

Thrombotic Complications in Venous Malformations: Are There Differences Between Facial and Other Localizations?

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Abstract

Venous thrombosis (VT) is a frequent complication in venous malformations (VM) in relation with blood stasis and localized intravascular coagulopathy (LIC). Our aim was to describe the clinical characteristics and the treatment of patients with facial and non facial VM with VT. We implemented an observational retrospective study of patients with VM followed between 2002 and 2017. We compared features of facial and non facial VM. Descriptive and bivariate statistics were computed and the P value was set at 0.05. Fifty patients were included between 2002 and 2017. 24 of them were women (44%). The median age of the patients at diagnosis was 16,5 [8-31] years. The median follow up was 2 [2; 4] years. In non facial VM venous thrombosis occurred in 12 cases. In facial VM, 3 patients had thrombotic complication (15%). We demonstrate no difference of VT between facial VM and other localization. No patients had clinical risk factors for VT at diagnosis. Our study showed that VT is a frequent complication of VM and its proportion is not different between facial and non facial VM. Studies are needed to confirm the role of LIC in VT in VM, particularly in facial VM.

Keywords

venous malformations, venous thrombosis, localized intra vascular coagulation, D dimers

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Introduction

Venous malformations (VM) are frequent slow-flow vascular malformations, present in 1% of the population and represent the half of all vascular anomalies.¹ VM can be part of complex syndromes and may occur with lymphatic, capillary or arterio-venous malformations. Recently some causative somatic mutations have been reported as TIE2 and PIK3CA.² Clinically present as bluish or purpl lesions mainly localized on the skin and mucosa, they can be present in any anatomic or tissue location, but facial location is frequent.³ Main complications are malformation extension, pain and thrombosis possibly leading to post thrombotic syndrome but also, deep vein thrombosis, pulmonary embolism and post embolic pulmonary hypertension.⁴

(SVT), 1 patient had acute DVT and 36% of patients experienced residual SVT or DVT. Hence, data on proportion and risk factors of venous thrombosis in VM is lacking. Main risk factor for venous thrombosis (VT) is blood stasis explaining the high frequency of VT in large or deep VM. VT can be also explain by aberrant venous anatomy in some cases.¹

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The presence of a localized intravascular coagulopathy (LIC) is frequently described⁴ in VM due in part to blood flow stagnation. In the series of Mazoyer et al. LIC was observed in 19 of 24 patients with extensive and painful malformation.⁷ LIC was characterized by a decrease in fibrinogen, an increase in D-Dimers and presence of soluble complex of fibrin but without a decrease in platelets count. LIC is associated with large and/or deep VM. Low-molecular-weight heparin is used to treat the pain and prevent decompensation into disseminated intravascular coagulopathy.⁸ It is thought that LIC could lead to venous thrombosis and deep venous thrombosis (DVT). Despite that, the role of LIC is still unclear and there is no recommendation for routine LIC testing in VM.

To date, VT in facial VM has not been investigated. We hypothesized that frequency of VT in facial VM is lower than other location, because of lower size and absence of blood stasis. Our aim was to describe the proportion of venous thrombosis in patients with VM in an expert center and compare clinical characteristics and the rate of venous thrombosis between facial and non facial VM.

Methods

Population

We retrospectively included all patients with VM followed in a single center which is a reference center for vascular malformations between January 2002 and December 2017. Inclusion criteria were VM confirmed by Doppler ultrasound or MRI and informed patient's consent. Exclusion criteria was patient's refuse to participate.

Following data were collected from medical charts and patient's questionnaire: age, sex, VM type and location, previous medical or surgical treatment. We also collected data of DVT location, type and duration of treatment. If D Dimers were measured, we recorded the time and level of measure. Risks factors of thrombosis were recorded at the date of thrombosis (immobilization, recent surgery, oral contraceptives, pregnancy and known active malignancy, family history of venous thrombosis). We determined the prevalence of DVT, localization and the treatment strategy. Venous thrombosis was diagnosed by Doppler ultrasound realized for symptoms as pain or edema.

All adverse events and bleeding complications were collected in patients treated with anticoagulant. A Doppler ultrasound was systematically realized at 3 months of treatment as current practice in our center since 2002. A good outcome was defined as the absence of symptoms initially described.

Statistical Analysis

All numbers are expressed as medians with corresponding interquartile ranges (IQR). Statistical analysis was performed using statistical software R version 3.5.1

Ethical Considerations

The study was conducted in accordance of Helsinki declaration and was declared to the Commission Nationale Informatique et Liberté (CNIL), France. All patients received a written information.

Results

50 patients were included between 2002 and 2017. All patients had a VM and 5 of them presented with a Klippel Trenaunay syndrome. 24 of them were women (44%). The median age of the patients at diagnosis was 16,5 [8-31] years. The median follow up was 2 [2; 4] years. 20 patients had a facial VM (40%), 8 of them were women (42%). Facial VM localization was mucosal in 8 patients.

A Doppler ultrasound was performed in all patients at diagnosis. A magnetic resonance imagery was performed in 23 patients (58%) and a computed tomography was performed in 8 patients (20%). The medical ward analysis did not found any treatment associated with venous thrombosis.

