

Arteriovenous malformations in the neonatal period: case report and literature review

Mariana C. Abreu¹, Joana Pinto², Gustavo Rocha², Maria Garcia³, Maria do Bom-Sucesso⁴, António Miguel Madureira⁵, Hercília Guimarães^{2,6}

¹Department of Pediatrics, Centro Materno-Pediátrico, Centro Hospitalar Universitário São João, Porto, Portugal

²Neonatal Intensive Care Unit, Department of Pediatrics, Centro Materno-Pediátrico, Centro Hospitalar Universitário São João, Porto, Portugal

³Pediatric Surgery Department, Centro Materno-Pediátrico, Centro Hospitalar Universitário São João, Porto, Portugal

⁴Pediatric Hematology-Oncology Department, Centro Materno-Pediátrico, Centro Hospitalar Universitário São João, Porto, Portugal

⁵Radiology Department, Centro Hospitalar Universitário São João, Porto, Portugal

⁶Faculty of Medicine, University of Porto, Porto, Portugal

Abstract

Congenital vascular anomalies are a heterogeneous group of lesions, subdivided into vascular tumors and vascular malformations. Incorrect nomenclature and misdiagnoses are frequent. Arteriovenous malformations (AVM) are potentially the more aggressive type of vascular malformation. They are formed by a complex network of malformed arteries and veins without intervening capillary bed resulting in arteriovenous shunting. The clinical presentation ranges from tissue swelling to serious clinical issues, as right heart failure.

We report the case of a female newborn affected by an AVM stage IV of Schobinger, evidenced in the immediate neonatal period, despite the lack of prenatal diagnosis. She underwent two endovascular embolizations procedures with Onyx 18®, with effective devascularization of the AVM. Although advantageous, embolization is a challenging procedure and the risks are real. Our patient experienced a life-threatening hemorrhage a few days after the first embolization. We considered that complete devascularization of the AVM was achieved after two embolization procedures. At 14 months old, she underwent surgery for resection of residual AVM, with fast postoperative recovery. Currently, she is 17 months old, and no AVM recidive occur until now.

We report a clinical case that evidences the difficulties of approaching an AVM Schobinger stage IV in the neonatal period. We also present a review of the literature on vascular anomalies with special attention to AVM.

Keywords

Congenital vascular anomalies, arteriovenous malformations, Schobinger classification stage IV, endovascular embolization, haemorrhage, devascularization.

Corresponding author

Mariana C. Abreu, MD, Pediatric Department, Centro Hospitalar Universitário de São João, Oporto, Portugal; e-mail: marianacgabreu@gmail.com.

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Introduction

Congenital vascular anomalies are considered to be the most complex vascular diseases and impose diagnostic and therapeutic challenges, even in the presence of increasing awareness of rare diseases [1]. They are a heterogeneous group of lesions, ranging from a simple “birthmark” to life-threatening entities. Incorrect nomenclature and misdiagnoses are common in patients with these anomalies [2]. Much has been learned over the last two decades with the growth of multidisciplinary teams, as the International Society for the Study of Vascular Anomalies (ISSVA). Reliable data regarding the number of affected patients is not available [1, 3-4].

Vascular anomalies are classically subdivided into vascular tumors and vascular malformations, depending on the intrinsic properties of endovascular cells. However, there are nearly a hundred diagnostic possibilities [5-7]. Whereas vascular tumors may regress with patient’s age, vascular malformations increase in size and spontaneous regression is not expected to occur [1, 6, 8].

The ISSVA classification system has helped to uniformize vascular anomalies nomenclature

worldwide [1, 7]. It preserves the two broad categories in which vascular anomalies were previously divided, but with the increasing knowledge of the genetic basis for these diseases, including the genetic mutations associated with many of them, both lists significantly grew in size [6, 7].

We report the clinical case of a congenital arteriovenous malformation (AVM) that evidences the difficulties of approaching an AVM Schobinger stage IV in the neonatal period. We also present a review of the literature on vascular anomalies with special attention to AVM.

