) for evaluation of carotid artery stenosis. The major limitations of unenhanced time-of-flight (TOF) sequences for MRA of the carotid arteries were restricted study volumes in the case of 3D TOF acquisitions, and saturation effects together with low spatial resolution and movement artifacts in the case of 2D TOF acquisitions. However, with the development of contrast-enhanced (CE-MRA) techniques,

MRA is today recognized as a primary non-invasive imaging modality, particularly in the neurovascular field where the risk of conventional catheter angiography (i.e., DSA) is greater.

CE-MRA of the carotid arteries is uniquely challenging among the various vascular territories because the very short arterial-venous circulation time in the brain leads to rapid jugular venous enhancement. Most studies of CE-MRA of the carotid arteries have been performed with standard gadolinium-based chelates that all have similar T1 relaxivity values. More recently new gadolinium chelates such as gadobenate dimeglumine (Gd-BOPTA, MultiHance; Bracco Imaging, Milan, Italy) have been developed which have inherently greater T1 relaxivity in vivo [1]. These contrast agents produce significantly greater intravascular signal enhancement and therefore are advantageous for use in CE-MRA applications. In the case of Gd-BOPTA the greater intravascular T1 relaxivity has been shown to produce a higher vascular peak enhancement of longer duration than that achieved with Gd-DTPA when injected at the same dose [2].

For diagnostic evaluation of the intracranial circulation, particularly for pretreatment evaluation of intracranial vascular malformations, DSA has long been the gold standard technique. In recent years, however, MRA has taken on an increasing role in evaluation of the intracranial circulation even though its application is still limited when compared to its use in the carotid arteries and other vascular territories. The intracranial applications for which unenhanced MRA techniques have primarily been of value include the evaluation of arterial and venous vessel stenosis and cerebral aneurysms. The development of CE-MRA techniques for intracranial applications may not only aid in overcoming some of the technical limitations of unenhanced MRA but also provide diagnostic benefits for the study of vascular malformations of the intracranial circulation.

Contrast agents for MR angiography

The two types of contrast agent that are suitable for MRA are the paramagnetic gadolinium chelates and ultrasmall superparamagnetic iron oxide (USPIO) particles [1]. However, whereas numerous gadolinium chelates are today available on the market, no USPIO agents have yet been approved. The USPIO agents that have undergone development for MRA applications all have long intravascular half-lives and have been developed as intravascular "blood pool" agents. Unfortunately, the principal disadvantage of these agents is a high T2* effect which adversely affects the vascular signal leading to decreased vessel sharpness and size.

The gadolinium agents that are suitable for CE-MRA can be subdivided into agents that do not interact with intravascular proteins and those that do interact either weakly or strongly with intravascular proteins. The gadolinium chelates that do not interact with serum proteins comprise the conventional gadolinium agents formulated at a concentration of 0.5 *M*, that is gadopentetate dimeglumine (Gd-DTPA), gadodiamide (Gd-DTPA-BMA), gadoterate meglumine (Gd-DOTA), gadoversetamide (Gd-DTPA-BMEA) and gadoteridol (Gd-HP-DO3A), as well as the newer agent gadobutrol (Gd-BT-DO3A) which is available as a 1 *M* formulation. Despite differences in their molecular structure, all are excreted exclusively by glomerular filtration through the kidneys and all have similar T1 relaxivity values, with resulting similar vascular enhancement performance [3, 4]. Due to the widespread availability of the nonprotein-interacting agents, most CE-MRA studies performed to date have been performed with these agents and most CE-MRA examinations in clinical practice are still performed with them. The principal benefit of the 1 *M* gadolinium agent compared to the traditional 0.5 *M* agents is that the overall doses to obtain sufficient contrast enhancement in the vessel of interest are lower. Moreover, the higher concentration permits the administration of a more compact bolus which enable greater enhancement of the signal-to-noise ratio (SNR).