Non Facial VM

In non facial VM, surgical treatment was performed in 8 patients (26.7%). Sclerotherapy was performed in 4 patients (13.3%). No systemic treatment was introduced. Venous thrombosis occurred in 12 cases (40%). In 6 of them, it was a superficial venous thrombosis restricted to the VM. In 5 cases, thrombosis event was a DVT and in one case a pulmonary embolism was diagnosed by CT angiography. No patients had clinical risk factors for venous thrombosis at the time of thrombosis. No patient had a family history of venous thrombosis.

Facial VM

In facial VM, 3 patients had thrombotic complication (15%). One patient had a superficial venous thrombosis with no treatment. One patient had a SVT of lower limbs treated by RIVAROXABAN during 3 months with a good outcome. Surgical treatment was performed in 9 cases (45%). Sclerotherapy was performed in 6 patients (20%) and 1 patient received intraleisional BLEOMYCIN injection. Systemic treatment by SIROLIMUS was introduced in 2 patients.

No patients had clinical risk factors for venous thrombosis at the time of thrombosis. No patient had a family history of venous thrombosis. There was no significantly difference in venous thrombosis rate between facial and non facial thrombosis (10% vs 40%, $P = 0.11$). Differences between facial and non facial VM are reported in Table 1.

Treatment Procedures and Follow Up

One local thrombosis was treated by RIVAROXABAN, 4 others were treated by aspirin and the last one by vitamin K antagonist therapy during 3 months. All patients had a good

Table 1. Comparison of Clinical Characteristics of Facial and Non Facial VM.

Characteristic	Facial VM (n = 20)	Non facial VM (n = 30)	
Median age at diagnosis	25.83	21.76	<i>P</i> = 0.49
Median Follow up	1,7	1,8	<i>P</i> = 0.1
Sex ratio	0.42	0.53	<i>P</i> = 0.76
Surgical treatment n, (%)	9 (45%)	8 (26.7%)	<i>P</i> = 0.5
Sclerotherapy n, (%)	4 (13.3%)	6 (20%)	<i>P</i> = 0.3
Thrombosis n, (%)	3 (15%)	12 (40%)	<i>P</i> = 0.11

Legend: n: number.

outcome with no symptoms at 3 months. No bleeding complication was reported.

For DVT, one was treated by RIVAROXABAN, 3 were treated by low molecular weight heparin at curative dose and one by low dose aspirin (75 mg per day). All patients were followed clinically and by Doppler ultrasound at 3 months. All symptoms disappeared and Doppler ultrasound showed no residual thrombosis.

Discussion

Our study showed that DVT is a frequent complication of VM and the proportion of venous thrombosis is not significantly different between facial and non facial VM. To date, it is the first study which investigate VT according VM location, in particular in facial VM.

The mean age was 28 years at diagnosis, which is consistent with previous studies.^{6,9} Comparatively to the general population of venous thrombosis¹⁰ our population is young, explained by the frequent diagnosis of VM during childhood.¹¹

The median follow up was 2 years. This follow up is explained by our tertiary center recruitment. A unique expert evaluation was performed for 5% of patients. 40% of patients had a facial VM, which is consistent with the known epidemiology of VM.^{3,12}

There was no statistically difference of thrombosis events rate according to VM localization contrary as the study of Mazoyer et al⁷ who described a frequent coagulopathy in large VM and that venous thrombosis is more frequent in large VM. Our results could suggest that thrombosis is frequent in VM and is not systematically in relation with VM size or location.

Usual venous thrombosis risk factors are rarely present in VM thrombosis⁷ and in facial VM thrombosis, blood stasis is rare. In our series, no patient had classical venous thrombosis risk factors.

Coagulation activation in VM has been already described as LIC,⁴ that could explain VT without blood stasis in VM. Unfortunately, biological markers for LIC were not systematically recorded in our series. A prospective study with systematic LIC

evaluation in all VM thrombosis could be useful to explain this apparent paradox. More data are needed to confirm the link between VM thrombosis, blood stasis, VM size and LIC.

As described here VM thrombosis can be asymptomatic. The coagulation activation hypothesis could lead to D-Dimer testing in patients with VM to screen for thrombosis. Moreover a prophylactic treatment as anticoagulant or aspirin might be used in patients with elevated D-dimers, but data are lacking.

4 patients have been treated by RIVAROXABAN at the usual dose of 20 mg daily. The use of RIVAROXABAN was recently described by Mack et al¹³ with good outcome and no serious adverse event. In our series, we report the effectiveness and the safety of RIVAROXABAN in VM. Other studies showed that other oral anti Xa (DABIGATRAN) was effective in treatment of VM venous thrombosis.¹⁴ Our study underline that RIVAROXABAN, despite the lack of recommendation, is used in daily practice in VM thrombosis, but more data are needed to recommend antiXa treatment in VM thrombosis.

Our study has several limitations. First of all the retrospective design of the study can lead to underestimate the number of patients with VM diagnosed in our center by loss of follow up.

Secondly, biological data are lacking in most patients. It can be explained by the absence of recommendation of the measurement of biological parameters for the diagnosis or management of VM.¹⁵ Patient's treatment is guided by clinical and radiological findings.²

Conclusion

To our knowledge, this is the first study to evaluate characteristics of facial VM and VT in facial VM. We report that venous thrombosis frequency is not different between facial and non facial VM. Further studies are needed to explore physiopathological pathways of VT in VM and the link between LIC and blood stasis. We also report a safe and effectiveness use of oral antiXa for VT in VM.

Authors' Note

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Declaration of Conflicting Interests

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