REVIEW



The prospects and pitfalls in the endovascular treatment of moyamoya disease–associated intracranial aneurysms

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Abstract

Moyamoya disease (MMD) is characterized by progressive stenosis or occlusion of the distal internal carotid artery and simultaneous formation of collateral vasculature. The fragile alteration and increased hemodynamic stress in the intra- and extracranial vasculature would conjointly result in the formation of intracranial aneurysms in MMD patients. According to our classification, the MMD-associated aneurysms are divided into the major artery aneurysms (MAAs) and non-MAAs. The non-MAAs are further subdivided into the distal choroidal artery aneurysms, moyamoya vessel aneurysms, transdural collateral aneurysms, and anastomosis aneurysms. Currently, endovascular treatment (EVT) has become the main stream for the MMD-associated aneurysms. There is no difference to EVT for the MMD-associated MAAs of the non-stenosed major arteries with that in the non-MMD patients. While it is a big challenge to perform EVT for MMD-associated aneurysms in the stenosed arteries. Generally speaking, the parent arteries of the non-MAAs are slim, and super-selective catheterization is technically difficult. Most of the times, parent artery occlusion with liquid embolic agents or coils can only be performed. The vasculature in MMD patients is fragile; perioperative management and meticulous intraoperative manipulation are also very important to avoid complications during EVT. In spites of the complications, the EVT can bring good outcome in selected cases of MMD-associated aneurysms.

Keywords Moyamoya disease · Intracranial aneurysm · Endovascular treatment

Introduction

Moyamoya disease (MMD) is characterized by progressive stenosis or occlusion of the distal internal carotid artery (ICA) and simultaneous formation of collateral vasculature [39]. Histologic analysis showed that the intracranial vessels in MMD patients have attenuated media and fragmented elastic lamina [15]. In MMD, intracranial blood flow would experience redistribution, which can lead to increased hemodynamic stress in the nonoccluded vessels and collaterals [26]. The fragile

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alteration and hemodynamic stress in the intra- and extracranial vasculature would conjointly result in the formation of intracranial aneurysms in MMD patients [39]. Aneurysms can occur across all of the involved intraand extracerebral arteries, of which the prevalence was reported to vary from 3.4 to 14.8% [20, 29, 72]. They might be single or multiple [21, 47, 61]. For most of them, aggressive interventions, including open surgery and endovascular treatment (EVT), are necessary [72]. Open surgery has the risk of compromising the collaterals, which might result in ischemic complication and even catastrophic consequence [49, 72]. However, the EVT is relatively noninvasive and is advantageous to protect collateral. Furthermore, the development of finer and more easily navigated microcatheter is in favor of EVT [17]. Currently, EVT should be considered as a first choice for MMD-associated aneurysms. Considering the complexity of EVT for MMD-associated aneurysms, no onesize-fits-all approach exists. There are a couple of issues to be open to discussion. This review would further expound the EVT for MMD-associated aneurysms from an updated viewpoint.

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Fig. 1 The classification of MMD associated aneurysms. a Angiogram of the right ICA in AP (left) and lateral (right) views shows stenoocclusive alteration at the beginning of the right MCA, 2 aneurysms (arrow) are noted at the anterior communicating artery and A2 segment of the ACA. b Angiogram of the right ICA in lateral view (left) and 3D reconstruction (right) shows steno-occlusive alteration of the ICA terminus. An aneurysm (arrow) originates from the beginning of the OphA. c Angiogram of the right ICA (left) in AP view shows steno-occlusive alteration of the ICA terminus. Angiogram of the left VA (right) in AP view in the same patient reveals an aneurysm (arrow) at the basilar artery apex. d Angiogram of the left ICA in AP (left) and lateral (right) views shows steno-occlusive alteration of the ICA terminus. A distal AChA aneurysm (arrow) is noted. e Angiogram of the left ICA in AP (left) and lateral (right) views shows steno-occlusive alteration at the beginning of the left MCA. An aneurysm (arrow) is located at the distal LSA. f Angiogram of the right CCA in AP (left) and lateral (right) views shows steno-occlusive alteration of the right ICA. A transdural collateral aneurysm (arrow) is noted at the anastomotic site between MMA and MCA. g (left) Angiogram of the right ICA in AP view reveals a pseudoaneurysm (arrow) in the moyamoya vessels. Head CT shows intraparenchymal hemorrhage of the right temporal lobe in the same patient. h Angiogram of the left VA in 3D reconstruction (left) and super-selective angiogram (right) of the left PCA reveal a dissecting aneurysm (arrow) at the left PCA. ACA, anterior cerebral artery; AChA, anterior choroidal artery; AP, anteroposterior; CCA, common carotid artery; CT, computed tomography; ICA, internal carotid artery; LSA, lenticulostriate artery; MCA, middle cerebral artery; MMA, middle meningeal artery; MMD, moyamoya disease; OphA, ophthalmic artery; PCA, posterior cerebral artery; VA, vertebral artery

