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Peripheral Arteriovenous Malformations and their Response to Treatment Modalities: Experience at Tertiary Care Hospitals

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ABSTRACT

Background: Arteriovenous malformations result in abnormal communication between veins and arteries. Treatment of AVMs can be surgical or non-surgical. This study aimed to assess the response of Peripheral Arteriovenous Malformations (AVMs) to various treatment modalities.

Methodology: This cross-sectional study was performed at Combined Military Hospital Lahore, Rawalpindi, and Midcity Hospital, Lahore Pakistan, from January 2016 to June 2020. Patients were divided into two groups based on gender. Their demographic data, clinical presentation, and treatments provided were assessed and comparison was done using Chi-Square Test.

Results: Of the 43 patients, 74.4% (n=32) were females with a male-to-female ratio of 1:3. Mean age was 27± 6 years (males) and 17± 4 years (females). Low-flow AVMs were more prevalent in females (81%, n=27). In males, 50% (n=5) AVMs were on the trunk whereas in females 93.9% (n=31) AVMs were on limbs. Doppler-guided foam sclerotherapy (DGFS) as the sole treatment was used in 95.3% (n=41) patients while 32.5% (n=14) patients underwent DGFS followed by surgical excision. In 4.6% (n=2) cases, angioembolization followed by surgical excision was done. One patient was treated with sirolimus. Recurrence was found in 20.9% (n=9) cases, of which 66.6% (n=6) had high-flow AVMs.

Conclusion: Male patients presented late and with mostly high-flow head and neck AVMs. Sclerotherapy alone or surgical excision with preoperative sclerotherapy or embolotherapy is an efficacious curative treatment for AVMs while sirolimus can be offered as a palliative option.

Key words: Arteriovenous Malformations, Enbucrilate, Sclerotherapy, Vascular Malformations

Authors' Contribution:
[1,2]Conception; Literature research; manuscript design and drafting; [2,3] Critical analysis and manuscript review; [5,6] Data analysis; Manuscript Editing.

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Introduction

AVMs are found as congenital defects which arise due to errors in embryogenesis resulting in abnormal communication between veins and arteries.[1] In the centre of the AV malformation lies the nidus, which is the tangle of abnormal vessels of the AVM. According to the International Society of

the Study of Vascular Anomalies, AVMs are benign lesions that directly connect the arterioles and venules and they lack intervening capillaries, thus causing dilation of veins which become tortuous over a period causing deformity of that body region.[1,2] AVMs belong to a group of defects known as Congenital Vascular Malformations (CVMs), which also include other more common defects like venous malformations.[1,2] Treatment of AVMs can either be surgical or nonsurgical.[3] Nonsurgical options are sclerotherapy, angioembolization, and immunomodulation. AVMs are uncommon, accounting for 10-15% of CVMs having a prevalence of 5 to 613 in 100,000.[4,5] Over 90% of AVMs are intracranial, which makes peripheral AVMs even rarer.[6] These lesions are known to develop during early gestation and can be evident at birth. They tend to grow over time and become more prominent under the influence of trauma or hormonal changes during puberty or pregnancy. Although there are a substantial number of studies on cerebral AVMs, there is insufficient data regarding peripheral AVMs. This study was intended as a pilot project. Patients presenting with peripheral AVMs were assessed whether there were any gender differences in disease presentation and the response of AVMs to various available treatment modalities.

Methodology

This cross-sectional study was performed at Combined Military Hospital Lahore, Rawalpindi, and Midcity Hospital Lahore Pakistan, from January 2016 to June 2020. The formal approval for the study was obtained from the Institutional Ethical Review Committee (IRB Number: 68/18/05/21). All patients diagnosed with an AVM and willing to undergo treatment were included. Informed consent was taken from all patients. Children less than five years of age, unwilling patients, patients who had documented complications of the sclerosant, and pregnant patients were excluded from the study. Furthermore, patients who did not complete a minimum of six months of follow-up were excluded. Doppler Guided Foam Sclerotherapy (DGFS) was performed using a 30mg/ml injection of Sodium Tetradecyl Sulfate (STS). The foam was prepared in a ratio of 1:2:2 of STS: water: air using Tessari's method. All patients received compression on the injected area for at least 2 weeks. Patients were counselled regarding the importance of strict post-procedure compliance to instructions such as those for compression therapy. Regular follow-ups were done for a minimum of 6 months. At each visit, clinical evaluation along with Doppler was done with the LOGIQ Book GE Medical ultrasound system to assess treatment efficacy in terms of the requirement of further sessions. Total treatment sessions and treatment modalities offered were recorded. Other treatment modalities used were surgical excision alone or in combination with DGFS and immunotherapy with Silolimus followed by DGFS.