Case report

We present the case of a female newborn, the second daughter of young, healthy and non-consanguineous parents, with a healthy first child. The pregnancy was uneventful, except for the finding of thrombocytopenia in the third trimester of unexplained cause. The newborn was delivered at 41 weeks of gestational age, by cesarean section at a level II center. The Apgar score was 4/6/8 at 1st/5th/10th minutes. She required aspiration of meconium from the oropharynx and ventilation with positive pressure, with progressive improvement of respiratory distress. She maintained hypoxia without response to supplemental oxygen. The birth weight and height were in the 3rd-10th percentile, and head circumference in 50th percentile. The clinical examination revealed an extensive frontal mass, without antenatal diagnosis, and a cardiac murmur (**Fig. 1**). The remaining physical examination was normal. She was transferred in



Figure 1. Extensive frontal mass in the left supraorbital region, violaceous, with a vascularized aspect and cutaneous erosion, on day 1 of life.

the immediate postpartum period to our level III Neonatal Intensive Care Unit (NICU) because of suspected congenital heart disease. She was admitted on spontaneous ventilation, with 0.5 l/min supplemental oxygen, presenting tachypnea, with other vital signs stable. The cardiological evaluation identified a structurally normal heart and pulmonary hypertension (maximum systolic pressure in the right ventricle 87 mmHg), requiring treatment with diuretics. She presented thrombocytopenia, with a minimum platelet value of 34,000/mm³ on day 4. No changes were detected in coagulation study. Abdominal and cranial ultrasounds were normal. A spontaneous resolution of thrombocytopenia was observed on day 8. The cerebral magnetic resonance imaging (MRI) showed an extensive epicranial left fronto-palpebral AVM, with arterial feeding mainly derived from branches of the left external carotid artery and intracranial venous drainage by the ophthalmic veins for the cavernous sinuses (Fig. 2).

The clinical case was discussed by the Interdisciplinary Group of Vascular Anomalies of our center, and the newborn was submitted, on day 20, to a transcatheter arterial embolization. Selective arteriograms of the left external carotid documented a large vascular malformation with

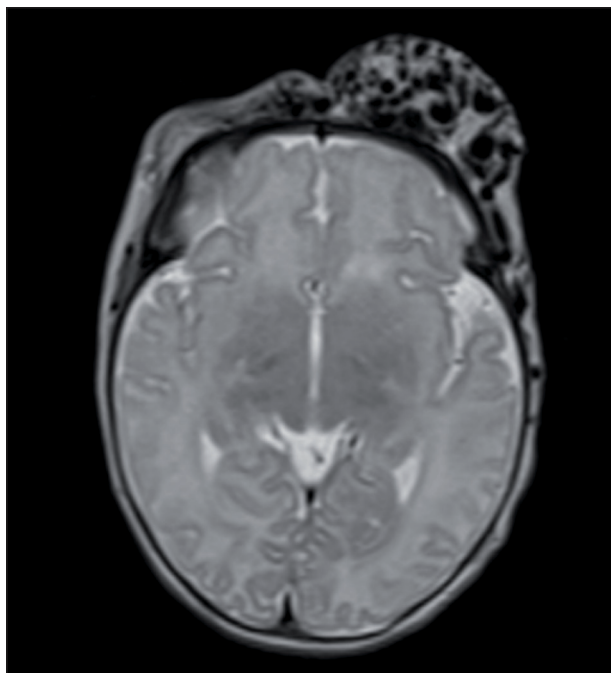


Figure 2. Cerebral magnetic resonance imaging (MRI) showing an epicranial left fronto-palpebral extensive arteriovenous malformation (AVM), formed by a conglomerate of multiple ectasic and tortuous vascular structures, with arteriovenous shunt.

high-flow arteriovenous shunting, suggesting the diagnosis of an AVM grade 4 of Schobinger (Fig. 3). The embolization procedure was performed with superselective catheterization and embolization of the distal superficial temporal artery with Onyx 18® (Fig. 4). After this, regression of pulmonary hypertension was observed and it was possible to suspend diuretics. On day 28, during a dressing change of the AVM, AVM rupture occurred with massive hemorrhage, hypovolemic shock and cardiorespiratory failure. She was resuscitated

