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Research Article

Clinical Presentations and Treatment Outcomes of High Flow Malformations of the Lower Extremity

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ABSTRACT

Objective: We aim to reveal real world data according to clinical presentations, radiological findings and treatment results of high flow vascular malformations of the lower extremity among patients in the AVM Register.

Methods: We included all patients presenting with high flow malformations of the lower limb who were treated in Inselspital from 2008 to 2018; demographics, clinical presentations, radiological data, laboratory findings as well as interventional treatment including outcomes were analyzed. We compared patients with solely arteriovenous malformations with those presenting Parkes Weber Syndrome in terms of symptoms and therapy results separately.

Results: 31 Patients (16 women, 15 men) with a median age at the time of the first diagnosis of 27 years [range 10-33] and a median age of first presentation of 26 years [8-30] were included. 22 patients (71%) presented solely Arteriovenous Malformation (AVM); nine were diagnosed with Parkes Weber Syndrome (PWS). The malformations were localized in the lower limb in 17 cases and in the foot in 19 cases. The most common symptoms were pain (n = 25; 80.6%) swelling (21; 67.7%) and soft tissue hypertrophy (13; 41.9%). PWS patients presented with significantly more recurrent bleedings (66.7% vs. 2.5% p<0.001), recurrent infections of the lower limb (44.4% vs. 4.55% p=0,017) and length difference of the lower extremity (55.6% vs. 13.6% p=0.027). Laboratory tests revealed local intravascular coagulopathy in 87.5% PWS patients with a median level of d-dimer of 17,256 µg/L (norm <500µg/L). The AVM group revealed normal d-dimer testing (median d-dimer 322µg/L). Radiological findings showed an elevated net shunt volume in the femoral artery of median 700 ml/min [150 - 1100], and there was a significant difference between PWS and AVM group (1500 ml/min [1300 – 2800] vs. 400 ml/min [150 - 950] p=0,011). In total, 16 patients (51%) underwent alcoholic embolization, three (9.7%) surgery and five (16.1%) mixed procedure. The treatment resulted in reduction of net shunt volume to a median level of 100 ml/min [0-300]; the median net shunt volume in the AVM group at the end of treatment was significantly lower at 50 ml/min; however, the end flow volume in PWS group did not change. Nevertheless, therapy resulted in lowering of the d-dimer level in the PWS group at a mean level of 6063µg/L. 3 PWS and no AVM patient died as a result of the disease (33.3% vs. 0% p=0,019).

Conclusions: There are common characteristic features among high flow malformations of the lower extremity which should evoke the diagnosis. Patients with

solely arteriovenous malformations without involvement of the capillary system can be effectively treated with intervention. Patients with Parkes Weber Syndrome present symptoms that are more serious and have a worse prognosis than those with AVM. New therapeutic approaches for treating this type of complex high flow malformation are needed.

INTRODUCTION

Congenital Vascular Malformations (CVM) is anomalies of blood and lymphatic vessels which develop due to deficient vasculogenesis in variable localizations secondary to sporadic gene mutations [1]. They are classified according to the International Society for the Study of Vascular Anomalies (ISSVA) [2]. As symptoms are complex and variable, congenital vascular malformations are considered rare diseases; data on the various types are vague and no standard treatment for CVM is established. Arteriovenous Malformations (AVM) and Arteriovenous Fistulas (AVF) are congenital and often do not provoke symptoms until they are large enough to cause hemodynamic disturbances. Progression can be triggered by environmental factors such as activity, trauma or hormonal changes as occurring during puberty or pregnancy [3]. They are most frequently localized in the head and neck, but can develop anywhere [4]. In this article we focus on high-flow vascular malformations of the lower limb with AVM and Parkes Weber Syndrome (PWS), comprising port wine stains, arteriovenous fistulas and limb overgrowth, which is extremely rare [5]. To provide best treatment for these patients, clinicians need a full understanding of the types of lesions, their natural history, appropriate diagnostic studies, and indication for treatment. Treatment options include surgery, embolization, laser, and pharmacotherapy, but representative cohorts are lacking [6-8]. Another problem is the heterogeneity of outcome measurements further complicating comparison of existing cohorts [9]. Several small exclusively Korean cohorts include AVM treatment of the foot (29 patients) [10], of the trunc and extremities (66 patients) [11] and of the hands (31 patients) [12]. The only non-Asian cohort consists of 272 patients with AVM of extracranial location treatedat Harvard Medical School, lacking demographic details as well as information on precise AVM location [5]. The Division of Angiology at the University Hospital of Bern treats patients with CVM since 2008 and is the Swiss Reference Center for Vascular Malformations.