Classification of MMD-associated aneurysm

In the classification of MMD-associated aneurysm, the most widely accepted classification is two principle subtypes, that are major artery and peripheral artery aneurysms, the former ones are those located along the circle of Willis, while the later ones are located in or near the collateral vessels [15, 65]. However, this classification is ambiguous. Hence, we further divided these aneurysms into five subgroups in 2015: major artery aneurysms (MAAs), anterior choroidal artery (AChA) and posterior choroidal artery (PChA) aneurysms, lenticulostriate artery (LSA), and thalamo-perforating artery (TPA) aneurysms, meningeal artery aneurysms, and anastomosis aneurysms [72]. This classification seems more rational and has been accepted by some authors [15, 45, 62]. In this paper, we would like to make some minor revision of our previous classification. The aneurysms in MMD were divided into the MAAs and non-MAAs. The non-MAAs are further subdivided into the distal choroidal artery aneurysms (CAAs), moyamoya vessel aneurysms, transdural collateral aneurysms (TCAs), and anastomosis aneurysms. Besides, they can also be divided into the saccular or dissecting aneurysms, true or pseudoaneurysms according to their histological characteristics. Most of the MAAs are saccular true aneurysms, while non-MAAs are often dissecting aneurysms and become pseudoaneurysms after rupture [29, 71, 72]. The anatomical location and histological characteristics always determine the specific strategy of EVT. For MAAs, the parent artery must be preserved. But, most of the time, parent artery occlusion (PAO) is the only choice in case of non-MAAs. The new classification of MMD-associated aneurysms is illustrated in Fig. 1.

Characteristics of MMD-associated aneurysm and the strategy for EVT

Major artery aneurysm

According to Yeon et al.'s report, the MAAs can be found in 3.6% of the adult patients with non-hemorrhagic MMD [65]. Of the MMD-associated aneurysms, about 39% are MAAs [49]. In MMD, MAAs mainly originate from the circle of Willis or near its tributaries, involving both the anterior and posterior circulations. Posterior circulation MAAs are more common, especially at the basilar artery (BA) apex and the P1 segment of the posterior cerebral artery [4, 21, 41]. MMDassociated MAAs can also originate from the main trunk of BA [50, 70]. Those originating from the vertebral artery are extremely rare and often concurrent with other anomalies [16]. Most of the MAAs in the anterior circulation are located at the terminal of ICA, such as posterior communicating (Pcom)-ICA, AChA-ICA, and ophthalmic artery (OphA)-ICA aneurysms [25, 39, 52]. Of note, the OphA-ICA aneurysms are extremely rare (Fig. 1b). When the anterior cerebral artery (ACA) is reserved, MAAs can originate from the ACA. In the case of unilateral MMD, MAAs can also originate from the contralateral ICA [69]. Most of the MMD-associated MAAs would progressively grow and rupture; hence, aggressive EVT was necessary [7, 24, 25]. There is no dispute on the EVT for MMD-associated MAAs in the posterior circulation, while the EVT of aneurysms in the ACA depends on the specific circumstances. When only the beginning of middle cerebral artery (MCA) is involved and the ACA is spared, the ACA aneurysm should be aggressively managed [69]. When the beginning of the ACA is also stenosed, close observation of an unruptured ACA aneurysm is reasonable. Because during the progressive steno-occlusive alteration of the ACA, the aneurysm can spontaneously disappear [57]. MMDassociated aneurysms at the BA apex and ACA are illustrated in Fig. 2 and Fig. 3, respectively. For the MMD-associated MAAs, there is no difference with those in non-MMD patients to perform EVT. Stent-assisted coiling is commonly used. In unilateral MMD, the EVT is relatively safer for the reservation of more normal arteries. For dissecting aneurysms on the major artery trunk, parent artery occlusion (PAO) is also feasible (Fig. 4).