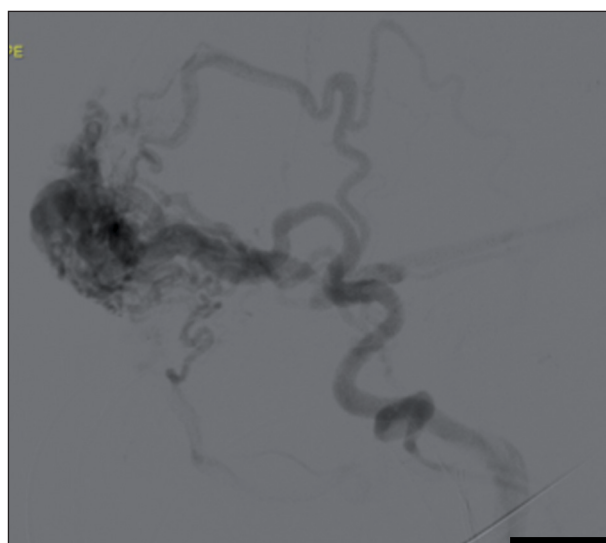


Figure 3. Diagnostic angiography. Major arterial afferents: superficial temporal artery, internal maxillary artery and facial artery; principal venous drainage through the left ophthalmic vein, left superficial temporal vein and left internal maxillary vein.

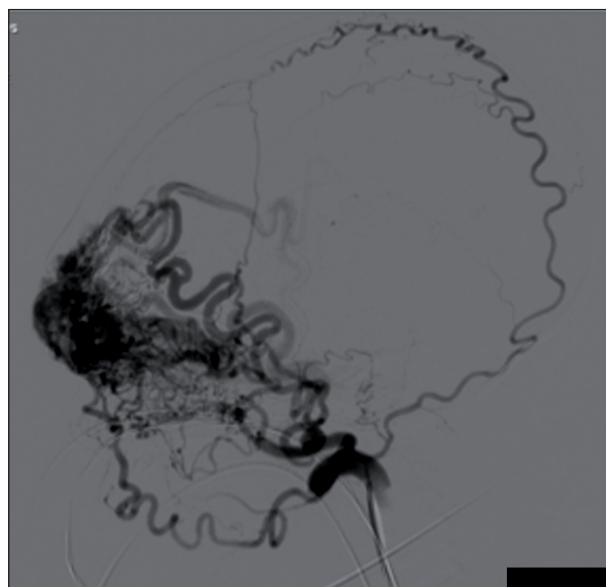


Figure 4. Superselective catheterization and embolization of the distal superficial temporal artery with Onyx 18®.

after advanced cardiopulmonary resuscitation maneuvers, with the need of volume and blood administration by two intraosseous accesses. Hemostatic control was achieved with surgical suture (Fig. 5). She was submitted to new AVM embolization on day 35, resulting in additional AVM devascularization, without complications (Fig. 6). On day 82, she was submitted to a new angiography, with no indication for embolization because of spontaneous regression of the remaining shunt (Fig. 7).

She was discharged home at 12 weeks of post-natal age, thriving well. At 9 months old (Fig. 8),



Figure 5. Surgical suture after massive hemorrhage during dressing care.

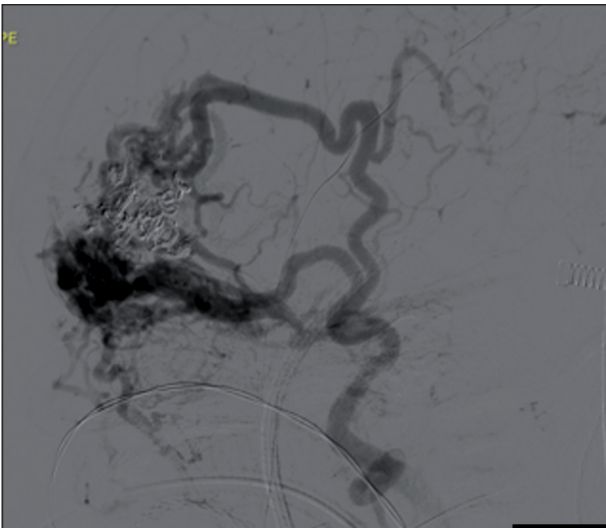


Figure 6. Superselective catheterization and embolization of the distal superficial temporal artery with Onyx 18®, resulting in additional arteriovenous malformation (AVM) devascularization. Distal superselective catheterization of the facial artery, attempted Onyx 18® embolization not achieved because very high flow in this artery did not allow polymerization of Onyx 18®.

