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Factors associated with thrombotic complications in pediatric patients with vascular malformations

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ABSTRACT

Background and objectives: Thrombosis is an uncommon disorder in children. Patients with slowflow vascular malformations have higher risk of developing localized intravascular coagulation, which is closely related to the presence of thrombotic events. These episodes cause pain, can be recurrent and determine a clear deterioration in the quality of life. Moreover, serious complications such as pulmonary thromboembolism and eventually death have been described. The aim of the present study is to identify clinical and laboratory risk factors associated with thrombotic events in pediatric patients with vascular malformations.
Methods: Case–Control study. Clinical records of patients who consulted the vascular anomalies study group (VASG). This group carries out interdisciplinary assessment of patients with vascular malformations. From June 2008 to December 2014, 110 patients were assessed of whom 46 patients met the inclusion criteria, with half of them presenting a thrombotic complication and the others not, these latter serving as controls. Statistical analysis included multivariate logistic regression analysis to determine major risk factors for thrombosis.
Results: In the bivariate analysis we found a significant association between increased levels of Ddimer and thrombotic complications (OR 17.1 [95% CI 3.95–73.95; $p < 0.01$]). In addition, a surface area ≥ 10 cm^2 (OR 6.18 [95% CI 1.59–23.99; $p < 0.01$]) and the presence of palpable phleboliths (OR 20.17 [95% CI 2.32–165.77; $p < 0.01$]) were associated with a significant higher risk of thrombosis. Multivariate analysis identified older age (OR 1.33; $p = 0.013$), a surface area ≥ 10 cm^2 (OR 8.19; $p = 0.042$) and palpable phleboliths (OR 85.29; $p < 0.01$) as significant risk factors.
Conclusions: Our study suggests the existence of clinical factors associated with higher risk of thrombotic complications, such as the extent of the malformation, palpable phleboliths and increased age among children with vascular malformations.

The clinical presentation of vascular malformations is quite variable and heterogeneous, ranging from asymptomatic localized anomalies to diffuse lesions that can involve all organs and systems. Musculoskeletal localization is especially associated with pain because of soft-tissue involvement and the presence of bleeding or thrombosis, which can lead to functional impairment depending on the affected organ and the extent of the lesion [1,2].

Among serious complications, localized intravascular coagulopathy (LIC) is particularly relevant since it is closely related to bleeding and thrombotic events [3]. It was first described by Dompmartin A et al., in a cohort of 140 adult and pediatric patients demonstrating a statistically significant association between LIC and large venous malformations, the presence of palpable phleboliths and increased levels of D-dimer [4]. However, no study so far has been focused exclusively in the pediatric population.

Thrombotic events are mainly described in low-flow vascular malformations, with an incidence of 40%–60% in venous or combined malformations, and around 22% in patients with Klippel–Trenaunay Syndrome (KTS) [5,6].

Thrombotic events themselves produce morbidity, as they are associated with an increase in volume, edema, and especially pain. Chronic or recurrent pain is of special importance at the pediatric age, since antalgic positions alter development and hinder rehabilitation, which further deteriorates the musculoskeletal function of patients, and determines an impaired quality of life, school dropout and the inability to perform daily activities [7].

Although the prevalence of serious complications in children with LIC is not clear, pulmonary thromboembolism, pulmonary hypertension and mortality have been described [8,9].

The aim of our study is to identify clinical and laboratory variables that are associated with increased risk of presenting thrombotic events in pediatric patients with low-flow vascular malformations.

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1. Materials and methods

1.1. Study design

Observational retrospective case–control study with data collected over a period of 6 years and 6 months (June 2006–December 2014) from the Vascular Anomaly Study Group (VASG) database in Chile, the national referral center for these types of diseases.

The Ethics Committee of the Pontificia Universidad Católica de Chile approved the study and provided an informed consent waiver on April 1, 2014.

1.2. Definition of cases and controls

Cases were defined as pediatric patients (≤18 years) with vascular malformations with at least 1 episode of thrombotic complication diagnosed by clinical acute pain plus changes in physical exam, such as edema, heat, erythema, and a Doppler ultrasound compatible with thrombosis. Controls were pediatric patients diagnosed with vascular malformations but without confirmed episodes of thrombotic complications.

1.3. Patients and selection process

We reviewed medical records in the VASG database from June 2008 to December 2014 containing 110 patients from all over Chile, evaluated by vascular anomalies. Sixty-four patients were excluded (Fig. 1). Forty-six patients were finally included. All had a final diagnosis of vascular malformation confirmed by imaging, and remained under control in our institution. Of these cohort, 23 patients developed a confirmed thrombotic complication over time, and the other 23 did not, thus serving as controls.

