Clinical presentation of simple and combined or syndromic arteriovenous malformations

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ABSTRACT

Objective: Arteriovenous malformations of the lower extremities (AVM^{LE}) can present as simple or complex combined or syndromic forms (eg, Parkes Weber Syndrome). We aimed to characterize the differences in clinical presentation and natural history of these potentially life- and limb-threatening congenital vascular malformations.

Methods: We conducted a retrospective analysis of a consecutive series of patients with AVM^{LE} who presented to a tertiary referral center in Switzerland between 2008 and 2018. Clinical baseline characteristics, D-dimer level, and course were summarized and differences between simple, non-syndromic and combined or syndromic AVM^{LE} determined. Odds ratios (ORs) and 95% confidence intervals (CIs) were estimated using logistic regression models.

Results: Overall, 506 patients were prospectively enrolled in the Bernese Congenital Vascular Malformation Registry, 31 (6%) with AVM^{LE}. There were 16 women and 15 men, with a mean age of 18 years at first diagnosis (range, 1 month to 72 years). Simple AVM^{LE} was present in 22 (71%) and combined or syndromic AVM^{LE} with limb overgrowth in 9 patients (29%), respectively. Common symptoms and signs were pain (n = 25; 81%), swelling (n = 21; 68%), and soft tissue hypertrophy (n = 13; 42%). Among combined or syndromic patients, three patients died from wound infection with sepsis or disseminated intravascular coagulation with bleeding complications (intracranial hemorrhage and bleeding from extensive leg ulcers). Combined or syndromic patients presented more often with bleeding (67% vs 5%; $P < .001$), malformation-related infection (44% vs 5%; $P = .017$) and leg length difference (56% vs 14%; $P = .049$). D-dimer levels were elevated (mean, 17,256 μg/L; range, 1557-80,000 μg/L) and angiographic appearance showed complex, mixed type of AVMs, including interstitial type IV, in all patients with combined or syndromic AVM^{LE}.

Conclusions: Patients with congenital simple AVM^{LE} most often present with benign clinical features and rarely with complications related to hemodynamic changes. Patients with combined or syndromic AVM^{LE} often face serious outcomes dominated by complications other than direct high-flow-related heart failure. (J Vasc Surg Venous Lymphat Disord 2022;10:705-12.)

Keywords: Simple arteriovenous malformations; Syndromic arterio venous malformations; Combined arteriovenous malformation; Hing-flow vascular malformations; Clinical presentation

Congenital vascular malformations (CVMs) are anomalies of blood and lymphatic vessels, which develop due to deficient vasculogenesis in variable localizations. They are classified according to the International Society for the Study of Vascular Anomalies.[1]

A subgroup of CVMs are extra-cranial arteriovenous malformations (AVMs), a rare disease with a large variety of clinical presentations.[2] Textbooks and medical literature emphasize the severity and potentially life- and limb-threatening course of AVM as the most dangerous form of CVM.[3-5] The description of symptom patterns is often limited to the Schobinger classification, which provides a basic clinical classification from quiescent stage I with skin warmth and discoloration; progressive stage II with enlarged veins, pulsation, and bruit; destructive stage III with skin ulcerations and bleeding due to arterial steal; to the decompensating stage IV with high-output cardiac failure.[6] AVMs can be further classified by their angiographic appearance as type I, II, III, and IV as proposed by Wayne Yakes,[7-9] which is important for treatment planning and its clinical complexity.