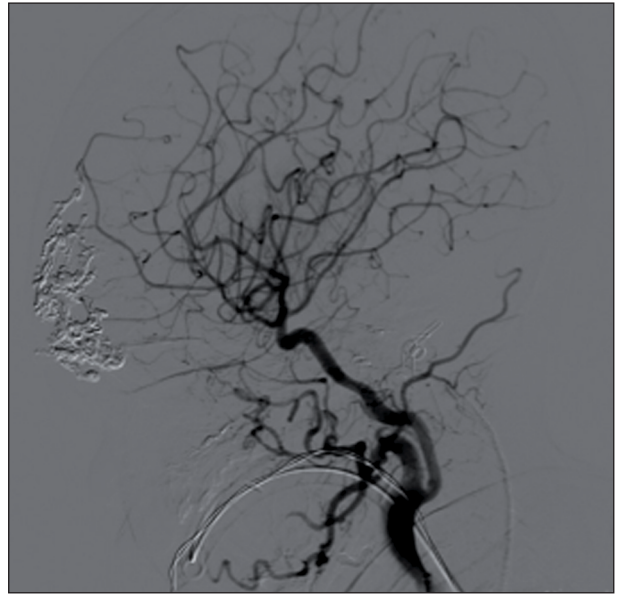


Figure 7. Selective arteriograms of the left external carotid artery document minimal arteriovenous shunt, without formal indication for embolization.



Figure 8. Cicatricial lesion in the left frontal region after two endovascular embolizations procedures; dark skin discoloration of the overlying skin due to Onyx 18® deposition.

cerebral MRI evidenced frank AVM volume reduction (Fig. 9).

She underwent surgery for resection of residual AVM at 14 months old, with fast postoperative recovery. The histology revealed a conglomerate of vessels (arteries and veins) obliterated by embolizing agent. Currently, she is 17 months old and presents residual scarring in the left frontal region (Fig. 10). At the follow-up consultations, she

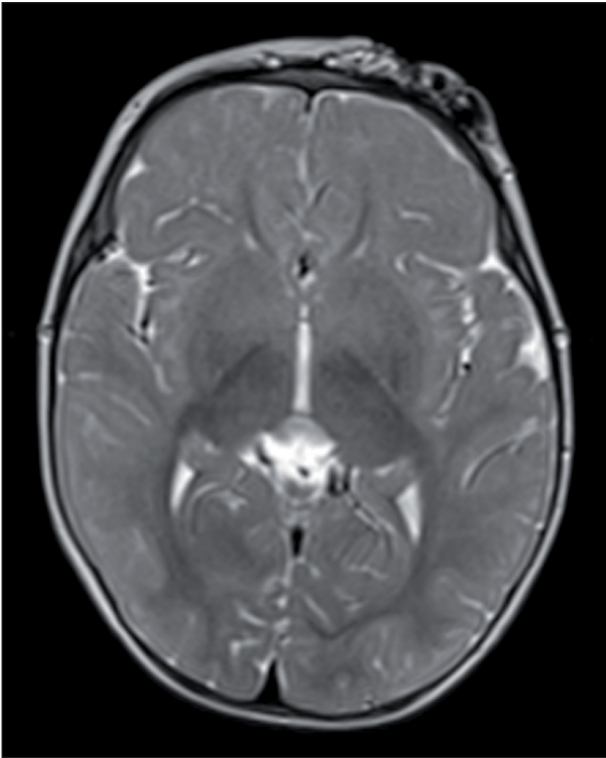


Figure 9. Cerebral magnetic resonance imaging (MRI) at 9 months old: substantial volume reduction of arteriovenous malformation (AVM), without further changes.



Figure 10. Residual scarring in the left frontal region after surgical resection of arteriovenous malformation (AVM).

demonstrates good clinical and imaging progress. She presents adequate growth and developmental milestones. She maintains multidisciplinary follow-up.

