REVIEW ARTICLE

MANAGEMENT OF THE UPPER LIMB ARTERIOVENOUS MALFORMATIONS

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Abstract

Introduction: *Arteriovenous malformations (AVMs) involving the upper limb constitute 10% of the total AVMs. In the upper limb, AVMs are more frequent in the hand than in the arm, being the hand one of the body's regions more frequently associated with AVMs, coming after the head and neck. The total prevalence of the upper limb AVMs remains unknown and there is currently no definitive consensus for the treatment of upper limb AVMs. The purpose of this study was to review the best evidence of the treatment for the upper limb AVMs and describe their clinical characteristics and diagnosis. The majority of patients with asymptomatic AVMs follows a conservative management. In the symptomatic patients, the treatment with surgery and or chemical embolization is beneficial. The amputation can be necessary in the case of life-threatening and massive AVMs, constituting the first step in patient's rehabilitation. Although the most common option for the management of symptomatic or functional AVMs is the embolo-sclerotherapy combined with surgery, different outcomes should be taken into account to plan the treatment, specially the presence of symptoms, bleeding and heart failure.*

INTRODUCTION

The knowledge of upper extremity arteriovenous malformations (AVMs), among other vascular disorders has greatly advanced in the last 20 years. Indeed, scientific medical community gained a deeper knowledge of its pathogenesis, clinical manifestation, diagnosis and treatment. However, there's no consensus for the treatment of upper limb AVMs. A detailed description of the present state of treatment for upper extremity in AVMs is presented. The data used were identified by a search in PubMed with the keywords "arteriovenous malformation", "AVM" in combination with the term "upper extremity". For this study, the authors focused on publications in the past 20 years and published in English.

EPIDEMIOLOGY

Despite constituting the most common pediatric abnormality, occurring in approximately 1% of children, AVMs are rare.[1,2] prevalence of AVMs is estimated to be 1 in 100.000 in Caucasians.[3] The AVMs can be evident at birth, being evident in 40% of the cases according to a study of a population with 200 cases of AVMs.[4] The female-to-male ratio is 1:1.[4] AVMs can occur in the entire body, being more frequent in the head, neck and hand. In the upper limb the prevalence of AVMs represents 10% of the total caseload. In the upper limb, AVMs are more frequent in the hand than in the arm [6,7]. The exact prevalence and incidence of the upper limb AVMs remains unknown.[8]

PATHOPHYSIOLOGY

The origin of AVMs occurs between the 4th and 10th weeks of embryo development and is related with focal defects in vascular development in utero[3, 4,9,10] A possible mechanism of AVMs lesions is the persistence of primitive vascular elements and in the literature the majority of the studies defend that AVMs result from an error in vascular development during embryogenesis.[4] It is believed that AVMs developed because primitive arteriovenous shunts fail to undergo apoptosis.[11-14] The majority of AVMs are sporadic, however a minority of patients presents an aggregation. The molecular studies show that different genes are involved in the development of AVMs, including mutations in ALK-1, RASA1 and PTEN.[15] The reasons for the progression of patients' conditions of AVMs are still unknown and sometimes the arteriovenous communication at the resting state are reopen due to hemodynamic changes and local ischemia induced by trauma, which can aggravate the patients' condition.[8] No demographic or environmental risk factors for upper limb AVMs have been identified clearly so far.[16] Thus, upper limb AVMs are located in the hand and/or in the arm and can be described as a congenital lesion with no capillary bed and thus with shunting of blood directly from the arterial to venous circulation through one or more fistulae (Figure 1).[17] The cells found within the nest generally demonstrated chronic modifications and are generally nonfunctioning. In addition, since no capillaries can be found, the arterial and venous elements commonly show signs of hypertrophy in their walls. Moreover, the arteries commonly have a deficient muscularis layer, while the veins frequently are dilated, causing high velocity of blood flow through the fistulae (Figure 1).[16,18,19]