The exact incidence of extra-cranial AVM is unknown, but is estimated to be approximately 1 per 100,000 person-years, with >50% involving head and neck,[5,8]

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but they can develop anywhere.[10,11] As extra-cranial AVM is rare, large series are limited.[7,8,12] There are several Korean series, one with 29 patients with AVM of the foot,[13] one with 66 patients with AVM of the trunk and extremities,[14] and one with 31 patients with AVM of the hand.[15] In United States and European cohorts, 14 to 30 patients with extracranial AVM have been described.[16-23] The only larger non-Asian series consists of 272 patients with extra-cranial AVM treated at Boston Children's Hospital between 1980 and 2008. However, information on factors such as demographics, AVM localization, and symptoms were not reported in detail.[24] Previously published series have focused primarily on diagnosis, genetic background, and treatment outcomes and not on clinical symptoms or complications associated with the disease per se. AVM of the lower extremities (AVM^{LE}) can be present as simple, non-syndromic, or as combined or syndromic AVM^{LE}. Diagnosis of combined or syndromic AVM is based on the additional combinations of AVM with capillary, venous, or lymphatic malformations and with other anomalies as limb overgrowth including typical syndromic Parkes-Weber syndrome (PKWS).

The aim of the present study is to describe the clinical presentations, characteristics, and natural history of patients with high-flow AVM^{LE} with special consideration of patients who present with simple, non-syndromic AVM^{LE} as compared with patients with combined or syndromic AVM^{LE}.

ARTICLE HIGHLIGHTS

- **Type of Research:** Single-center cohort study of consecutive patients with arteriovenous malformations of the lower extremities (AVM^{LE}).
- **Key Findings:** The majority of patients presented with Schobinger stage I and II disease, and no patient died from heart failure. Patients with combined or syndromic AVM^{LE} (eg, Parkes Weber Syndrome) have more serious complications as compared with patients with simple AVM^{LE}. Three patients with combined or syndromic AVM^{LE} died from infectious (sepsis) or bleeding complications (due to disturbed hemostasis), respectively. Localized intravascular coagulopathy was present in all patients with combined or syndromic AVM^{LE} and in none of the patients with simple AVM^{LE}.
- **Take Home Message:** In patients with combined or syndromic type of AVM^{LE}, the association of high-flow vascular malformation, lymphedema, and localized intravascular coagulopathy can build up to a vitally dangerous complication cascade and therefore mandates consequent simultaneous control of all vascular malformation components to prevent serious complications.

METHODS

Study participants. In 2008, a malformation counseling program, including a standardized diagnostic and therapeutic algorithm, was established at the University Hospital of Bern, Switzerland. Since then, consecutive patients with CVM have been enrolled in an independently monitored, prospective cohort, the Bernese Congenital Vascular Malformation Registry, with long-term, yearly follow-up. For the present study, data are from those patients enrolled from the start of the cohort in 2008 until December 31, 2018, comprising 506 patients. These patients were retrospectively reviewed to identify those with AVM^{LE}. Patient selection was performed by first filtering the database by the search term, arteriovenous malformation, and further filtering those with AVM by localization in the lower extremities. All patients signed a general informed consent for anonymized data analysis. The Ethics Committee of the Canton of Bern (local ethics board number 2018-02327) approved the study.

Data collection. Baseline demographic data collection, including gender and age, were collected at first diagnosis. Clinical presentations related to CVM were systematically collected by the attending physician, including information on pain, limb overgrowth, soft tissue hypertrophy, swelling, localized increase in skin temperature (without signs of infection such as sharp-bordered reddening), recurrent bleeding, recurrent infection, and reduced exercise capacity. Pain was recorded semi-quantitatively using a numeric rating score between 1 and 10, with 1 defined as low pain and 10 as the worst pain the patient could imagine,[25] and was further dichotomized into no pain (0) or any pain (1-10). Limb overgrowth was objectively assessed by long-leg radiography. Soft tissue hypertrophy was qualitatively assessed by visual estimation and photo documentation. Pain, palpable localized increase in skin temperature, recurrent bleeding, recurrent infections, and reduced exercise capacity were assessed by means of a structured interview with self-reporting of the patient. The physician filled in a standardized electronic worksheet including patient's history (pain, recurrent bleeding, recurrent infection, reduced exercise capacity) and objective findings from imaging and laboratory evaluation, as well as clinical examination (limb overgrowth, soft tissue hypertrophy, swelling, and localized increase in skin temperature).