Discussion

We reported the clinical case of an AVM, potentially the more aggressive type of vascular malformation [2]. Vascular malformations are composed of abnormal vessels without cellular proliferation or hyperplasia [8]. The ISSVA classification subdivided vascular malformations into four categories: simple malformations – composed of a single vessel type and further categorized based on the type of vessel affected (arteriovenous, capillary, venous or lymphatic); combined – those with two or more types of vascular components forming the lesion; of a major vessel – including anomalies of number, origin, course, length, diameter, valves or communication of a vessel; and vascular malformations associated with other anomalies. The last could be found in multiple syndromes and are one of several presenting anomalies in those patients [1, 6, 8]. Vascular malformations are always present at birth, even if asymptomatic, but may be quiescent for a long time, before mechanical or hormonal influence stimulates them to grow [1, 8].

AVMs comprise up to 4.7% of all vascular anomalies [9] and distribution among sexes, race or ethnicity is equal [3]. They are high-flow lesions, included in the differential diagnosis of high-flow vascular anomalies, but overall less common than many high-flow tumors [8]. AVMs are formed by a complex network of malformed arteries and veins, with direct arteriovenous communications known as nidus, resulting in arteriovenous shunting [2, 4, 6, 10]. According to the localization into or outside the central nervous system, they are divided into central and peripheral AVMs [10]. Their clinical severity is graded using the Schobinger classification, which distinguishes four stages. Stage I represents a clinical inactive AVM presenting with local skin hyperthermia; stage II is for lesions with increase of arteriovenous shunting, expanded and with presence of pulsation and bruit. In stage III, there are signs of tissue destruction with adjacent ulcers, hemorrhage, bone lytic lesions and pain; stage IV reflects decompensated AVM with development of heart insufficiency or cardiac failure in a patient with stage III lesion [1, 8].

Although AVMs are always present at birth, they may manifest at any time during life and most commonly do not come to clinical attention upon second or fourth decades of life [3, 5, 11]. They grow proportionately with the child and clinical

presentation depends on the localization, size and degree of arteriovenous shunting through the lesion [11]. Clinical manifestations range from tissue swelling, enlarging red and warm lesion with pulsation or bruit, intermittent pain or serious clinical issues, as bleeding and even right heart failure [2, 10, 12]. In our report, despite the absence of prenatal diagnosis, the peripheral location of the lesion, and its large dimensions, evidenced the AVM immediately after birth. Our patient showed an extensive AVM with an important arterial component shunting blood away directly into draining veins, causing pathologic venous hypertension and cardiopulmonary overload – a Schobinger stage IV AVM. This is a rare and dangerous presentation of AVM [12].

AVMs may be associated with other vascular and nonvascular anomalies. They occur sporadically or are inherited as part of other syndromes, such as hereditary hemorrhagic telangiectasia (HHT) syndrome or capillary malformation – arteriovenous malformations (CM-AVM) syndrome [2, 12]. In our patient, there was no family history of vascular malformations and to date no other anomalies besides the reported one were found. Whole-exome and genome sequencing on AVM tissue has recently been used to identify disease-specific pathogenic mutations in patients with sporadic AVMs. Prior studies have reported somatic mutations in *MAP2K1*, the gene encoding MEK1, and also in *KRAS* and *BRAF* genes [9, 12, 13].

Although AVM may be evidenced on noninvasive imaging, the gold standard for diagnosis is a formal catheter-based angiogram [3]. Angiography demonstrates arterial feeders, nidus configuration, draining veins and its hallmark of early drainage pattern [1, 3]. On the other hand, catheter angiography remains a prerequisite for treatment decisions of AVMs [1].

AVMs are the most challenging vascular anomaly to treat successfully [9] because they invariably progress due to the fast flow in the arteriovenous connections [1]. Treatment, including surgical resection and embolization, has a high recurrence rate [9, 10].

Surgical resection of AVMs is feasible in early-stage lesions; however, usually surgery is avoided due to higher risk of bleeding, damaging of vital structures and incomplete vascular eradication [11].

Endovascular embolization has been suggested as a treatment option for AVMs since the early

1970s [11] and could be used with different aims: complete occlusion with embolization alone or a first step treatment to prepare for a further procedure (surgery or radiosurgery) [14, 15]. Nowadays it is the first-choice treatment for AVMs [10, 16] and the intention is the complete obliteration of the nidus with limited tissue involvement [14]. Although advantageous, these are technically challenging procedures because of the risk of nontarget embolization and/or incomplete treatment [10]. The presence of multiple feeding arteries was described as the only independent predictor of incomplete occlusion [14]. Preferably, the embolization procedure is performed simultaneously with the diagnostic angiography, particularly in the pediatric population [3].