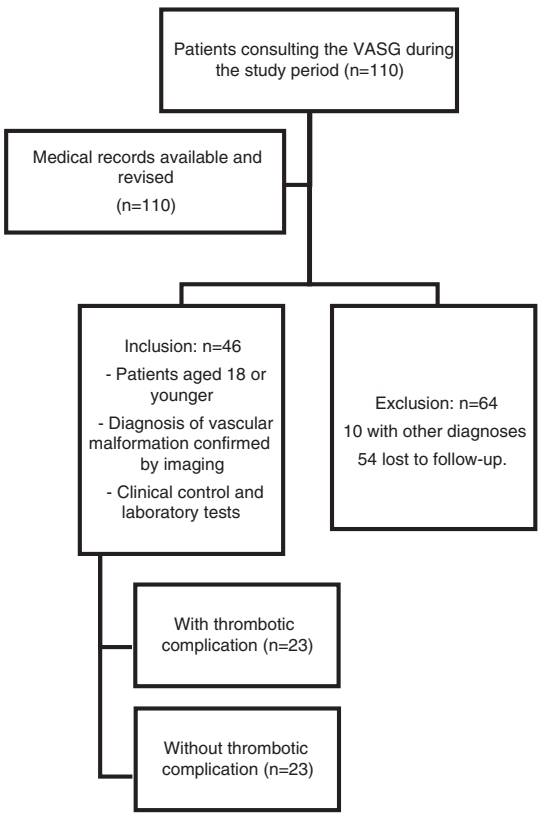

Fig. 1. Patient selection flow-chart. Inclusion criteria: Patients less than 18 years old, diagnosis of vascular malformation by imaging (Doppler ultrasound or angioresonance), clinical control and laboratory tests (platelet counts, D-dimer, Fibrinogen, PT and aPTT). Exclusion criteria: patients carrying thrombophilia, with known neoplasia, with other diagnoses and without follow-up at our institution.

1.4. Procedures

In the reviewed records, we found a detailed anamnesis and clinical history according to the guidelines established by the VASG, with the aim of determining the extent of the lesion and presence of thrombotic events.

Patient blood tests were performed by extracting blood from a peripheral vein, measuring platelets (reference range: 140–400 × 10^3/mm^3) using an automated method (blood cell counter) or phase contrast microscopy (Neubauer counting chamber); D-dimer (reference range: up to 500 ng/mL) using the ELFA (Enzyme Linked Fluorescent Assay) method; fibrinogen (reference range: 200–400 mg/dL) using the Nephelometric method (ACL 9000); prothrombin time (PT) (reference range: 70–120%) using the Nephelometric method (ACL 9000, ACL TOP); and activated partial thromboplastin time (aPTT) (reference range: 26–40 s) using the Nephelometric method (ACL 9000, ACL TOP).

All patients were subjected to imaging evaluation: magnetic resonance angiography of the affected zone with the aim of determining the extent of the vascular malformation, or Doppler ultrasound searching for signs of thrombotic complications.

The 2014-ISSVA classification (The International Society for the Study of Vascular Anomalies) was used to categorize the type of lesion.

1.5. Analyzed variables

The following variables were selected: age, sex, type of vascular malformation (determined by imaging studies), location (head and neck, trunk, extremities, and genitals), size (<10 cm^2 or ≥10 cm^2), palpable phleboliths, platelet counts, D-dimer, fibrinogen, PT and aPTT.

1.6. Statistical analysis

The statistical analysis was carried out using IBM SPSS Statistics 20. The differences between categorical variables were determined with the chi-squared ($\chi 2$) test. We used the Mann–Whitney test for non-parametric numerical data, Student's *t*-tests for continuous variables and Fisher's exact test for small samples.

To investigate variables associated with increased risk of thrombotic complications in patients with vascular malformations, odds ratios (OR) were calculated. Finally, we used multivariate logistic regression in search of the best predictive model for factors associated with complications.

2. Results

Of the 46 patients, male predominated (58.7%), with a median age of 9 years (ranging between 0.16–18 years).

As for the type of lesion, most (52.17%) were simple, predominantly venous (39.1%), followed by the combined (23.9%), and a lower percentage (21.7%) was associated with other anomalies (SKT).

Concerning the location of the vascular malformation, a large percentage was located in the lower extremities (69.6%), followed by trunk and upper extremities, both with 19.6%, and genitals with 4.3%. A 63% had a surface area of ≥10 cm^2 and 26.1% showed palpable phleboliths.

Of the 23 cases, 2 patients developed a deep vein thrombosis (DVT) in the affected extremity, and 21 had a localized thrombosis in the malformation. All complications were visualized by Doppler echography. The patients with DVT had in common to be carriers of SKT and a thrombosis located in a deep anomalous venous system.

The association of the different independent variables with the presence or absence of thrombotic complications was analyzed. For categorical variables (sex, type of vascular malformation, location, surface area ≥ 10 cm^2, palpable phleboliths) we used the chi-squared test and Fisher's exact test for small samples. We found significant differences ($p < 0.01$) with respect to the surface area ≥ 10 cm^2 and the presence