Fig. 2 Basilar artery apex aneurysm concurrent with MMD. a Head CT shows SAH concentrated in the basal cistern. b CTA shows steno-occlusive alteration at the beginning of the bilateral MCAs. An aneurysm is noted at the basilar artery apex. c, **b** Angiogram of the bilateral ICAs in AP view shows stenoocclusive alteration at the beginning of the bilateral MCAs, the bilateral ACAs are spared. e, f Angiogram of the right VA reveals a basilar apex aneurysm, which is successfully coiled. ACA, anterior cerebral artery; AP, anteroposterior; CT, computed tomography; CTA, computed tomography angiography; ICA, internal carotid artery; MCA, middle cerebral artery; MMD, moyamoya disease; VA, vertebral artery



Non-major artery aneurysm

The natural history of MMD-associated non-MAAs is unclear; they can experience rapid enlargement or spontaneous disappearance [8, 28, 57, 62]. Currently, prompt EVT for accessible non-MAAs is advocated [62]. But conservative treatment is a last resort if technical access is difficult [54]. The parent arteries of the non-MAAs are often slim, and superselective catheterization is technically difficult. Most of the times, PAO with liquid embolic agents or coils can only be performed [54]. Super-selective provocative testing with amobarbital to assess the safety is a requisite to decide if the PAO can be tolerated [19, 58].

Liquid embolic agents include n-butyl cyanoacrylate (NBCA) (Histoacryl, Yocan Medical, Toronto, CA) and Onyx (Medtronic Neurovascular, Minneapolis, MN) [67].

Compared with Onyx, NBCA has a tendency to go straight to the target. Hence, for PAO of MMD-associated non-MAAs, NBCA is more popular [3, 12].

Distal choroidal artery aneurysm Choroidal artery collateral system comprises collaterals from the distal AChA and PChA [32, 55]. During the progression of MMD, due to the increase of hemodynamic stress, distal CCAs can originate from this collateral system which include distal AChA and PChA aneurysms [18, 37]. Distal CCAs aneurysms are prone to rebleed, ranging from 1 day to 4 months after the first rupture. Hence, aggressive treatment is recommended [27]. For these small and deep-seated CCAs, the main strategy is PAO [32]. These choroidal arteries are always straight in MMD patients, which facilitate the implementation of PAO [31]. In order to avoid devastating infarct, the site of PAO should be distal to

Fig. 3 AComA aneurysm concurrent with MMD. a, b Angiogram of the bilateral ICAs in AP view shows stenoocclusive alteration at the beginning of bilateral MCAs. An AComA aneurysm is noted. c Angiogram of the right ICA in AP view shows the AComA aneurysm is successfully coiled. d Xray in lateral view shows the aneurysm is coiled with stent assistance. ACA, anterior cerebral artery; AComA, anterior communicating artery; AP, anteroposterior; ICA, internal carotid artery; MMD, moyamoya disease



the plexal point in case of a distal AChA aneurysm. Besides, the aneurysm should also be embolized or it might rebleed due to retrograde collateral flow from the PChA [10].

Moyamoya vessel aneurysm With the progression of MMD, vasculature in the brain base, which mainly includes LSA, TPA, and those nameless vessels at the skull base, would give rise to dilated moyamoya-like collaterals [56]. These collaterals at the brain base play important role in brain perfusion. Moyamoya-like vessels are prone to develop dissecting aneurysms [34, 49]. Due to the tortuous course and relatively small diameter of the parent LSA, access to the distal LSA aneurysm with microcatheter can also be limited. EVT can only be performed in highly selected cases [35, 36]. As for TPA aneurysm, due the small diameter of TPA, EVT is more difficult [38]. The cases illustrated in Fig. 1 e and g are difficultly approached through EVT.