D-dimer levels were routinely measured in venous blood samples. D-dimers were determined using an immunoturbidimetric method with pathologic result defined as D-dimer >500 μg/L.[26,27] Patients were classified according to the Schobinger classification, a staging system to define hyper-dynamic circulatory signs and symptoms of CVM. Stage I was defined as quiescent

disease, stage II as local expansion, stage III as destruction (ulceration or gangrene) of surrounding tissue due to ischemic steal, and stage IV as decompensation with cardiac failure and symptomatic local steal syndrome, respectively.[6]

On first presentation, the anatomical location and hemodynamic characterization of the lesion was recorded by duplex ultrasound or digital subtraction angiography, and in some cases, magnetic resonance imaging or computed tomography differentiating leg, foot, and involvement of both legs and feet. We applied the angiographic classification according to Wayne Yakes for describing the type of nidus of the AVM and for comparison between simple, non-syndromic AVM as compared with patients with combined or syndromic AVM^{LE}.[7]

Statistical methods. Patient data were collected via ClinWinData (E&L Medical Systems, Erlangen, Germany). Data were analyzed using the statistical program R. Descriptive statistics of baseline data were calculated for all patients and by simple AVM^{LE} and combined or syndromic AVM^{LE}, where age is presented as mean and range and other data are presented as number (%). Unadjusted and adjusted odds ratios (ORs) and 95% confidence intervals (CIs) were estimated to determine if there was a difference in clinical presentations for those with simple non-syndromic AVM^{LE} and combined or syndromic AVM^{LE}, using logistic regression. Models were adjusted for age (continuous) and sex (dichotomized as male/female), as they may be potential confounders of clinical presentation in AVM^{LE}.

RESULTS

At the time of the present study, 506 patients were represented in the Bernese Congenital Vascular Malformation Registry, of which 61 (12%) had been diagnosed with extra-cranial AVM. Of these patients, 31 (6%) had AVM^{LE} and were included in the present analysis.

Baseline characteristics are displayed in Table I. There were 15 male (48%) and 16 female (52%) patients, respectively. The mean age at diagnosis was 22 years (ranging from 1 month to 72 years). Overall, 22 patients (71%) were diagnosed as having simple non-syndromic AVM^{LE}, whereas nine (29%) were diagnosed with combined or syndromic AVM^{LE}. The diagnosis of AVM was based on clinical presentation, duplex ultrasound, and digital subtraction angiography in all cases. Additional magnetic resonance imaging was performed in 24 cases and computed tomography in 4 cases. Patients with combined or syndromic AVM^{LE} were younger at the time of diagnosis with mean age of 17 years vs 25 years in the simple, non-syndromic AVM^{LE} group. Simple AVM was localized and limited to the leg in six cases, restricted to the foot in 14 cases, and involved leg and foot in two cases. In the combined or syndromic AVM^{LE} group, distribution was more diffuse and in none of the patients limited to the foot. Moreover, the angioarchitecture was more complex in patients with combined or syndromic AVM^{LE} as compared with those with simple AVM with a more common presence of an interstitial AVM type IV (100% vs 45%) or combination of different types of AVM including type IV (44% vs 23%). Representative examples of simple AVM of the foot in comparison to the foot of a patient with syndromic AVM of the foot are shown in Fig 1. Fig 2 shows the comparison of a simple AVM of the leg (calf) in comparison to the leg of a patient with syndromic AVM.