Another means of obtaining greater intravascular signal on CE-MRA is to use a gadolinium agent that interacts with serum proteins. Possibly the best known and most extensively studied of these agents is Gd-BOPTA, whose higher T1 relaxivity in blood is due to weak and transient interaction of the Gd-BOPTA chelate with serum proteins, particularly albumin [2, 3, 5]. The higher T1 relaxivity of this agent has been shown in numerous studies to bring about a significantly greater enhancement of the intravascular signal intensity compared to that obtained with conventional gadolinium agents at equivalent dose [2, 6–8]. The optimal dose of Gd-BOPTA for acquisition of high-quality diagnostic MRA images is 0.1 mmol/kg body weight [9, 10]. Whereas numerous studies have been performed in vascular territories elsewhere in the body [2, 6–11], comparatively few have been performed in the supraaortic region [12, 13]. A preliminary study by Pediconi et al. [12] revealed that as in other vascular territories, Gd-BOPTA demonstrates marked advantages over Gd-DTPA for imaging the carotid arteries. More recently, we have shown that the diagnostic accuracy of Gd-BOPTA-enhanced MRA for the detection and grading of carotid artery stenosis/occlusion is superior to that of unenhanced MRA and conventional DSA when compared to rotational DSA as the reference standard [13]. As is the case for most nonprotein-interacting gadolinium chelates, Gd-BOPTA has an excellent safety profile with a very low incidence of adverse events [14, 15].

Another class of contrast agent that is suitable for CE-MRA is the group of paramagnetic "blood pool"

agents. Like the USPIO agents, these agents have a longer intravascular residence time and can thus be used for steady-state vascular imaging in addition to conventional first-pass MRA. However, while the value of these agents for imaging vasculature territories elsewhere in the body has been reported [16], little has yet been published on their efficacy in the carotid or intracranial territories.

MR angiography of the carotid arteries

MRA of the carotid arteries has undergone a long period of evolution to become a routine imaging modality. Before the development of rapid acquisitions combined with bolus administration of gadolinium contrast agent, the major limitations of MRA for imaging the carotid arteries was the limited achievable study volumes when 3D TOF sequences were employed or saturation effects together with low spatial resolution and movement artifacts when 2D TOF sequences were employed. Although technical developments have overcome many of the limitations associated with unenhanced TOF approaches, conventional DSA was still considered the primary diagnostic tool for evaluation of carotid artery stenosis until the availability of CE-MRA (Fig. 1).

CE-MRA of the carotid arteries is uniquely challenging because the very short arterial-venous recirculation time in the brain leads to rapid jugular venous enhancement and hence the possibility of obscured visualization of the adjacent carotid arteries. In spite of this difficulty, CE-MRA has proven a highly suitable replacement for unenhanced MRA techniques for the evaluation of extracranial carotid artery disease [17–23]. Improvements in the MRA acquisition technique, i.e. random k-space encoding, allow longer scans with higher spatial resolution and no venous contamination [24].

The main advantage of CE-MRA over unenhanced MRA in the carotid territory is the larger imaging volume achievable. Thus, with CE-MRA it is possible to perform a complete and reliable evaluation of the internal carotid artery from the bifurcation to the intracranial segment. Additional benefits are an overall better accuracy in the depiction of tight stenosis and a more confident diagnosis of real carotid artery occlusion versus subocclusive stenosis [13, 25] (Fig. 2). Concerning the accuracy for depiction of stenoses, both unenhanced MRA and CE-MRA have previously been considered to overestimate the degree of stenosis compared to conventional DSA. However, we have recently shown that this is not the case [13]. In a study aimed at comparing unenhanced MRA, Gd-BOPTA-enhanced MRA and conventional DSA versus rotational DSA a better correlation was observed between rotational DSA and Gd-BOPTA-enhanced MRA than between rotational DSA and conventional DSA. These findings suggest that the multiplanar capability of MRA makes it superior to conventional DSA in two or three planes and that it is thus more likely to be conventional DSA that underestimates the degree of carotid artery stenosis than CE-MRA that overestimates it.