As reported, the newborn was submitted to a first embolization at the same time as diagnostic angiography. The complexity of the lesion and the low weight of our patient forced to interrupt the procedure and to plan a new embolization, on the basis of worries concerning radiation exposure and dimethyl sulfoxide (DMSO) volume needed. After the first embolization procedure, our patient achieved partial symptom relief and pulmonary hypertension was resolved, because blood flow to the nidus and arteriovenous shunting decreased. However, as described in the literature, several embolization procedures are generally needed [10].

Our patient experienced a serious life-threatening event, during a dressing change, 9 days after the first embolization procedure, with massive hemorrhage and cardiorespiratory failure. However, this situation was overcome and one further embolizing procedure was performed. After these, complete technical success was obtained.

The embolizing agent used was Onyx 18® (Covidien/ev3, Irvine, CA, USA), a nonadhesive liquid that consists of a plastic polymer (ethylene vinyl alcohol copolymer, EVOH) dissolved in an organic solvent agent (DMSO) and suspended in micronized tantalum powder for radiopacity. Onyx 18® has, therefore, fluoroscopic visibility and provide controlled embolization due to slow polymerization, which enables deep penetration in the nidus [4, 10, 11, 14-16]. However, the slow Onyx 18® injection increases the radiation dose given to the patient in case of large AVM [11]. Another disadvantage of this agent is the dark skin discoloration of the overlying skin after embolization, when subcutaneous deposition of the tantalum dissolved in the Onyx 18® occurs,

as experienced by our patient. It is expected that this discoloration regress, with persistence of only faint discoloration [11]. Newer formulations of EVOH, without tantalum, do not carry this risk. Embolization is not always possible for safety reasons and, when possible, can have limited short-term results because of frequent recruitment of new arterial feeders or be associated with disfiguring results [13].

Genotype-guided treatments are being developed for sporadic AVMs in which disease-specific pathogenic mutations are identified. MEK1 inhibitors, such as trametinib, that are approved to treat several forms of cancer, may be considered for patients with sporadic AVMs with mutations in *MAP2K1* [9, 12]. Patients with CM-AVM syndrome or HHT syndrome may benefit from other targeted agents, as vemurafenib or bevacizumab, respectively [12]. Genotyping of affected tissue, when accessible, should therefore be performed. It will be of prognostic value and nowadays offer the potential of personalized medical treatment, particularly in the context of the lack of effective therapy for complex AVMs [13].

In this patient, the strategy outlined was individually tailored and successively adjusted by the Interdisciplinary Group of Vascular Anomalies of our center. As explained, the complexity of the lesion and the low weight of our patient determined the need for progressive embolization procedures. This proved to be beneficial because after the second procedure we found a partial spontaneous regression of the AVM, with obliteration of the accessory branches not yet embolized and a third procedure was unnecessary. The patient remained hospitalized in the NICU during these procedures, with close monitoring of vital signs. Massive hemorrhage occurred during a period of clinical stability and was caused by AVM's tissue loss, an event that may occur after embolization. Surgical resection of residual AVM was performed about a year later for aesthetic reasons and in the perspective of complete vascular eradication.

After 17 months of follow-up, our patient remains asymptomatic and without additional abnormalities on cranial MRI. However, clinical and imaging surveillance are essential. Recurrence has to be expected and patients need to be informed of the possibility of multiple treatment sessions [10]. A highly specialized multidisciplinary team management and follow-up are required in patients with a diagnosis of vascular anomaly, particularly in the case of neonatal AVM.

Conclusions

Neonatal Shobinger IV AVM is a potentially life-threatening entity, with an aggressive clinical course, and treatment risks are real. Considering the present report and literature data, superselective arterial embolization with Onyx 18® can effectively help to control a neonatal Shobinger IV AVM. The authors emphasize that close follow-up of these patients is needed, particularly after the embolization procedure, for the risk of massive hemorrhage due to AVM's tissue loss, as experienced by our patient.

Declaration of interest

The Authors have no conflicts of interest to declare.

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