Table I. Baseline characteristics of patients with arteriovenous malformation of the lower extremities

	All (N = 31)	Simple (n = 22)	Complex/ syndromic (n = 9)
Sex			
Male	15 (48)	11 (50)	4 (44)
Female	16 (52)	11 (50)	5 (56)
Age at diagnosis, *years*	22 (17)	25 (18)	17 (13)
Localization			
Only foot	14 (45)	14 (64)	0 (0)
Only leg	12 (38)	6 (27)	6 (67)
Foot and leg	5 (16)	2 (9)	3 (33)
Angiographic AVM classification[9]			
Type I	0 (0)	0 (0)	0 (0)
Type II	6 (19)	5 (23)	1 (11)
Type IIIa	1 (3)	1 (4)	0 (0)
Type IIIb	14 (45)	11 (50)	3 (33)
Type IV	19 (61)	10 (46)	9 (100)
Mixed	9 (29)	5 (23)	4 (44)

AVM, Arteriovenous malformation; *AVM^{LE}*, arteriovenous malformation of the lower extremities.
Patient characteristics are presented for all and the subgroups of simple AVM^{LE} and combined or syndromic AVM^{LE}.
Data are presented as number (%) or mean (standard deviation).

Overall, most common symptoms and signs were pain (n = 25; 81%), swelling (n = 21; 68%), and soft tissue hypertrophy (n = 13; 42%). Patients with combined or syndromic AVM^{LE} presented more often with limb overgrowth (OR, 7.6; 95% CI, 1.4-72.6), swelling (OR, 8.8; 95% CI, 1.1-197.1), bleeding (OR, 81.9; 95% CI, 6.7-88.0), and malformation-related infection of the affected leg (OR, 18.2; 95% CI, 1.9-453.6). ORs for pain, soft tissue hypertrophy, reduced exercise capacity, hyperthermia of the affected leg, and atypically located varicose veins were higher in combined or syndromic AVM^{LE} than in simple AVM^{LE}; however, the 95% CI crossed the null value of 1 (Table II).

Patients mainly presented with a Schobinger stage I or II disease (81% in total, 82% in the simple AVM^{LE} group and 78% in the combined or syndromic AVM^{LE} group). Ulcerations were present in eight of nine patients with combined or syndromic AVM^{LE}, related to lymphedema