Recurrence of AVM was defined as re-growth after a Doppler recorded complete healing. Recurrence and other complications were also recorded. Statistical analysis was done using Statistical Package for the Social Sciences Version 24 (SPSS© Inc., IL, USA). Quantitative variables were expressed as Mean ± Standard Deviation (SD). Qualitative variables were expressed as Frequency and Percentage. Based on gender, patients were divided into two groups. The comparison was done using Chi-Square Test and a P-value of ≤ 0.05 was considered statistically significant.

Results

A total of 49 patients diagnosed with an AVM were initially included in the study. However, 12.2% (n=6) of patients did not complete the mandatory 6 months follow-up and hence were excluded.

Of the 43 total cases, there were 23.2% (n=10) males and 74.4% (n=32) females (M: F ratio 1:3). Mean age in males was 27± 6 years (Range 19 -40) and in females 17± 4 years (Range 11-22) with a statistical difference (P value 0.003); suggesting that a younger population of females presented with AVMs [Table 1]. In terms of AVM type, in males, 60% (n=6) AVMs were high flow while in females low flow AVMs were more prevalent (81%, n=27). Moreover, 50% (n=5) of AVMs in males were on the trunk followed by the head and neck (30%) and limbs (20%). However, in females, this ratio was reversed with the limb being the most prevalent site (93.9%) and the trunk being the least affected site (3%).

DGFS was performed in 95.3% (n=41) of patients. DGFS was employed as monotherapy in 63.4% (n=26) of these patients [Figure A]. All had low-flow AVMs and 53.8% (n=14) of them showed complete recovery after a single session of DGFS. 30.7% (n=8) patients needed two sessions and 15.3% (n=4) patients needed more than two sessions; however, complete healing was achieved in all cases. A total of 32.5% (n=14) patients underwent DGFS followed by surgical excision [Figure B]. Of these, 35.7% (n=5) patients had low-flow AVMs while the remaining 64.2% (n=9) patients had high-flow AVMs. It is worth noting that all those patients who had high-flow AVMs needed multiple sessions of DGFS [Figure C]

One patient had a high-flow AVM involving the entire side of his face which was not amenable to formal excision. He opted for novel immunotherapy and therefore underwent 2 sessions of intravenous sirolimus which were followed by 3 sessions of DGFS. On follow-up, small remnant pockets of active blood flow were still present. However, there was a significant size reduction of the AVM which was cosmetically acceptable.

In 4.6% (n=2) of cases, preoperative angio embolization was performed followed by surgical removal within the same week.

Recurrence was recorded in 20.9% (n=9) cases, in these 66.6% (n=6) patients were having high-flow AVMs. Hence the recurrence rate was 50% (n=6) in high-flow AVM patients while it was 9.6% (n=3) in the low-flow AVMs. In patients undergoing DGFS, there was local pain and swelling in noted 51.2% (n=21), skin necrosis/ulceration in 19.5% (n=8), and superficial local thrombophlebitis in 17% (n=7) patients. However, none of these complications needed further treatment. Other minor complications included small hematoma formation in 27.9% (n=12), seroma in 23.2% (n=10), and superficial surgical site infection in 6.9% (n=3) cases.

Table I: Types and location of AVM

	Male (n=10)	Females (n=33)	P value
Age in years (mean SD)	27 +/- 6	17 +/- 4	0.003
Type of AVM			
High flow (%(n))	50 (6)	50(6)	0.322
Low flow [%(n)]	12.9 (4)	87.1 (27)	0.005
Site of AVM			
Limbs [%(n)]	6.2 (2)	93.9 (31)	0.005
Head and Neck [%(n)]	75 (3)	25 (1)	0.07
Trunk [%(n)]	83.3 (5)	16.7 (1)	0.04

Figure A: AVM of lip presenting with ulceration and bleeding (left). One month post-DGFS (Right)

FIGURE B: AVM in upper calf treated with surgical excision (Note the aberrant arterial connection arising from the popliteal artery).