Transdural collateral aneurysm In MMD, the transdural collaterals are common, including middle meningeal artery (MMA), occipital artery, internal maxillary artery, and ethmoid artery [68]. In rare circumstances, intracranial aneurysms can occur in the transdural collaterals in MMD progression [11, 14, 51, 72]. Those aneurysms located at their anastomosis with the brain arteries are called TCA [51, 59]. The TCAs can be located at the brain surface or located at the deep brain parenchyma [11, 14, 33, 40, 43]. The TCAs often

present with intracranial bleeding, and aggressive treatment is warranted. They are pseudoaneurysms, which means targeted embolization of the responsible aneurysm without sacrificing the parent is impossible [46]. In case of easier endovascular access to the TCAs, EVT is a less invasive and first-choice option. However, as a result of the small caliber and tortuosity of the parent artery, to approach the TCAs super-selectively is very difficult. Hence, PAO could not be avoided during EVT of these aneurysms [33]. Besides, Of note, sporadic case of spontaneous remission of the TCAs was also reported which were speculated to be secondary to intraaneurysmal thrombosis [60]. Hence, in case of TCAs, conservative treatment and intense imaging follow-up could be considered as an alternative solution in stable patients when EVT is risky. However, potential catastrophic hemorrhage should be borne in mind.

Aneurysm at the site of anastomosis Direct superficial temporal artery (STA)-MCA bypass is often performed in MMD patients [20]. At the site of STA-MCA anastomosis, de novo aneurysms can develop due to continuous hemodynamic stress [1, 13, 48]. The pathological mechanism of STA-MCA anastomosis aneurysms includes intraoperative disruption of the internal elastic lamina and media of the anastomosed arteries, hemodynamic stress, hypertension, and specific bifurcation angle [66]. The intrinsic fragility of the vessels in MMD patients could also play a pivotal role [1, 48]. As Fig. 4 PCA aneurysm concurrent with MMD. a Head CT shows SAH at the basal cistern. b. c Angiogram of the bilateral ICAs in lateral view shows stenoocclusive alteration of the ICA terminus and extensive intracranial collateral formation. d Angiogram of the left VA in AP view reveals an aneurysm (arrow) at the P2 segment of the PCA. e Super-selective angiogram of the PCA aneurysm (arrow). f Postoperative angiogram of the left vertebral artery in AP view shows disappearance of the aneurysm after PAO with coils (arrow). AP, anteroposterior; CT, computed tomography; ICA, internal carotid artery; MMD, moyamoya disease; PCA, posterior cerebral artery; PAO, parent artery occlusion; SAH, subarachnoid hemorrhage; VA, vertebral artery



the STA-MCA bypass is of utmost importance to the patients, preservation of the bypass should be guaranteed during treatment of the anastomosis aneurysms. Most of the reported cases underwent surgical clipping of the aneurysms and/or revascularization when necessary [1, 13, 48, 66]. EVT has not been reported in anastomosis aneurysms.

Complications of EVT for MMD-associated aneurysms

The complications of EVT for MMD-associated aneurysms are similar to those in other neurovascular diseases, including hemorrhagic, ischemic, and equipment-related complications [22]. But the reserve of cerebral vasculature in MMD patients is poor [15, 44, 63]. EVT procedures tend to pose a higher risk of perioperative hemorrhagic and ischemic complications in MMD patients [5, 6]. Hemorrhagic complication and equipment-related complications mainly occur during the process of aneurysm embolization, which might be intraoperative rupture or piercing of the parent artery by microwire [52]. A case of MMD-associated PCom aneurysm is presented in Fig. 5. During coiling, the aneurysm ruptured. In another case of MMD-associated LSA aneurysm, the LSA was pierced by the microwire toward aneurysm navigation (Fig. 6). Ischemic complications are not uncommon. In MMAs, it can be due to inadvertent occlusion of the neighboring artery or subsequent occlusion from equipment-related injury of the artery [53, 65]. Besides, most of the MMD associated no-MAAs would undergo PAO, which might lead to permanent neurologic deficit by obliteration of distal arteries or obliteration of proximal parent artery due to liquid embolic agent reflux.