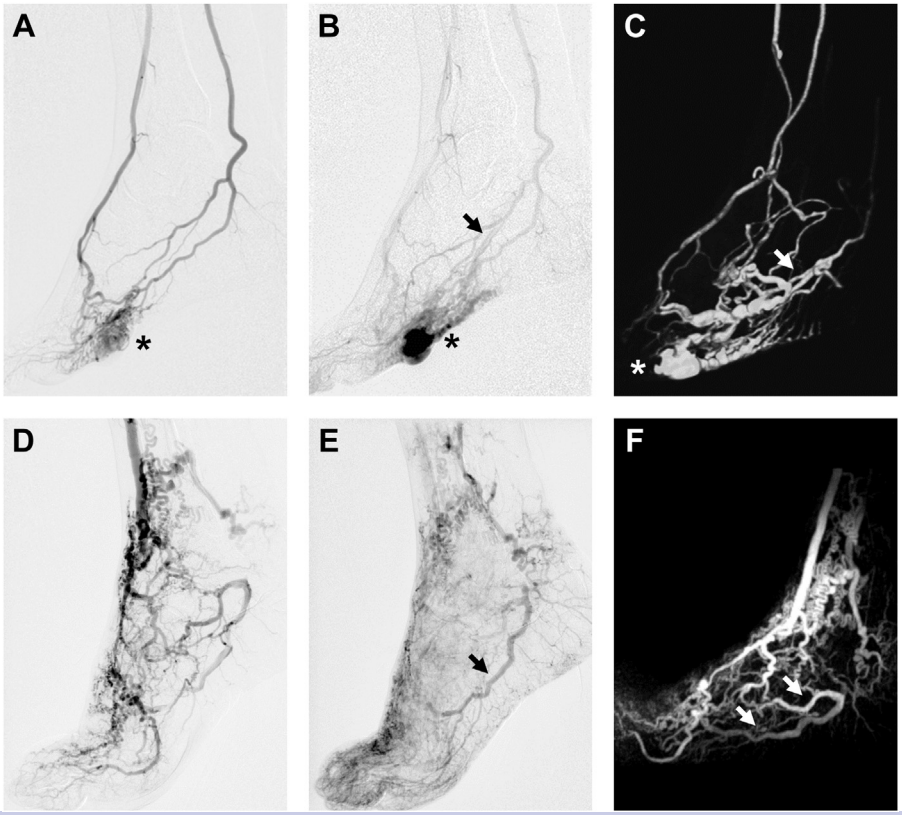

Fig 1. Digital subtraction angiography (**A/D** = early phase; **B/E** = late phase) and contrast enhanced magnet resonance angiography (**C, F**) of the foot with a simple arteriovenous malformation (AVM), type IIIB (**A-C**) in comparison with a syndromic AVM, mixed type II and IV (**D-F**). **Nidus (simple AVM); → Venous drainage.*

and venous hypertension in six patients and due to an ischemic steal phenomenon in two patients, respectively. One-fifth of the patients in both groups reported subjective reduced exercise capacity, but only one patient in each group had moderate left ventricular dilatation and augmented cardiac output determined by cardiac ultrasound without any other cardiac anomalies, (ie, Schobinger stage IV disease) (Table III).

None of the patients died from heart failure. Three patients with combined or syndromic AVM^{LE} died. Two of them had bleeding complications due to disseminated intravascular coagulation, one died from intracranial hemorrhage, the other from major bleeding from ulcerations 3 years after above knee amputation. The third patient died from wound infection with sepsis, 49 years after above-knee amputation. None of the patients with simple non-syndromic AVM^{LE} died.

Baseline laboratory testing revealed elevated D-dimer levels, as a marker for localized intravascular coagulation (LIC), in all patients with combined or syndromic AVM^{LE}, with a mean D-dimer level of 17,256 μg/L (range, 1557-80,000 μg/L; normal <500 μg/L). Patients with non-syndromic AVM^{LE} had normal D-dimer levels with a mean of 364 μg/L (range, 45-489 μg/L) (Table IV).

DISCUSSION

In the present consecutive series of 31 selected patients with AVM^{LE}, we found pain, swelling, and soft tissue hypertrophy to be the most common clinical symptom and signs at first presentation. The hemodynamic effects of these high flow AVM^{LE} were less dominant than expected. Only four patients presented with Schobinger stage III or IV disease, defined as tissue loss based on an ischemic steal mechanism or heart failure. However, a predefined subgroup analysis, which compared combined or syndromic AVM^{LE} with simple AVM^{LE}, showed a more serious course and more complications including death in patients with combined or syndromic AVM^{LE}. Moreover, considerably elevated D-dimer levels, representing LIC, were found in patients with combined or syndromic AVM^{LE} as compared with normal levels in all patients with simple AVM^{LE}.

The interplay of various vascular malformation components in patients combined or syndromic AVM^{LE} can built up to a dangerous complication cascade with recurrent bleeding and infections due to fragile skin conditions or even spontaneous bleeding complications due to LIC, that may progress to disseminated intravascular coagulopathy. Moreover, in patients with combined or syndromic AVM^{LE}, the AVM angioarchitecture seems to

