Pediatric Noncerebral Thromboembolism: Etiological Assessment and Outcome

Thromboses Vasculaires extracérébrales chez l'Enfant: Étiologies et Évolution

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RÉSUMÉ

Introduction: Objectifs: Décrire la présentation clinique et identifier les facteurs favorisants des thromboses vasculaires extracérébrales chez l'enfant.

Méthodes: Étude rétrospective des cas de thromboses vasculaires extracérébrales colligés dans le service de Médecine Infantile A de l'Hôpital d'Enfants de Tunis sur 08 ans.

Résultats: Nous avons colligé 14 cas de thromboses vasculaires extracérébrales. Ces accidents constituent 0,26‰ des étiologies d'hospitalisation dans le service. L'âge moyen des patients était de 56±41 mois [25 jours-12 1/2 ans]. Le sex-ratio était de 1,8. L'accident touchait les veines dans 2/3 des cas. La présentation clinique était dominée par une tuméfaction douloureuse dans quatre cas, une dyspnée d'installation brutale et une hématémèse dans trois cas chacune et la thrombose était localement asymptomatique dans quatre cas. Les localisations étaient les thromboses veineuses profondes des membres (n=6), de la veine cave (n=1), les thromboses portes (n=4) et l'embolie pulmonaire (n=3). Les facteurs favorisants identifiés étaient les pathologies tumorales dans sept cas, la thrombophilie et le cathétérisme dans quatre cas chacun, le traumatisme, la chirurgie et la maladie de Behçet dans un cas chacun. Onze patients ont reçu un traitement anticoagulant, il s'agissait de l'héparine non fractionnée dans trois caset de l'héparine de bas poids moléculaire dans les autres cas. Tous les malades ont survécu et quatre ont gardé des séquelles.

Conclusion: Les thromboses vasculaires sont rares en pédiatrie. Elles sont essentiellement veineuses et surviennent sur un terrain de pathologies chroniques en présence de cathéters centraux. Le traitement anticoagulant, facteur déterminant de l'évolution, est bien toléré par les enfants.

Mots-clés

Thrombose vasculaire;thrombophilie; cathétérisme; tumeurs; pédiatrie; traitementanticoagulant

SUMMARY

Objective: To report clinical presentation and etiologic investigation findings during pediatric noncerebral thromboembolism.

Methods: Retrospective study of cases of vascular non cerebral thromboses admitted in Medicine infantile A Department of the Children's Hospital of Tunis over 08 years.

Results: We confirmed 14 cases of non cerebral vascular thromboses. So that these accidents constitute 0,26 ‰ of the overall etiologies of hospitalizations in the Department. The mean age of our patients was 56±41 months [25 days-12 1/2 years]. The sex ratio was 1.8. The vascular incident was venous in 2/3 of cases. The clinical presentation was mainly painful swelling in four cases, abrupt dyspnea and hematemesis in three cases each and the incident was locally asymptomatic in four cases. Thromboses locations included deep vein thrombosis of limbs (n=6), vena cava thrombosis (n=1), portal thrombosis (n=4) and pulmonary embolism (n=3). The promoting factors identified were: tumors in seven cases, thrombophilias and catheterization in four cases each, trauma, surgery and Behçet disease in one case each. Eleven patients received anticoagulant treatment including unfractioned heparin in three cases and low molecular weight heparin in the other cases. No one died while four patients developed sequelae.

Conclusion: Vascular thromboses are rare in children. They are mostly venous and diagnosed in ill children especially those having central venous catheters. Outcome of pediatric thromboembolism depends on efficient anticoagulation therapy which is well tolerated by children.

Key-words

Vascular thrombosis; thrombophilia; catheters; tumors; pediatrics; anticoagulant therapy.

INTRODUCTION

Vascular thromboembolism (TE) and especially in the non cerebral location is rare in children, it's 100 times less frequent than that among adults [1,2]. However, the prevalence of this pathology is in clear increase over the past several decades [3]. Indeed, the recent advances in the field of the neuro-imaging allow a precise and early diagnosis. Besides, the considerable progress in resuscitation, oncology, cardiac surgery and organ transplantation has improved the survival of critically ill children and, together with the increase of the use of vascular catheterizations, have contributed to the increased incidence rate of TE.

In this article, we present data related to the clinical features and outcome of non cerebral thromboses diagnosed in the Pediatric A Department of Children's Hospital of Tunis. The aim of this report was to assess the etiological investigation findings and outcome.