Fig. 5 PComA aneurysm concurrent with MMD. a CTA shows disappearance of the bilateral MCAs and ACAs. An aneurysm is located at the right ICA terminus. b, c Angiogram of the bilateral ICAs in lateral view shows occlusive alteration of the ICA terminus. The bilateral PComAs are patent and an ICA-PComA aneurysm is also noted at the right side. d Intraoperative angiogram of the right ICA in lateral view shows intraoperative rupture of the aneurysm during coil embolization. E, After completion of the embolization, partial extrusion of the coils is noticed. f Postoperative Xper-CT shows leakage of the contrast agent into the subarachnoid space. ACA, anterior cerebral artery; AP, anteroposterior; CT, computed tomography; CTA, computed tomography angiography; ICA, internal carotid artery; MCA, middle cerebral artery; MMD, moyamoya disease; PComA, posterior communicating artery



Furthermore, ischemic complication might also be related to perioperative hypercapnia, hypocapnia, hypotension, and hypovolemia, which are reported to impair the vascular reserve [30].

The prognosis of MMD-associated aneurysm undergoing EVT

In general, in spite of various complications, the prognosis of EVT in MMD-associated aneurysms is acceptable [29, 69].

For MMD-associated MAAs, EVT has been tried since the 1990's [42]. Since then, the reports with satisfied EVT effect has been continuing, for instance, in 2011, Yeon et al. reported successful EVT of 6 MAAs with satisfying outcome [65]. For broad-necked MAAs, stent-assisted coiling is also a safe

strategy [9]. The patients with MMD-associated distal CAAs often have good local collaterals, which means they can tolerate super-selective PAO well; PAO can bring good outcome [32, 64]. NBCA, Onyx, and coils can be good candidates; especially, NBCA has good delivery ability for distal lesions, which was popularly used [10]. For instance, In Kim et al.'s report (2009), successful EVT of 6 cases with distal CAAs using NBCA was obtained [31]. In MMD patients, the implementation of EVT for LSA and TPA aneurysms should be very cautious [2, 23]. In highly selected cases with good access route, the EVT could bring good outcome. For instance, Lama et al. (2014) reported 2 cases of MMD-associated LSA aneurysms, who experienced successful PAO and good outcome [34]. For these vessel aneurysms, if possible, preoperative provoking test is necessary for safe PAO [19]. For TCAs,

Fig. 6 LSA aneurysm concurrent with MMD. Angiogram of the a right ICA in AP and b lateral views shows steno-occlusive alteration of the right ACA. An aneurysm (arrow) is noticed at the LSA. c Intraoperative angiogram of the right ICA reveals extrusion of the contrast agent (multiple asterisks) indicating perforation of the LSA, the arrow showing the aneurysm. d Unsubtracted angiogram of the right ICA after PAO with coils (arrow) shows disappearance of the parent artery and LSA aneurysm. Leaked contrast agent (asterisks) is also noted. e Postoperative angiogram of the right ICA in lateral view confirms occlusion of the LSA. f Postoperative CT confirms the leaked contrast agent in the region of the right basal ganglia. ACA, anterior cerebral artery; AP, anteroposterior; CCA, common carotid artery; CT, computed tomography; ICA, internal carotid artery; LSA, lenticulostriate artery; MMD, moyamoya disease; PAO, parent artery occlusion



if the collaterals were properly preserved during EVT, favorable outcome is anticipated [40]. As TCAs might be situated in the net-like collaterals, direct occlusion of the aneurysms is very difficult. In this case, decreasing the blood flow by PAO is always effective and can lead to delayed spontaneous remission of the aneurysm [33].

Conclusions

In summary, intracranial aneurysms in MMD can be divided into two main types and subdivided into five subtypes. The EVT of MMD-associated aneurysms should be in a case-bycase approach, of which it is easier for MAAs. Most of the time, PAO is chosen for the non-MAAs. Hence, to avoid the inadvertent complications, careful selection of appropriate patients is of utmost importance in case of non-MAAs. The poor reserve of vasculature in MMD, perioperative management, and meticulous intraoperative manipulation are also very important. In spite of the aforementioned complications, the EVT can bring good outcome in highly selected cases.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Informed consent Informed consent was obtained from all individual participants included in the study.

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