Despite the above-mentioned, other distinct theories can be found in the literature and the origin of AVMs remains an investigative issue.[20]

The expansion of the lesions constitutes the primary cause of morbidity and the enlargement of AVMs occurs due to an increased blood flow causing collateralization, dilatation of vessels, and also the thickening of adjacent arteries and veins. The latent arteriovenous shunts may open, and this mechanism can stimulate hypertrophy of surrounding vessels from increased pressure. On the other side, aneurysms may increase the size of the lesions. Additionally, angiogenesis and vasculogenesis are also be involved in AVMs expansion. Frequently, the primary stimulus for AVMs growth is neovascularization but it also could be a secondary event, after stimulators of angiogenesis, including ischemia and trauma. On the other side, the elevated blood flow is responsible for the production of vascular endothelial growth factor.[5]

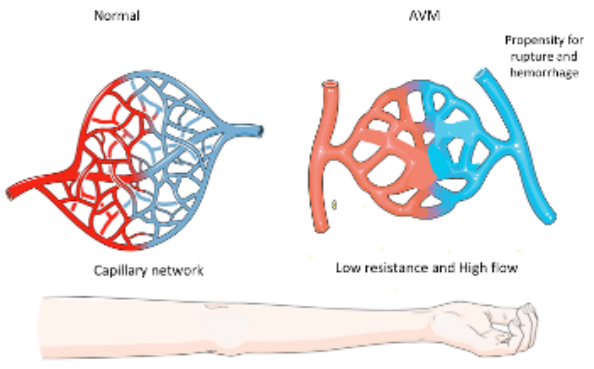

Figure 1 *Schematic representation of upper arteriovenous malformations (AVMs).*

CLINICAL PRESENTATION

Congenital AVMs may not become evident until childhood or even until adulthood. Generally, congenital AVMs are clinically silent until the first event that frequently translates in hemorrhage or alteration of the skin color.[5] In the case of arterial bleeding, the bleeding generally occurs superficially, namely at skin or mucosal levels but can also occur more deeply.[6] The color of the skin due to the presence of the shunt can be pale.[7, 8] However, the clinical manifestations of AVMs are extremely varied and the lesions can present a wide spectrum.[9] From barely noticeable, to unspecific signs, including, small, strawberry birthmarks to massive clusters of engorged vascular channels that may extensively deform an extremity and also congestive heart failure due to high flow.[10] Ultimately, AVMs can also cause the disfigurement, destruction, and obstruction of vital structures of the upper limb. Regarding the symptoms, due to ischemia AVMs can be associated with pain, ulceration, spontaneous bleeding, nerve compression, including palsy.[5]

DIAGNOSIS AND CLASSIFICATION

The diagnosis of upper limb AVMs is mainly made by medical diagnosis, and using the commentary imaging methods, including ultrasonography (US) magnetic resonance imaging (MRI) (Figure 2). The anamnesis and the physical examination are enough to make the proper diagnosis of AVMs in 90% of the cases.[11, 12] In the other cases, high-quality imaging studies are the key for diagnosis and staging of upper limb AVMs. Thus, in the case of suspicion, the diagnosis can be confirmed by US generally associated with color Doppler by identifying a fast-flow and shunting in positive cases. In fact, the Color Doppler imaging (CDI) is nowadays considered an essential tool in the diagnostic of AVMs. This technique allows accurate flow and resistance measurements, which can be a key in the initial evaluation and also constitute noninvasive parameters for follow-up after therapy.[13] MRI can be performed with and without contrast to better demonstrate characteristics of AVMs, including the site, size, flow characteristics, and involvement of contiguous structures.[14] MRI can accurately distinguish between high-flow and low-flow malformations and also the relationship to adjacent structures, such as muscles, nerves, and organs, confirming the diagnosis. For the treatment plan is essential to perform MRI, being needed even