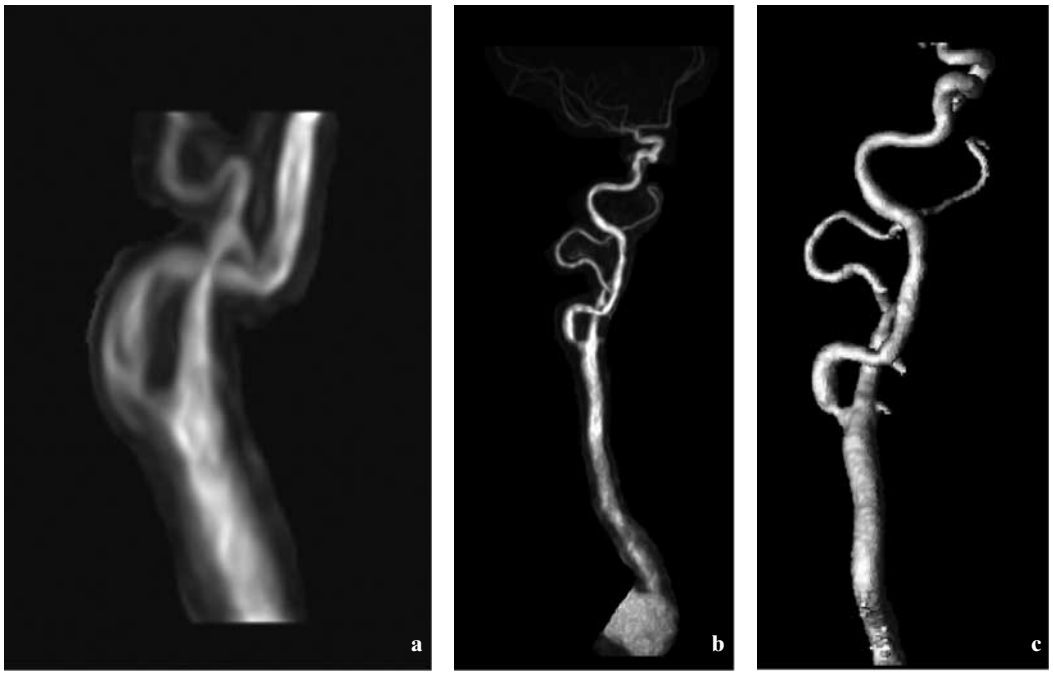

Fig. 1a-c Tight stenosis of the internal carotid artery. **a** 3D TOF MRA does not clearly demonstrate the degree of stenosis due to the presence of movement artifacts. **b**, **c** The stenosis is better demonstrated by 3D CE-MRA both with MIP (**b**) and 3D SSD (**c**) reconstructions