METHODS

Patients

We included 31 Patients (15 men, 16 women) with a mean age of 30.5 years [range 10-73] at first consultation who were diagnosed or treated at University Hospital of Bern, Switzerland, between 2008 and 2018 for arteriovenous malformations - AVM (22 patients) or Parkes Weber Syndrome (9) of the lower limbs. 16 patients were treated previously: Seven with surgery only, nine underwent mixed procedure (sclerotherapy and/or alcohol embolization in combination with surgery). All patients signed general informed consent and the study was approved by Bernice Cantonal Ethics Committee as a part of AVM Registry.

Procedures

Since 2008, a special malformation counselling program, with a standardized diagnostic and therapeutic algorithm was established at the University Hospital of Bern. Patients undergo following steps: vascular assessment including Duplex Ultrasound (DUS) and flow volume measurement, followed by dynamic MRI-angiogram if interventional therapy is needed. Results are discussed by an interdisciplinary malformations' board consisting of an angiologist, a plastic and a vascular surgeon, a dermatologist and a childrens' oncologist. Interventional treatment options are percutaneous or retro-venous alcohol embolization in repeated sessions every 4-6 weeks with two control consultations at the first and 14th day after each procedure. If surgery is performed, patients are controlled after completing procedure. Standard examination consists of photographical and thermographic documentation, clinical examination as well as DUS. After treatment, patients are controlled every year.

Medical record review

Patients who attended our consultation and were diagnosed with AVM or PWS of the lower extremity were retrospectively reviewed. Initial clinical manifestation, medical history, laboratory parameters, and initial net shunt volume were extracted from the consultation reports. Further, we reviewed electronic medical records in terms of therapy type (surgery, alcohol embolization, laser therapy and conservative procedure), major complications (death, limb amputation), and final net volume shunt as well as laboratory findings.

Statistical considerations

We used standard epidemiological descriptive methods to characterize the patient population and the classification of the malformations. Continuous variables are presented as median with lower and upper quartile, categorical variables as n (%). Effect sizes are presented as Hodges-Lehmann median difference or risk difference. Continuous variables are compared using Wilcoxon-Mann-Whitney tests, categorical variables using Fisher's exact test.

Results

In total, 31 patients (48, 4%male) with a median age of 37 years [range 10-73] at first consultation were included. 22 patients (71%) presented with arteriovenous malformations (AVM) solely; nine (29%) were diagnosed with Parkes Weber Syndrome (PWS) of the lower limbs. Median age at the time of the first diagnosis was 27 years [10-33] and median age of first presentation of 26 years [8-30]. First manifestation of PWS was earlier than AVM (15 [0-15] vs. 19 [10-30]p=0,11). The malformations were localized in the lower limb in 17 cases and in the foot in 19 cases as presented in Diagram 1.

The most common symptoms were pain 25 (80.6%) swelling 21(67.7%) and soft tissue hypertrophy 13 (41.9%). PWS patients presented with generally more symptoms (4.3 symptoms per PWS patient vs. 2.4symptoms for AVM patient) and suffered significantly more recurrent bleedings (66.7% vs. 2.5% p<0.001), recurrent infections of the lower limb (44.4% vs. 4.55% p=0.017) and length difference of the extremity (55.6% vs. 13.6% p=0.027). The rate of intolerance of physical exertion, overheat of the limb, varicose vein were similar in both groups. Initial symptoms are presented in Table 1. Initial laboratory testing revealed Localized Intravascular Coagulopathy (LIC) in 87.5% PWS patients with a median level of d-dimer of 17,256 [6,185- 52,929µg/L] (norm <500µg/L). The AVM group revealed normal d-dimer testing (median d-dimer 322µg /L). Furthermore, chronic anemia was diagnosed in three PWS patients and none AVM patient (3 (42.9%) vs. 0 p=0.013).