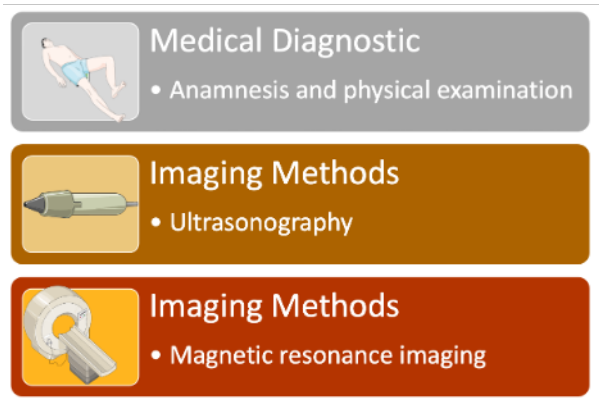

Figure 2 *Main diagnostic methods used in the upper limb arteriovenous malformations (AVMs).*

if US shows a positive AVM. MRI can be associated to angiography (MRA) and may identify AVMs greater than 1 cm in size, being however inadequate to delineate the morphology of feeding arteries and draining veins and using this technique, the small aneurysms can be easily missed.[15] If the diagnosis of the upper limb AVMs remains unclear after US and MRI, selective angiography should be performed. Angiography is also useful if embolization or resection is planned. MRI fully replaced computed tomography (CT), which is of interest only if AVMs involves the bone. The biopsy and the histopathological examination are rarely performed due to the complications associated of profuse bleeding and reactive expansion of the lesion. [16]

The International Society for Study of Vascular Anomalies (ISSVA) has categorized vascular anomalies into vascular tumors and vascular malformations. The vascular malformations have been further subcategorized as being low-flow or high-flow malformations.[17]

The lesions of AVMs despite being quiescent are considered dynamic since they can progress over time and may recur after treatment. Since AVMs can be so diverse in nature, the AVMs of the upper limb can be classified according to the Schobinger staging system (Table 1).[18]

Differential diagnosis of AVMs of the upper limb, includes among others, anterior circulation stroke, cardioembolic stroke, dissection syndromes, fibromuscular dysplasia, digital lesions, such as osteomyelitis, Buerger's disease, ischaemia from emboli and tropical diseases. [15, 19]

TREATMENT

After diagnosis, one of the major decisions is to determine whether therapy is indicated.[13] In the case of superficial AVMs, the patients should apply hydrated-petroleum to prevent desiccation and ulceration. [20] The use of compression garments is controversial for the upper extremities AVMs since their use can reduce pain and swelling but can in some cases worsen the neurologic symptoms. The treatment plan for upper limb AVMs is generally conducted to ameliorate symptoms (e.g., bleeding, pain, ulceration), to preserve vital functions (e.g., movement, manipulate objects), and minimize the deformity.[20] The treatment for upper limb AVMs can be conservative, minimally invasive and surgery, combined in a multimodal approach or isolated according to the clinical situation (Figure 3).

In the case of need for treatment, approximately three-fourths of patients with upper limb AVMs will require treatment in childhood or adolescence and the remaining patients will need the treatment when adults.[16] Since AVMs generally are diffuse, involving an extended region, the cure is very rare, being the main goal of the treatment to control the malformation.[21] The invasive management options include endovascular embolization and/or surgical resection and also focal beam radiation.[6] The pharmacological treatment can be also a possible option but only in selected cases.[22] In fact, until now no randomized clinical trials exist comparing invasive treatments versus medical management. [23-25]

Taking in consideration the stages of Schobinger, in the asymptomatic Stage I, the management should be individualized taking into account the degree of deformity that would be caused by excision and reconstruction. For instance, a Stage I AVMs can progress to a larger stage and for that reason should be resected, especially if located in an anatomically important location of the upper limb (proximal extremity vs distal extremity). The Stage II intervention has a lower threshold for treatment than Stage I. In the case of Stage III and IV, the intervention is mandatory to control pain, bleeding, ulceration, or congestive heart failure. Despite the above-mentioned, the only absolute indication for urgent surgery procedure is cardiac decompensation, which is rare but can occur associated with extensive arteriovenous shunting.[26]