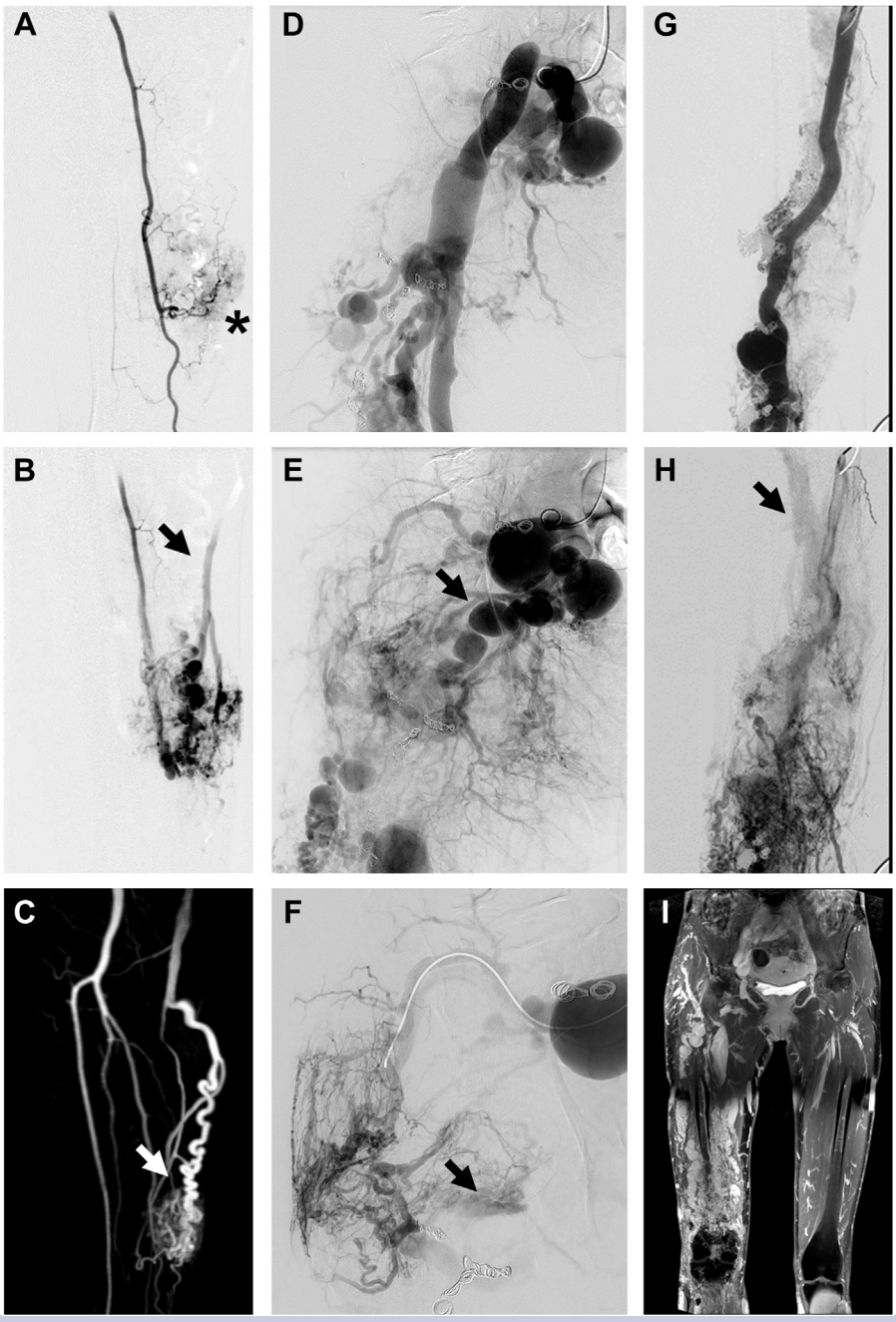

Fig 2. Digital subtraction angiography (**A, D, G, F** = early phase; **B, E, H** = late phase), and contrast-enhanced magnetic resonance angiography **(C)** and contrast-enhanced magnetic resonance angiography blood pool imaging **(I)** of lower extremity arteriovenous malformations (AVMs) of a patient with a simple AVM type II of the lower leg **(A–C)** in comparison with a multifocal, syndromic AVM, mixed type II, III, and IV (Parkes Weber Syndrome, **D-I**; **D-F** pelvis; **G, H** distal thigh). **Nidus (simple AVM), → Venous drainage.*

be considerably more complex, with tissue infiltration poorly amenable to local treatment. In patients with combined or syndromic AVM[LE], the association of high-flow vascular malformation, increased vessel fragility, lymphedema, and localized intravascular coagulopathy therefore mandates consequent simultaneous control of all malformation components to prevent the initiation of even minor complications.[28-31] Whereas embolosclerotherapy, in particular using coils and ethanol, is effective and even can heal simple AVM, the diffuse and infiltrative character of combined or syndromic AVM often limits therapeutic options.[32,33] We recommend discussing the decision about treatment in patients with combined or syndromic AVM[LE] on an interdisciplinary platform after weighing the risks and possible benefits for the individual patient. In patients