Radiological findings showed an elevated net flow volume of median 700 ml/min [150-1100], and there was a significant difference between PWS and AVM group (1500 ml/min [1300-2800] vs. 400 ml/min [150-950] p= 0,011). Therapy was performed in 24 patients; 16 (51%) underwent repeated alcoholic embolization, three (9.7%) surgery and five (16.1%) mixed procedure (sclerotherapy and/or alcohol embolization in combination with surgery). Different reasons led to conservative, noninvasive therapy: continuing the treatment in other hospitals (2), small, asymptomatic lesions (2), malformations of solely type IV (intestinal) (1) and patients preferences (2). The treatment resulted in reduction of net shunt volume to a median level of 100 ml/min [0-300]; the median net shunt volume in the AVM group with a level of 50 ml/min was significantly lower at the end of the treatment; however, theflow volume in PWS group didn't change (1500ml/min [1500-8100]). Nevertheless, therapy resulted in lowering of the d-dimer level in the PWS group to 6,063µg/L. 3 PWS and no AVM patient died as a result of the disease (33.3% vs. 0% p=0.019).

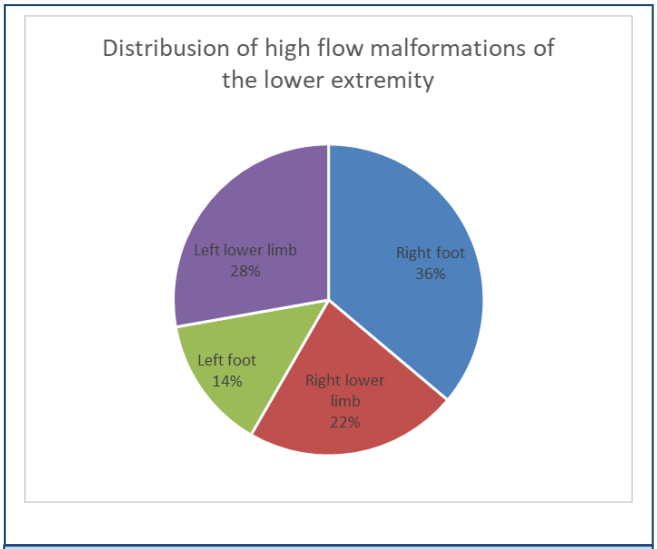

Diagram 1: Localization of the malformation.

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Table 1: Descriptive table of symptoms, categorical variables are presented as n (%). Effect sizes are presented as Hodges-Lehmann median difference or risk difference.

	Total (N=31)		PWS(N=9)		AVM(N=22)		Hodges-Lehmann median difference or risk difference (95% CI)	*P*-value
	n	number (%)	n	number (%)	n	number (%)		
Pain	31	25 (80.6%)	9	7 (77.8%)	22	18 (81.8%)	-0.040 (-0.356 to 0.275)	1.00
Swelling	31	21 (67.7%)	9	8 (88.9%)	22	13 (59.1%)	0.298 (0.008 to 0.588)	0.21
Soft tissue Hypertrophy	31	13 (41.9%)	9	5 (55.6%)	22	8 (36.4%)	0.192 (-0.190 to 0.574)	0.43
Overgrowth	31	8 (25.8%)	9	5 (55.6%)	22	3 (13.6%)	0.419 (0.064 to 0.774)	0.027
Recurrent bleeding	31	7 (22.6%)	9	6 (66.7%)	22	1 (4.55%)	0.621 (0.301 to 0.941)	<0.001
Intolerance of physical performance	31	6 (19.4%)	9	2 (22.2%)	22	4 (18.2%)	0.040 (-0.275 to 0.356)	1.00
Recurrent infect	31	5 (16.1%)	9	4 (44.4%)	22	1 (4.55%)	0.399 (0.063 to 0.735)	0.017
Overheat	31	3 (9.7%)	9	0 (0.000%)	22	3 (13.6%)	-0.136 (-0.280 to 0.007)	0.54
Visible varicosis	31	3 (9.7%)	9	2 (22.2%)	22	1 (4.55%)	0.177 (-0.108 to 0.462)	0.19
Steal phenomenon	31	1 (3.23%)	9	0 (0.000%)	22	1 (4.55%)	-0.045 (-0.132 to 0.042)	1.00

CONCLUSIONS

A description of high flow vascular malformations affecting the lower extremities of Caucasians was lacking in the international literature. Our patients' population represents a sample of specific symptoms with pain, swelling and soft tissue hypertrophy that should alarm physicians to screen for AVM. Although there are some studies describing AVM of the lower extremity [10,11], we conducted the first study to compare clinical presentation and therapy outcomes of AVM and Parkers Weber Syndrome (PWS) of the lower extremities in a Caucasian cohort. These two conditions, despite hemodynamic and clinical similarities, have profound pathophysiologic differences, which critically influence the outcomes. Therefore, we suggest performing diagnostic and therapeutic procedures in specialized centers. Our experience in treatment of the AVM is similar to the results of international acknowledged centers of vascular malformations with an interdisciplinary approach [6,10]. In this setting AVM patients can be treated safely and effectively. We propose a primarily percutaneous or transvenous approach using 96% alcohol and coil embolization to occlude AVM. Some centers use particles [13] or other substances for occluding the nidus with variable effects [14]. Surgical excision may be performed depending on location and extension of AVM primarily or secondarily after embolization.