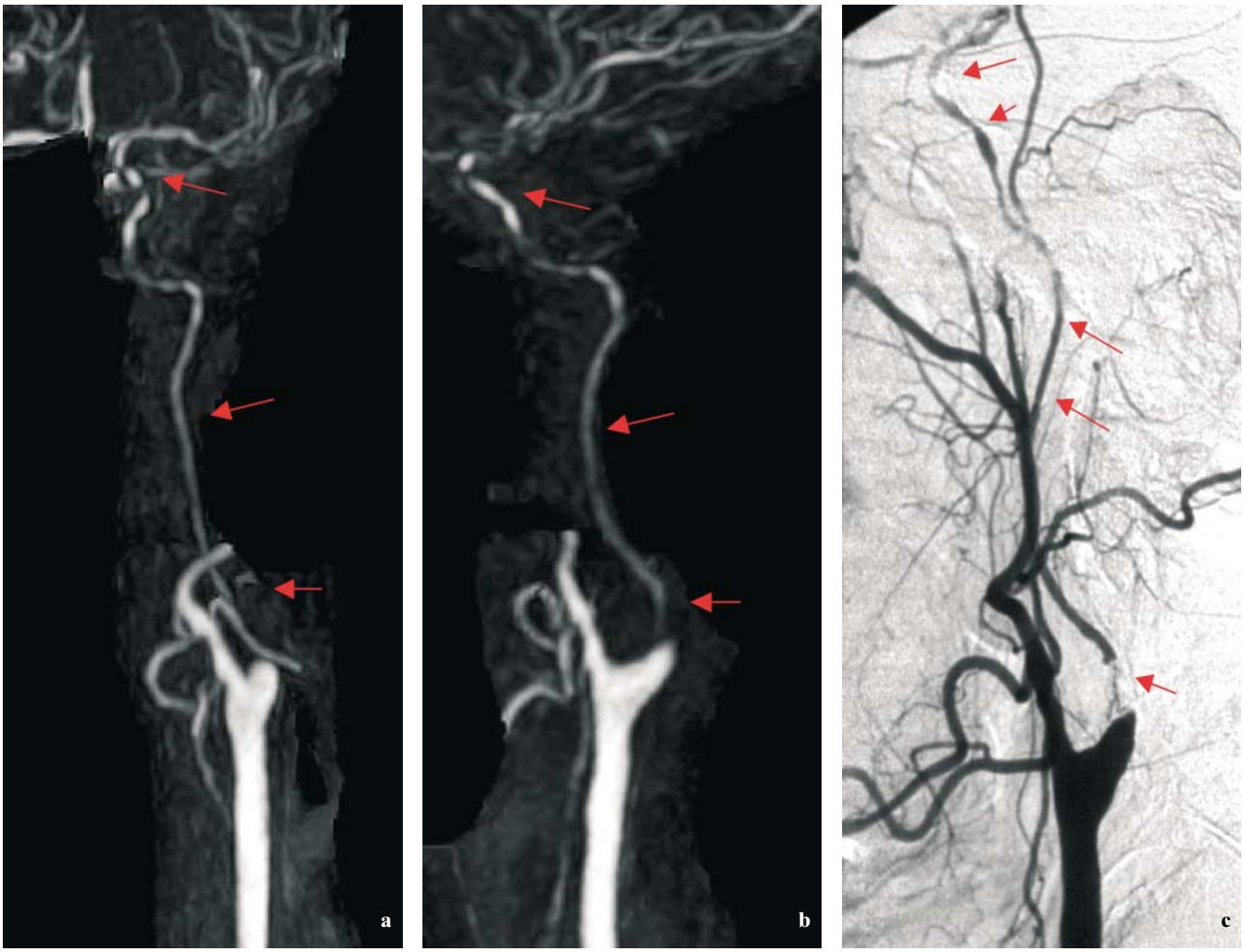

Fig. 2a-c Subocclusion of the internal carotid artery. **a**, **b** CE-MRA in two projections shows the presence of residual slow flow in the internal carotid artery. The visualization is equivalent to that seen on DSA (**c**)

Although most published studies to date have utilized conventional gadolinium chelates for CE-MRA of the carotid arteries, a recent phase III clinical trial has been performed with 0.1 mmol/kg body weight Gd-BOPTA in 238 patients to assess the accuracy of CE-MRA with this agent for the detection of carotid artery stenosis [26]. Overall, the diagnostic accuracy of Gd-BOPTA-enhanced MRA for the detection of significant (>60%) carotid artery disease increased from 78.3–82.2% on unenhanced 2D TOF MRA to 87.8–89.7% on CE-MRA. The benefit of Gd-BOPTA compared to other agents is the possibility to obtain higher vascular signal at an equivalent dose and thus better quality diagnostic images. The increased signal intensity enhancement can be utilized to increase spatial resolution in order to obtain better images that offer greater sensitivity for the evaluation of carotid stenosis.

MR angiography of the intracranial circulation

Prior to the advent of non-invasive vascular imaging techniques, DSA played a major role in the diagnosis of diseases of the intracranial vasculature. Nowadays MRA has gained ground in the diagnosis of most cerebral vascular pathologies although certain intrinsic technical limitations still restrict its application to the diagnosis of arterial and venous vessel stenosis and cerebral aneurysms. For the pretreatment evaluation of intracranial vascular malformations, DSA remains the gold standard technique. Evaluation of the normal arterial and venous circulation is typically performed using different methodological approaches. In large part, this is due to the overall complexity of the intracranial vascular system and to the rapid (5–6 s) circulation time.

Arterial circulation

Currently, the arterial circulation is most often studied using 3D TOF MRA. This non-invasive technique allows the visualization of the major intracranial arteries and peripheral branches in a relatively short time and generally does not require the use of contrast agent [27]. Nevertheless its major limitation is that the distal arterial branches are often less optimally visualized on maximum intensity projection (MIP) reconstructions due to the progressive saturation of these vessels during image acquisition. The result is an overall reduction of diagnostic accuracy [28].