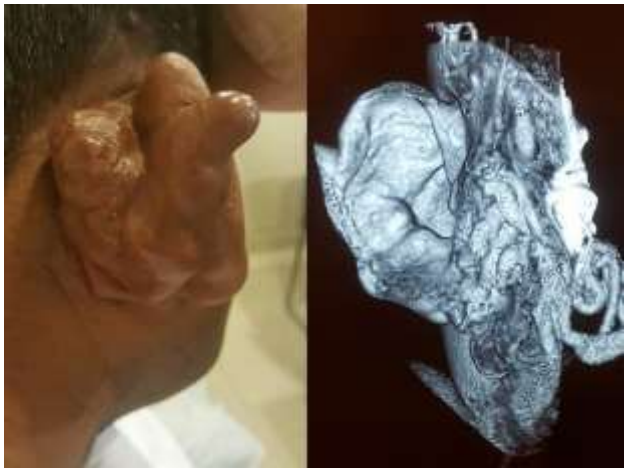

FIGURE C: High flow AVM involving the right pinna and postauricular region.

Discussion

Although AVMs are present at birth, these lesions may only clinically appear later in life, as their growth tends to parallel that of the rest of the child's body. The Male to female ratio is commonly reported as a 1:1 ratio for AVMs however we found a higher number of females in our study group.[7] Moreover the average age of presentation in females was much less as compared to males. There may be more than one plausible factor for this. As AVMs tend to grow under hormonal influences, they enlarge at puberty and in pregnancy.[8] This could be a reason why it becomes apparent and is picked up early in females. Males were more likely to have an AVM involving the trunk whereas AVMS on the limbs were more prevalent in females. While the such difference in gender on the presentation of intracranial AVMs was found in some studies but further studies are needed before the same can be concluded for non-intracranial AVMs.[9] The diagnosis of AVMs is made based on imaging findings. MRI, which has a wider observable range than ultrasound, is better suited for initial workup and to rule out vascular neoplasms such as hemangiomas. Invasive investigations such as selective angiography are also used in the workup of AVMs. AVMs are the only CVMs requiring a diagnostic angiography.[3,] Unlike other CVMs that can be monitored closely and left untreated if asymptomatic, AVMs require early and aggressive treatment. This is because AVMs can threaten life or limb. AVMs if large enough, are also found to cause high-output cardiac failure, which usually accounts for most of the capacitance in a vascular circuit. Artery steal syndromes can also occur resulting in under-perfusion of tissues leading to skin ischemia and soft tissue and muscle necrosis with resulting gangrene. A large AVM in close vicinity of a long bone can also cause limb-length discrepancy.[10]

Endovascular techniques which include sclerotherapy and angio embolization have long been used as a 2nd line of treatment for those lesions which are unsuitable for formal excision, but currently, these are often combined with surgical excision for higher success rates.[11]

Sclerotherapy has been used for the treatment of vascular malformations. The sclerosing agent used in our study was STS, which is a fatty acid salt with detergent properties that allow it to modify the surface tension around endothelium, resulting in vascular injury.[12] Such injury to the vessel then results in fibrotic changes and occlusion of the

lesions.[13] Side effects of STS are self-resolving swelling and skin necrosis and these were noted in more than 50% of cases in our study. An important but uncommon adverse effect is hemoglobinuria which arises due to self-limiting hemolysis and can be prevented by prophylactic hydration before the procedure and the use of diuretics if required. No such case developed in our study. STS has been found a very effective option for the treatment of AVMs since there was complete resolution in the 26 patients in our study who underwent DGFS as monotherapy. Similar results have been procured by other studies using STS for the treatment of AVMs elsewhere.[14,15.]