Table II. Clinical presentation of patients with arteriovenous malformation of the lower extremities

Clinical presentation	All (N = 31), No. (%)	Simple (n = 22), No. (%)	Complex/syndromic (n = 9), No. (%)	*P* value[a]	Unadjusted OR[b] (95% CI)	Adjusted OR[c] (95% CI)
Pain	25 (81)	18 (82)	7 (78)	1	0.8 (0.1-6.5)	0.6 (0.1 5.7)
Swelling	21 (68)	13 (59)	8 (89)	.235	5.5 (0.80-112.16)	8.8 (1.1-197.1)
Soft tissue hypertrophy	13 (42)	8 (36)	5 (56)	.99	1.4 (0.3-6.9)	1.1 (0.2-5.9)
Limb length overgrowth	8 (26)	3 (14)	5 (56)	.049	7.9 (1.4-54.7)	7.6 (1.1-72.6)
Recurrent bleeding	7 (23)	1 (5)	6 (67)	.001	42.0 (5.0-65.8)	81.9 (6.7-88.0)
Reduced exercise capacity	6 (19)	4 (18)	2 (22)	1	1.3 (0.2-8.3)	1.4 (0.2-10.0)
Recurrent infections	5 (16)	1 (5)	4 (44)	.028	16.8 (2.0-371.1)	18.2 (1.9-453.6)
Palpable hyperthermia	3 (10)	3 (14)	0 (0)	.62	NA	NA
Visible varicose veins	3 (10)	1 (5)	2 (22)	.4	6.0 (0.5-141.4)	4.9 (0.4-120.0)

AVM, Arteriovenous malformation; *AVM*^{LE}, arteriovenous malformation of the lower extremities; *CI*, confidence interval; *OR*, odds ratio.
Patient's symptoms are presented for all and the subgroups of simple AVM^{LE} and combined syndromic AVM^{LE} estimating the odds for clinical outcomes for non-syndromic AVM^{LE} vs syndromic AVM^{LE}.
[a]χ^2 test.
[b]Unadjusted model.
[c]Adjusted for age and sex.

with combined or syndromic AVM^{LE}, clinicians must also pay attention to potential complications related to disturbed hemostasis and increased risk of infection in addition to hemodynamic consequences of AV shunting. LIC led to recurrent, non-fatal bleeding in 68% (6/9) patients with combined or syndromic AVM^{LE}, and in two cases, directly to death as a consequence of intracranial hemorrhage and major bleeding from ulcers. Patients with combined or syndromic AVM^{LE} need careful monitoring of coagulation (D-dimer and fibrinogen at least) and initiation of prophylactic oral anticoagulation[34] or low molecular heparin[35] in case of reduced fibrinogen levels or symptomatic bleeding. Platelet inihibitors such as aspirin and therapeutic dose vitamin K antagonist are not effective in treatment of LIC.[26] Furthermore, infections were present in 44% of patients with combined or syndromic AVM^{LE} and they led to death in two cases. Skin care, manual decongestive therapy, and lymphatic drainage, as well as adapted footwear, are important prophylactic measures. Infectious disease specialists should be involved for the management of recurrent infections. However, there is some hope that the growing knowledge about the genetic pathobiology of CVM might open the horizon for molecularly targeted treatment options in the future.[22,36]

Table III. Schobinger classification in patients with AVM^{LE}

Schobinger classification	All (N = 31), No. (%)	Simple (n = 22), No. (%)	Complex/ syndromic (n = 9), No. (%)
Stage I (quiescent)	10 (32)	10 (46)	0 (0)
Stage II (expansion)	15 (48)	8 (36)	7 (78)
Stage III (destruction)	4 (13)	3 (14)	1 (11)
Stage IV (decompensation)	2 (7)	1 (5)	1 (11)

AVM^{LE}, Arteriovenous malformation of the lower extremities.
The distribution of the Schobinger classification is presented for all and the subgroups of simple AVM^{LE} and combined or syndromic AVM^{LE}.