The first approach to increasing the quality of MRA images of the intracranial circulation was to combine the 3D TOF MRA technique with the intravenous infusion of gadolinium contrast agent [29, 30]. However, while this technique improved visualization of the more distal portions of the intracranial arterial circulation, the relatively long acquisition times (between 8 and 10 min/volume acquisition) and the rapid distribution of contrast agent resulted in the overlapping visualization of cerebral arteries and veins. Additionally, the presence of contrast agent in the capillary-venous compartment was shown to lead to increased signal intensity of the stationary encephalic tissue.

Recently, with the introduction of stronger gradients and the development of ultrafast sequences (acquisition times of 20–50 s as opposed to 8–10 min), 3D CE-MRA has been reconsidered for the diagnosis of intracranial vascular pathologies [24, 31]. The technique, which requires a rapid intravenous injection of gadolinium contrast agent, has been shown to be more sensitive and more selective then previous techniques. These results are possible due to recent developments in k-space sampling in which the central portion of the k-space is the first to be acquired.

Elliptically centric encoded acquisitions must be timed precisely to the arrival of contrast agent in the circle of Willis in order to minimize enhancement of the venous components. Although the overall scan time ranges from 20 to 50 s, with elliptical centric phase ordering the center of the K-space is filled very efficiently during the initial seconds of the scan. This permits a more selective visualization of major intracranial arteries without significant venous contamination.

More recently other "time-resolved" 3D CE-MRA techniques have been proposed which permit a high temporal resolution of approximately 1 s while maintaining adequate spatial resolution. Among these new techniques are those referred to as TRICKS [24] and CENTRA [32]. However, their clinical role and validity have still to be demonstrated (Fig. 3).

As an alternative to 3D CE-MRA a 2D thick-slice MR DSA (2D MR DSA) approach can be employed [33]. This method combines a series of 2D CE thick slices, each frame lasting 1–2 s, with subtraction of precontrast images from subsequent contrast-enhanced images. These techniques are currently utilized for the study of cerebral aneurysms and for the assessment of cerebrovascular occlusive diseases [33, 34].

Although 2D MR DSA is an available approach, 3D TOF MRA is currently a widely employed technique for the detection of intracranial aneurysms. However, 3D TOF MRA sometimes underestimates the size of aneurysms because of spin saturation effects. For this reason 3D CE-MRA is increasingly being considered the technique of choice for the study of large and giant aneurysms. Moreover, it has the inherent advantage over other techniques in facilitating depiction of the aneurysm from numerous projections following MIP reconstruction (Fig. 4).

A widely accepted application of MRA is in the follow-up of coiled aneurysms. Several studies have been performed that have demonstrated the feasibility and sensitivity of 3D TOF MRA in detection of aneurysm recanalization [35–37]. Recently the use of techniques with very short TR and TE has permitted marked reductions of artifacts. Moreover, the use of 3D CE-MRA with elliptic centric acquisition seems to have better sensitivity compared to 3D TOF MRA in demonstrating aneurysm patency [38].

Several studies have compared unenhanced MRA and CE-MRA in acute stroke and have demonstrated that the use of contrast agent increases the visualization of remnant patency of the tributary arteries of the ischemic territory [39].

Another field of interest for the application of 3D CE-MRA is in the study of cerebral arteriovenous malformations [40]. Due to the particular anatomical characteristics of these lesions and their hemodynamic features, the design of a targeted MRA sequence is particularly challenging and as yet no sequence has proven sufficiently diagnostic to completely replace DSA.