Many types of embolics may be used for embolic therapy, starting from mechanical coils to particles such as PVA and liquid embolics such as NBCA (N-butyl cyanoacrylate) and Onyx.[16] The agent used in our study was NBCA, a cyanoacrylate glue which polymerizes on contact with any ionic solution such as blood or contrast solution, forming a caste of the vessel instantly.[17] There is no evidence that nBCA causes endothelial injury, which means that although it is associated with a reduced risk of complications, the risk of recanalization is higher. Embolization before surgery results in a reduction of blood flow in the AVM, hence also resulting in less bleeding during surgery.[18] Moreover, it eliminates deep feeding arteries that are thought to be the limiting factor in the surgical respectability of large AVMs. The most important complication that is worth mentioning is that after the embolization procedure, there could be a blockade of non-target vessels, which can potentially result in ischemia and sepsis. Other, less devastating adverse effects include microcatheter blockage and catheter retention, both of which are due to premature polymerization of NBCA. Awareness of factors, for instance, the technique of injection and strength of NBCA dilution is paramount to minimize damage, since NBCA glue deposition is very unpredictable when tested in vivo.[19]

Sirolimus (rapamycin), an mTOR inhibitor can be used in the treatment of vascular malformations. mTOR is a kinase that promotes protein synthesis when activated. Furthermore, activation of mTOR results in the removal of inhibitory influences on protein translation, making it a very important regulator of cell multiplication.[20] This makes mTOR a plausible target for the treatment of AVMs, as its inhibition can potentially prevent angiogenesis.[21] Sirolimus can be combined with other modalities, such as sclerotherapy in our study. Sole treatment with sirolimus does not offer a complete cure, as evident by the persistence of positive blood flow pockets in the AVM of the patient who underwent treatment with sirolimus in our study. This is consistent with the findings of many other studies which also showed no or very small improvements with sirolimus.[22,23] However, it can be considered a palliative option, especially in such cases where formal excision is not possible.

An important limitation of our study was the sample size, and this was due to the rarity of the disease. Considering that it is a pilot study, our objective was to note any differences where present in the patient groups studied. However, we fully agree that all the findings in this study cannot be generalized to the overall population. For such, we need much larger and more powerful studies.

Conclusion

There is notable variance in AVMs in terms of size and type based on gender, with males having more prevalence of mainly high flow AVMs on the trunk while females have low flow AVMs mostly on limbs. Sclerotherapy or embolotherapy should be performed before a planned surgical excision since they reduce peri-operative complications and future recurrence.