A finding that has not been previously described is the relevant difference in the occurrence of LIC in patients with combined or syndromic AVM^{LE} as compared with those with simple AVM^{LE}. Only one prospective cohort study with follow up of 1 to 2 years measured D-dimer levels in three PKWS patients and found no elevation.[26] The authors proposed elevated D-dimers as a laboratory parameter to distinguish Klippel-Trénaunay syndrome from PKWS, a claim that cannot be maintained in view of our findings. LIC needs to be distinguished from Kasabach-Merritt phenomenon, characterized by predominant platelet trapping and consumption in hemangiomas, with secondary consumption of clotting factors.[37] Elevated D-dimer levels in combined or syndromic AVM^{LE} rather reflect intravascular coagulation with primary consumption of clotting factors in dysplastic venous channels and venous lacunas and rather late in the process of disturbed hemostasis consumption thrombocytopenia. Our study is the first study to show such findings in patients with combined or syndromic AVM but not in patients with simple AVM, which is why elevated D-dimers are probably related to other than the AVM component. Further studies are needed to distinguish if there are other reasons for D-dimer elevation (eg, arterial channel dilatation or micro dissection as known with aortic dissection) and the potential consequences in terms of differentiating simple from combined or syndromic AVM, treatment, and clinical outcome. Moreover, the combination of high venous pressure and LIC seems to put patients with combined or syndromic AVM^{LE} at particular risk of serious bleeding complications and need of careful surveillance. Although hemodynamic consequences of AVM^{LE} per se are often benign over the whole range of patients, it remains

Table IV. D-dimer level of patients with AVM^{LE}

D-dimer concentration, μg/L	All (N = 26), No. (%)	Simple (n = 17), No. (%)	Complex/syndromic (n = 9), No. (%)	Range of absolute values, μg/L
<500	17 (65)	17 (100)	0 (0)	45-489
>500	9 (35)	0 (0)	9 (100)	1557-80,000

AVM^{LE}, Arteriovenous malformation of the lower extremities.
D-dimer levels are presented for all and the subgroups of simple AVM^{LE} and combined or syndromic AVM^{LE}.

important to notice the differences in clinical presentation separating those at risk, with Schobinger stage III and IV disease, as well as syndromic manifestations, who represent a particularly fragile patient population that needs close follow-up and consequent management of disease complications.

CONCLUSIONS

Although there are several series describing AVM, our analysis uniquely differentiates simple non-syndromic AVM and combined or syndromic AVM^{LE} in a Caucasian series of patients. Despite hemodynamic and clinical similarities, there are profound differences, which critically influence therapeutic options and outcomes. AVM is rare, and therefore, it is difficult to assemble representative cohorts to thoroughly assess differences in clinical characteristics by syndromic patients and non-syndromic patients. This is highlighted in our study with its limitation of a small number of patients for comparisons, and thus wide confidence intervals and imprecise estimates. Additionally, we were limited by possible unknown confounding variables, which may result in residual confounding of our results. Future studies would benefit from a multicenter data collection and analysis of combined datasets. Yet, our results underscore the importance and necessity for comparisons of combined or syndromic and non-syndromic patients with simple AVM to understand and mitigate potentially serious complications.

AUTHOR CONTRIBUTIONS

Conception and design: SB, JL, IB
Analysis and interpretation: SB, AT, JL, FH, DH, UH, JR, MS, IB
Data collection: SB, AT
Writing the article: SB
Critical revision of the article: SB, AT, JL, FH, DH, UH, JR, MS, IB
Final approval of the article: SB, AT, JL, FH, DH, UH, JR, MS, IB
Statistical analysis: JL
Obtained funding: IB
Overall responsibility: IB

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