Venous circulation

Basic MRI combined with MRA has very high sensitivity for the detection of cerebral venous thrombosis. For accurate confirmation of the presence and extension of a venous thrombosis, 3D PC MRA techniques are generally preferred since TOF MRA sequences may be disturbed by artifactual metahemoglobin from subacute thrombus [41]. The use of 3D fast GE T1-weighted CE-MRA has recently been proposed as a more sensitive technique for the evaluation of dural sinuses, particularly in those regions (transverse sinuses, posterior part of superior sagittal sinus, transverse-sigmoid junction) where TOF MRA techniques, and to a lesser extent PC MRA techniques, are troublesome because of saturation or complex flow [42]. Although this technique appears

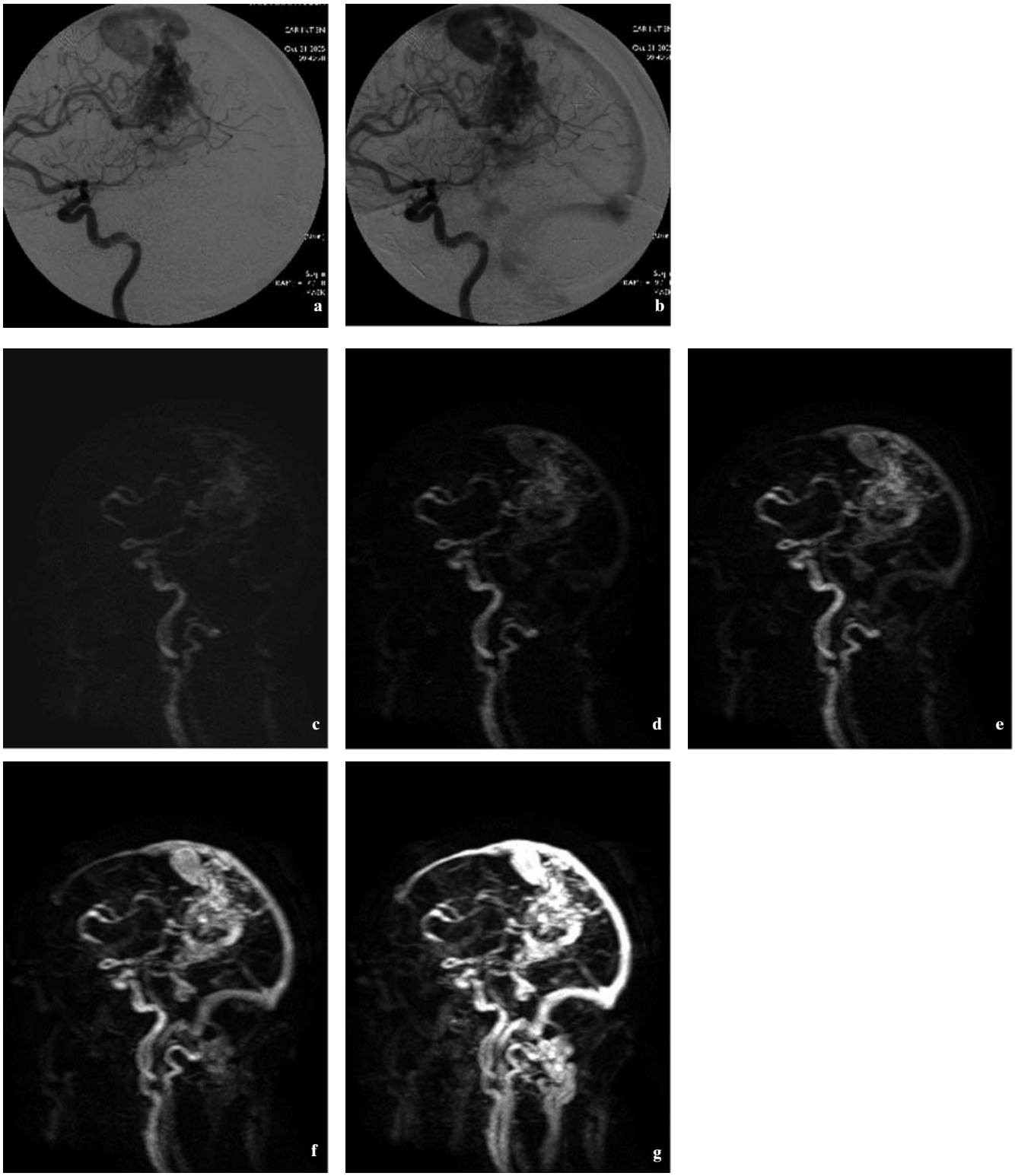

Fig. 3a-g Parietal arteriovenous malformation. **a**, **b** DSA shows the arterial and venous phases with representation of afferent and drainage vessels. **c–g** 3D CE-MRA with a temporal resolution of 0.8 s demonstrates the different arterial and venous phases