METHODS

Patients

This was a retrospective cohort study carried out at pediatric department A of Children's Hospital of Tunis over a period of eight years, from January 2008 to December 2016. Each patient's hospital records were reviewed.

In this study, we included those children aged less than 14 years of age who were hospitalized for non cerebral TE. Children followed for sickle cell disease or having been diagnosed with homozygous sickle cell disease after the ischemic incident were excluded from our study regarding the physiopathological specificities and the appropriate therapeutic protocol of the disease.

Methods

Each patient's hospital records were reviewed including: the age at admission, the gender, the family history and the child's personal history evoking or predisposing to hypercoagulability.

A diagnosis of TE was confirmed based on radiological investigations which included ULS, CT angiography, MRI and scintigraphy according to the location of the accident and the availability of the technical platform.

The thrombophilia workup included Protein C (PC) deficiency, Protein S (PS) deficiency, antithrombin III deficiency, activated protein C resistance (APCR), anti-phospholipid antibodies and hyper homocysteinemia. The diagnosis of thrombophilia was confirmed by at least 2 measurements identifying the abnormality.

Antithrombotic therapy included unfractionated heparin (UFH), low molecular weight heparin (LMWH), vitamin K antagonists, and platelet inhibitors. Information about the biological control of anticoagulant activity, the dose of anticoagulant required to achieve therapeutic range, duration of anticoagulation were collected.

Sequelae in survivors were clinically and radiologically evaluated based on the presence beyond 6 months during follow-up of symptoms consistent with post thrombotic syndrom (PTS) or damage to the involved organ/limb.

RESULTS

During the 8-year study period, there were a total of 52622 pediatric hospital admissions in Pediatric A Department. Thirty one patients had cerebral vascular thromboses while 14 patients had vascular noncerebral arterial and venous thrombotic incidents. Therefore, noncerebral thromboembolism constitutes 0,26‰ of the total of hospitalizations and one third of all vascular thromboses.

The mean age of our patients was 56 ±41 months (extremes: 25 days and 152 months). Sex ratio was 1.8. The vascular incident was venous in 11 cases, one patient (P12), as shown in Table I and II, had an extensive arteriovenous thrombosis of the hepatic veins associated with pulmonary embolism (PE) and the two remaining patients (P11 & 13) had PE .

Family medical history of thromboembolism was found in 10 cases. Personal medical history of patients, as well as their clinical presentation are summarized in Table I. Six patients had deep venous thromboses (DVT) of the limbs, including four cases of jugular thrombosis (JT) and two cases of DVT of the lower limbs. On examination, the sign of Homans was positive and peripheral pulses were present in both patients with DVT of the lower limbs.

Four patients had portal thromboses (PT). The incident was acute in one case (P10) and chronic in the others, revealed by hematemesis, splenomegaly and paleness. Among patients with chronic PT, two had hypersplenism.

Three patients had PE. Two patients suffered from abrupt dyspnea and one presented with seizures due to hypoxemia. Clinical examination showed tachycardia in both cases. The third patient (P13) was asymptomatic, his emboli was discovered during the work-up for spread of cancer. One patient (P14) had asymptomatic vena cava thrombosis.

Radiological investigations included ULS in seven cases, CT angiography in five cases, MRI and scintigraphy in one case each. The radiological findings are detailed in Table II.

Promoting factors revealed by clinical data, radiological investigations or laboratory assessments were: tumors in seven cases, thrombophilias and catheterization in four cases each, Behcet disease, surgery and trauma in one case each (table I). Regarding patients with hypercoagulability; the first one had combined protein S and C deficiency, the second one had PC deficiency, the third patient had APS and the last patient had PCAR. Family assessment for thrombophilias had shown the same abnormalities in first degree relatives in two cases. Indeed, all patients had thrombogenic factors.