References

1. Trotter JW, Kirkpatrick JP. Arteriovenous malformation: a real can of worms. Int J Radiat Oncol Biol Phys. 2021; 111(4):851-3. https://doi.org/10.1016/j.ijrobp.2018.08.068
2. Polubothu S. Genothype-guided medical treatment of arteriovenous malformation. Clin Exp Dermatol. 2021; 46(4):800-1. https://doi.org/10.1111/ced.14439
3. Mulligan PR, Prajapati HJS, Martin LG, Patel TH. Vascular anomalies: Classification, imaging characteristics and implications for interventional radiology treatment approaches. Br J Radiol. 2014; 87(1035):1–18. https://doi.org/10.1259/bjr.20130392
4. AlShamekh S. Arteriovenous Malformations. Dermatol Clin. 2022; 40(4):445-8.https://doi.org/10.1016/j.det.2022.06.012
5. Fernandez-Alvarez V, Suarez C, Bree R, Nixon IJ, Makitie AA, Rinaldo A, et al. Management of extracranial arteriovenous malformations of the head and neck. Auris Nasus Larynx. 2020; 47(2): 181-90. https://doi.org/10.1016/j.anl.2019.11.008
6. Soulez G, Gilbert P, Giroux MF, Racicot JN, Dubois J. Interventional Management of Arteriovenous Malformations. Tech Vasc Interv Radiol. 2019; 22(4): 100633.https://doi.org/10.1016/j.tvir.2019.100633
7. Lee BB, Baumgartner I, Berlien HP, Bianchini G, Burrows P, Do YS, et al. Consensus document of the International Union of Angiology. Current concept on the management of arterio-venous management. Int Angiol. 2013; 32(1):9–36. https://doi.org/10.1007/s00547-003-0844-2
8. Lee BB, Villavicencio JL. Rutherford's vascular surgery and endovascular therapy. 9th ed. Philadelphia: Elsevier; 2018. p. 2236-50. https://doi.org/10.1177/153100358900200209
9. Tong X, Wu J, Lin F, Cao Y, Zhao Y, Ning B, et al. The Effect of Age, Sex, and Lesion Location on Initial Presentation in Patients with Brain Arteriovenous Malformations. World Neurosurg. 2016; 87(2):598-606. https://doi.org/10.1016/j.wneu.2015.10.060
10. Bertino F, Frederic KA, Hawkins CM, Gill AE, Briones MA, Swerdlin R, et al. Congenital Limb Overgrowth Syndromes Associated with Vascular Anomalies. Radiographics. 2019; 39(2):491-515. https://doi.org/10.1148/rg.2019180136
11. Sohail M, Bashir M, Ansari H, Khan FA, Assumame N, Awan NU, et al. The Outcome of Management of Vascular Malformations of Lip. J Craniofacial Surg. 2016; 27(6):e520-e524.https://doi.org/10.1097/scs.0000000000002824
12. Ahmad S. Efficacy of percutaneous sclerotherapy in low flow venous malformations-a single centre series. Neurointervention. 2019; 14(1):53. https://doi.org/10.5469/neuroint.2019.00024
13. Stuart S, Barnacle A, Smith G, Pitt M, Roebuck DJ. Neuropathy after Sodium Tetradecyl Sulfate Sclerotherapy of Venous Malformations in Children. Radiology. 2015; 274(3):897-905. https://doi.org/10.1148/radiol.14132271
14. Kirkpatrick DL, Frenette A, Hasham HA, Custer B, Lemons S, Collins Z, et al. Successful Percutaneous Treatment of an Arteriovenous Malformation of the Toe. Ann Vasc Surg. 2020; 65(1):288.e5-288.e8. https://doi.org/10.1016/j.avsg.2019.11.034
15. Sitra G,Kayalvizhi AB, Sivasankari T, Vishwanath R. A new venture with sclerotherapy in an oral vascular lesion. J Basic Clin Pharm. 2015; 6(1):40. https://doi.org/10.4103/0976-0105.145778
16. Vollherbst DF, Chapot R, Bendszus M, Mohlenbruch MA. Glue, Onyx, Squid or PHIL? Liquid Embolic Agents for the embolization of cerebral arteriovenous Malformations and Dural arteriovenous Fistulas. Clin Neuroradiol. 2022; 32(1):25-38. https://doi.org/10.1007/s00062-021-01066-6
17. Khurana A, Hangge P, Albadawi H, Knuttinen MG, Alzubaidi SJ, Naidu SG. The Use of Transarterial Approaches in Peripheral Arteriovenous Malformations (AVMs). J Clin Med. 2018; 7(5):109.https://doi.org/10.3390/jcm7050109
18. Kansy K, Bodem J, Engel M, Freudlsperger C, Mohlenbruch MA, Herweh C, et al. Interdisciplinary treatment algorithm for facial high-flow arteriovenous malformations, and review of the literature. J Craniomaxillofac Surg. 2018; 46(5):765-72. https://doi.org/10.1016/j.jcms.2018.03.002
19. Hill H, Chick JFB, Hage A, Sirinivasa RN. N-butyl cyanoacrylate embolotherapy: Techniques, complications, and management. Diagnostic Interv

Radiol. 2018; 24(2):98–103.https://doi.org/10.5152/dir.2018.17432

20. Ji Y, Chen S, Yang K, Zhou J, Zhang X, Jiang X, et al. A prospective multicenter study of sirolimus for complicated vascular anomalies. J Vasc Surg. 2021; 74(5): 1673-81. https://doi.org/10.1016/j.jvs.2021.04.071
21. Maruani A, Tavernier E, Boccara O, Mazereeuw-Hautier J, Leducq S, Bessis D, et al. Sirolimus (Rapamycin) for slow-flow malformations in children: the observational – Phase Randomised clinical PERFORMUS Trial. JAMA Dermatol. 2021; 157(11):1289-98. https://doi.org/10.1001/jamadermatol.2021.3459
22. Gabeff R, Boccara O, Soupre V, Lorette G, Bodemer C, Herbreteau D, et al. Efficacy and tolerance of sirolimus (Rapamycin) for extracranial arteriovenous malformations in children and adults. Acta Derm Venereol. 2019; 99(12):1105–9. https://doi.org/10.2340/00015555-3273
23. Freixo C, Ferreira V, Martins J, Almeida R, Caldeira D, Rosa M, et al. Efficacy and safety of sirolimus in the treatment of vascular anomalies: A systematic review. J Vasc Surg. 2020; 71(1):318-27. https://doi.org/10.1016/j.jvs.2019.06.217