The complete cure of AVMs although challenging is possible. Endovascular therapy with embolization has been the core treatment of AVMs.[27] Embolization involving the delivery of an inert substance through a catheter proximal to the AVMs, aims to block the high-flow shunting of blood from the high-pressure arterial system into the venous system. 27 For this procedure general anesthesia is used and the embolic

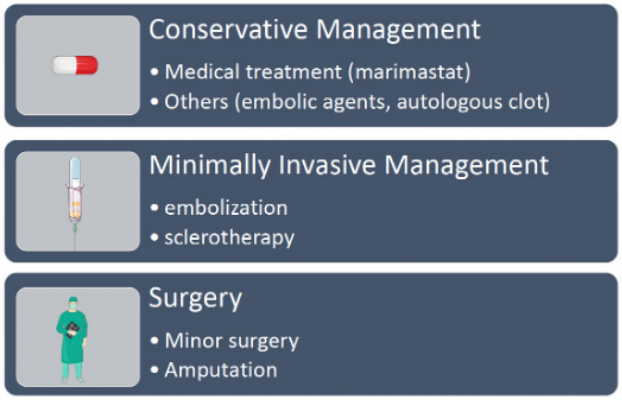

Figure 3 *Treatment options for upper limb arteriovenous malformations (AMVs).*

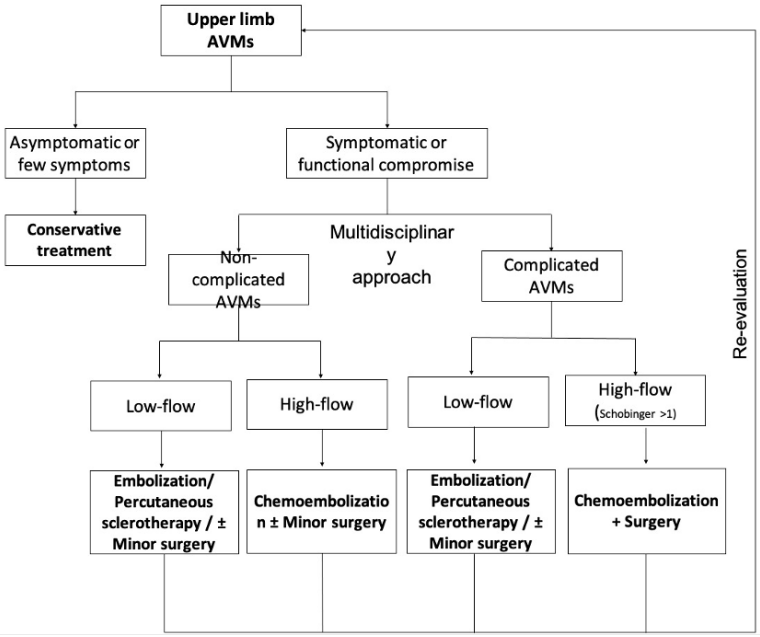

Figure 4 *Simplified algorithm for the treatment of upper limb arteriovenous malformations (AVMs).*

agent must reach to nidus, ideally to the point of initial venous drainage. [5] An excessively proximal arterial embolization is usually not recommended since recanalization is frequent and the lesion becomes inaccessible for future embolization. [28] Several embolic agents can be used to treat AVMs, being ethanol the most described. [29, 30] Other agents include autologous clot, gelfoam, polyvinyl alcohol particles (PVA), metallic coils with or without fibers, tissue adhesives (IBCA/NBCA), detachable balloons, ethibloc and sotradecol. The embolization can be executed in a single-stage or in multi-stages typically spaced by several weeks, and always aiming to the nidus. The use of a multi-stage approach seems to be more effective and safer. [31] In the majority of the cases this technique alone is not sufficient to completely obliterate the AVM. In fact, in most cases the lesions will expand after this treatment, having the Stage I AVMs a lower risk of recurrence rate than higher-staged lesions. Generally, recurrences will occur within the first year after embolization and 98% re-expand within 5 years.[16] However, this technique may effectively palliate an AVM by reducing its size, slowing expansion, and alleviating pain and bleeding. [16] The most frequent complications of embolization are ulceration and pain. In addition, distal migration of embolic material can also occur and may be responsible for ischemic injury. Compartment syndrome as well as nerve damage may also occur as side-effects of this procedure. [5]