In accordance to international reports, our experience shows poor prognosis of interventional PWS treatment; available case reports and one case series of ten children [15] report symptom-oriented treatment with short-term follow up. Long-term effects remain unclear [16]. PWS due to high flow component is a progressive illness. Since the older age of our patients (mean 18 years), symptoms were more serious and courses more dramatic. We still did not find a cure for the progressive nature of this illness; embolization and other invasive procedures seem to temporarily slow down the course. Single reports show promising effects of new pharmacological approaches using the mTOR-inhibitor Sirolimus [17], but further studies are needed in this field.

REFERENCES

1. Blei F. (2013). Medical and genetic aspects of vascular anomalies. Tech Vasc Interv Radiol. 16: 2-11.
2. www.issva.org
3. Frey S, Haine A, Kammer R, von Tengg-Kobligk H, Obrist D, Baumgartner I. (2017). Hemodynamic Characterization of Peripheral Arterio-venous Malformations. Ann Biomed Eng. 45: 1449-1461
4. Carqueja IM, Sousa J, Mansilha A. (2018). Vascular malformations: classification, diagnosis and treatment. International Angiology. 37: 127-142.
5. Liu AS, Mulliken JB, Zurakowski D, Fishman SJ, Greene AK . (2010). Extracranial arteriovenous malformations: natural

progression and recurrence after treatment. Plast Reconstr Surg. 125:1185-1194.

6. Rosen RJ, Nassiri N, Drury JE. (2013). Interventional Management of High-Flow Vascular Malformations. Tech Vasc Interv Radiol. 16: 22-38.
7. Lee BB, Baumgartner I . (2013). Contemporary diagnosis of venous malformation. Journal of Vascular Diagnostics. 2013: 25-34.
8. Lee BB, Baumgartner I, Berlien HP, Bianchini G, Burrows P, et al. (2013). Consensus Document of the Internaional Union of Angiology (IUA)-2013 Current concepts on the management of arterio-venouos malformations. International Angiology. 32: 9-36.
9. Horbach SER, van der Horst CMAM, Blei F, van der Vleuten CJM, Frieden IJ, et al. (2018). Development of an international core outcome set for peripheral vascular malformations: the OVAMA project. Br J Dermatol. 178:473-481.
10. Hyun D, Do YS, Park KB, Kim DI, Kim YW, et al. (2013). Ethanol embolotherapy of foot arteriovenous malformations. J Vasc Surg. 58:1619-1626.
11. Cho SK, Do YS, Shin SW, Kim DI, Kim YW, et al. (2006). Arteriovenous malformations of the body and extremities: analysis of therapeutic outcomes and approaches according to a modified angiographic classification. J Endovasc Ther. 13: 527-538.
12. Park HS, Do YS, Park KB, Kim DI, Kim YW, et al. (2011). Ethanol embolotherapy of hand arteriovenous malformations. J Vasc Surg. 53:725-731.
13. Osuga K, Hori S, Kitayoshi H, Khankan AA, Okada A, et al. (2002). Embolization of high flow arteriovenous malformations: experience with use of superabsorbent polymer microspheres. J Vasc Interv Radiol. 13: 1125-1133.
14. Tan KT, Simons ME, Rajan DK, Terbrugge K. (2004). Peripheral High-Flow Arteriovenous Vascular Malformations: A Single-Center Experience. Journal of Vascular and Interventional Radiology. 15: 1071-1080.
15. Giron-Vallejo O, Lopez-Gutierrez JC, Fernandez-Pineda I. (20113). Diagnosis and treatment of Parkes Weber syndrome: a review of 10 consecutive patients. Ann Vasc Surg. 27: 820-825.
16. Banzic I, Brankovic M, Maksimovic Z, Davidovic L, Markovic M, et al. (2017). Parkes Weber syndrome-Diagnostic and management paradigms: A systematic review. Phlebology. 32: 371-383.
17. Chelliah MP, Do HM, Zinn Z, Patel V, Jeng M, et al. (2018). Management of Complex Arteriovenous Malformations Using a Novel Combination Therapeutic Algorithm. JAMA Dermatology. 154: 1316-1319.