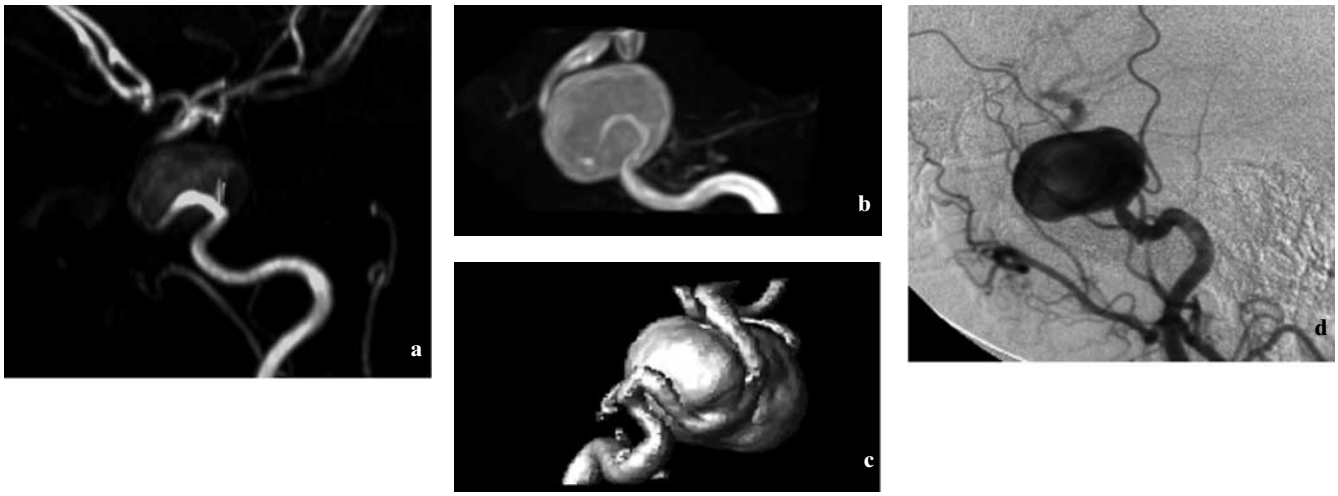

Fig. 4a-d Giant internal carotid artery aneurysm. **a** 3D TOF MRA fails to demonstrate correctly the morphology and relation of the aneurysm to the parent vessel. **b–c** 3D CE-MRA with MIP (**b**) and SSD (**c**) reconstructions shows both these aspects clearly, in a similar way to that seen on DSA (**d**)

promising there is as yet little information available concerning its application in pathological series in comparison with unenhanced MRA techniques.

Whereas unenhanced MRA acquisitions can differentiate between occlusion and focal stenosis of large sinuses, it may be difficult to rule out stenosis in cases of normal variants or sinus hypoplasia. In these cases diagnosis may be improved with the use of 3D CE-MRA.

Conclusion

Contrast-enhanced MR angiography is today an established technique for visualization of the carotid arteries and other vessels of the supraortic vasculature. Although challenging because of the rapid arterial-venous circulation time, the development of ultrafast imaging sequences, the possibility of acquiring large imaging volumes from the carotid bifurcation to the intracranial territory, and the absence of the various drawbacks associated with unenhanced MRA techniques, have resulted in the routine use of CE-MRA in daily clinical practice. The availability of contrast agents such as Gd-BOPTA which has markedly higher T1 relaxivity than standard Gd contrast agents represents a further substantial development in the evolution of carotid MRA. Specifically, the greater contrast enhancement at equivalent dose permits imaging of a larger supraortic volume and better time-resolved MRA.

Although CE-MRA of the intracranial vasculature has still to be routinely accepted, its use is becoming more widespread. In particular, the development of stronger gradients and the development of elliptically centric encoded sequences have proven beneficial for the evaluation of aneurysm patency and cerebral arterio-venous malformations on CE-MRA. The principal advantage of ultrafast intracranial CE-MRA is the possibility to perform more selective visualization of major intracranial arteries without significant venous contamination.

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