Sclerotherapy consists in a transcutaneous injection of a substance into the malformation that causes endothelial destruction and thrombosis. Thus, the fibrosis process of the vascular space decreases the size of the lesion. The most important risk of this technique is the potential of the agent to escape to the systemic circulation. Several agents can be founded in the market, being the most used ethanol, which must be used carefully since it can cause nerve damage. [5]

The combination of embolotherapy with sclerotherapy, specially using ethanol as both embolic and sclerosing agent is to be a more efficacious treatment for patients with upper limb AVMs in comparison with each technique alone. [32] A retrospective study performed by Park et al in 2012, involving 64 patients with hand AVMs treated in a single institute, concluded that the symptoms and characteristics of the lesions are important factors for the determination of the ideal treatment plan for hand AVMs. [33] Moreover, the authors concluded that embolo-sclerotherapy carried a potential risk for various complications. Skin necrosis was the major complication treated with embolo-sclerotherapy, being the risk of skin necrosis higher for the AVMs that involved the subcutaneous layer and the AVMs that extended diffusely. Despite being transient, neuropathic complications after embolo-sclerotherapy also occurred.[33] Moreover, Cho et al reported a case of permanent ulnar nerve palsy after embolotherapy of an AVM around the elbow. The authors concluded that embolotherapy of AVMs with a location close to major neurovascular structures should be carefully planned and individualized.[34] Moreover, a retrospective study conducted by Park et al, demonstrate that no therapeutic benefit exists in AVMs involving both the fingers and the palm using ethanol chemoembolization.[33]

Surgery, namely the resection of AVMs has a lower recurrence rate than chemoembolization alone and is considered for localized lesions.[35] The surgery of large and diffuse AVMs should be performed with caution since the cure is rare and the recurrence rate is very high. In the upper limb, the surgical resection of the AVM should preserve upper-limb function. However, the resection is often associated with blood loss, iatrogenic injury and morbidity. Therefore, surgical excision should be conducted systematically, involving steps to minimize the risk of uncontrollable intraoperative bleed-

ing and postoperative complications.[36] The surgical margins are best determined clinically, by assessing the amount of bleeding from the wound edges and the majority of the defects reconstructed by advancing local skin flaps.[18] Amputation can be necessary in the case of life-threatening and massive AVMs, being the first step in the patients' rehabilitation. Thus, if AVMs affect a large extent, amputation can be the first option if accepted by the patients. In the case of AVMs located exclusively in the hands, the resection is in general the first option even if the AVM is deeply located and involves the small muscles of the hand, due to the higher risk of distal ischemia from embolization. [4, 33] The use of postsurgical angiography can be done routinely to ensure that no residual AVM exists. However, as above-mentioned there are several cases reported in the literature of AVMs reappearance, years after a negative postresection angiogram. [37] Su et al reported a case report of a man with 32-years old that presented an upper limb that undergone rapid expansion causing significant pain, dyspnea and also high-output cardiac failure. In this case, due to the diffuse lesion, the patient required a major amputation despite repeated excision and reconstruction. [19] However, in one series of 33 patients with AVM of the upper limb, the majority of patients were successful treated by surgical excision. The authors present the surgical principles involved in resection of the upper limb AVMs, including: (1) maintain absolute hemostasis under tourniquet control; (2) carefully plan the dissection within a well-defined anatomic area; (3) preserve the nerves, tendons, and joint cavities; (4) avoid intraneural dissections; (5) avoid joint synovectomies and capsulectomies; (6) use separate procedures for each side of a digit, hand, or forearm; (7) avoid combined dorsal and palmar dissections; (8) eliminate the need for a reoperation in a scarred region by performing a thorough initial dissection; and (9) wait for return of function and softening of soft tissues before performing the next stage of the procedure. [14]

The combination of both excision and chemoembolization can be desirable since the embolization will facilitate the surgical procedure by reducing the size of the AVMs and consequently minimize blood loss, and creating scar tissue to aid the dissection, especially in high-flow cases. When combined, the excision should be conducted up to 72 hours after embolization technique, before the restoration of the blood flow to the lesion. In addition, a local anesthetic associated with epinephrine can be used to reduce the blood loss, being the use of a tourniquet also desirable. The combination of both techniques is especially useful for diffuse and large AVMs and they must be accessed for embolization.[38] For surgically inaccessible AVMs, generally embolization is preferred. [39] Recently, Sánches-Morales reported a case report of a male 35 year-old that was treated with multiple sessions of vessel embolization, sclerotherapy and surgery resections. The patient developed several complications, including ischemia, digit necrosis and infection. Thus, a distal forearm amputation was indicated.[40]

Since the exact mechanisms for AVMs pathogenesis and expansion is still not fully understood, pharmacotherapy is rarely the first option for the treatment of AVMs. To control AVMs, angiogenesis inhibitors or even estrogen antagonists could be useful to slow the natural progression of AVMs, reducing the need for intervention and also can be useful to increase the efficacy of both procedures used in association, i.e. embolization and surgery.[41] Novel therapeutic targets and more clinical trials are needed because the pharmacological treatment has the potential to treat the primary cause of AVMs. [22] Burrows et al, reported the case of a 3 years-old child with AVM involving the right upper extremity was treated with marimastat during 12 years, resulting in the relieve of symptoms and progression with no side-effects. [22] A single study using a pharmacological approach for the treatment of the upper limb AVMs was found in the literature, using marimastat, which is a metalloproteinases inhibitor and can be orally administered. This drug was chosen in a patient in which the osteolysis associated with the expansion of the upper limb AVM was related with the activity of metalloproteinases. [22] Moreover, laser has been proposed for the treatment of digital AVMs. Thus, digital AVMs affecting finger that generally requires complete excision of the lesion with complex advancement flap or skin graft reconstruction were successful treated with laser in a series of 5 patients having Schobinger stage I lesions. [42] In addition, the laser treatment was safe and a good alternative for the treatment of AVMs. Digital AVMs were also successfully treated with long-pulsed neodymium:yttrium-aluminum-garnet laser treatment. [43]

Figure 4 depicted an algorithm for the treatment of upper limb AVMs based on the presence or in the absence of symptoms.

However, the treatment of upper limb AVMs is challenging, and a multidisciplinary team should individually analyze each case. In this context, Lee et al have successfully utilized a multidisciplinary approach to the treatment of a high risk AVM lesion. [44] The authors combined both endovascular therapies with open surgical resection, resulting in an excellent outcome. [45]

CONCLUSIONS

The management of AVMs remains a challenge, particularly those involving the upper limb. The treatment is recommended only when the benefit exceeds the risks involved. However, in the case of upper limb AVMs there is no established clinical algorithm for surgical approach, although reintervention is the rule. Thus, not all upper AVMs warrant treatment nor is treatment feasible in some cases. The surgery combined with embolo-sclerotherapy seems to be the best option in symptomatic AVMs, however systematic studies with different outcomes are needed to determine the tailored option for the treatment of upper limb AVMs. [46] The treatment of upper-limb AVMs is best achieved with a multidisciplinary team that can contribute to minimize the morbidity and reduce recurrence of upper limb AVMs.

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