Table 1 : Clinical features and underlying diseases of thromboses

Patient	Age (months)	Gender	Underlying disease	Clinical presentation	Thrombosis location	Biological findings
P1	90	F	Lymphoblastic acute leukemia CVAD	Painful swelling	JT	
P2	27	M	Myeloblastic acute leukemia CVAD asparaginase chemotherapy	Painful swelling	JT	
P3	18	F	Cervical compressive mass related to non langerhansian histiocytosis	Dyspnea	JT	
P4	26	F		Convulsive seizure (locally asymptomatic)	JT	APS
P5	152	M	Behçet's disease Trauma of the lower limb	Painful swelling Functional impotence	DVT of the lower limb	
P6	42	M		Painful swelling Functional impotence	DVT of the lower limb	PC deficiency
P7	57	M	Umbilical catherization	Hematemesis Splenomegaly	chronic PT	
P8	54	M		Hematemesis Splenomegaly	chronic PT	APCR
P9	60	F		Hematemesis Splenomegaly	chronic PT	PC and S deficiency
P10	0.8	M	Umbilical catherization Surgery for congenital malformation of the digestive apparatus	Silent thrombosis	Acute PT	
P11	84	M	Metastatic rhamdomyosarcoma	Abrupt dyspnea Chest pain	PE	
P12	60	M	Metastatic neuroblastoma	Abrupt dyspnea Chest pain Seizures	PE	
P13	10	F	Metastatic hepatoblastoma	Work-up for spread of cancer	PE	
P14	110	M	Metastatic nephroblastoma	Work-up for spread of cancer	VC thrombosis	

F : female ; M : male, CVAD: central venous access device; JT: jugular thrombosis; DVT: deep venous thrombosis; PT : portal thrombosis; PE : pulmomary embolism; VC : vena cava ; APS : phospholipid antibody syndrom ; PC : protein C APCR : activated protein C resistance

Table 2 : Radiological diagnosis of thromboses

Patient	Radiological investigation	Result
P1	ULS	Isolated internal jugular vein thrombosis
P2	ULS	Thrombosis of the internal jugular vein extended to the brachiocephalic venous trunk
P3	CT	Cervical compressive mass associated with jugular vein thrombosis
P4	MRI	Thrombosis of the internal jugular vein extended to cerebral sinuses
P5	ULS	posterior tibial and left peroneal thrombosis
P6	ULS	femoral vein thrombosis extended to the left popliteal vein
P7	CT angiography	Portal cavernoma with hepatosplenomegaly
P8	CT angiography	
P9	ULS	Portal cavernoma
P10	ULS	Hyperechoic image of the lumen of the portal vein: acute portal thrombosis
P11	CT angiography	Bilateral and proximal massive PE with floating thrombus of the pulmonary bifurcation
P12	Hepato CT angiography	Basal PE with no parenchymal repercussions associated with localized thrombosis of the hepatic vein
P13	scintigraphy	Non perfused ventilated area, confirmatory CT
P14	ULS	Thrombosis of the inferior vena cava

ULS: ultrasonography; CT: computed tomography; MRI: magnetic resonance imaging; PE: pulmonary embolism

Excepted cases with chronic PT, all patients received anticoagulant therapy. Three children were treated with UFH including two cases of PE and one case of jugular thrombosis. They all have had a bolus of 75 IU/kg, relayed by a maintenance dose of 20 IU/kg/hour. TCA adjustment was performed in all cases with TCA targets between 60 and 86 seconds (2 to 3 times normal). No patients experienced adverse effects following the use of UFH.

LMWH was prescribed in 10 cases; the average dose was 225 ± 50,7 UI/kg/day (extremes: 100 UI/kg/day and 300 UI/kg/day), adjusted according to biological activity assessments. In JT, they were maintained for 6 months in the first case, they were stopped after 7 days in the second case because of recurrent epistaxis and in the last case, the central venous access device (CVAD) was removed after one month of anticoagulation. In lower extremity DVT, antiplatelet therapy was maintained because of PC deficiency in the first case and vitamin K antagonist (VKA) were kept long-term in the second case because of Behçet's disease. In PE, the average duration of anticoagulation was 105±45 days (extremes:60 and 150 days). LMWHs were maintained for three months in acute PT till radiological resolution of the clot and six months in the vena cava thrombosis.

As far as the outcome of our patients is concerned, after an average follow-up of 27±32 months (extremes: 7 and 61 months), no one died while four patients had sequelae. One patient had PTS with painful swelling and collateral venous circulation. Recurrent gastrointestinal bleeding was noted in all patients with chronic portal cavernoma. No sequelae of PE, vena cava thrombosis or thrombotic recurrence were noted.

DISCUSSION

In the present study, we showed that non cerebral thromboses are rare and non specific in children. They often complicate underlying conditions and have overall favorable outcome. The diagnosis of non cerebral thromboses is usually delayed. Indeed, despite the dramatic increase in their annual incidence reported by studies during the last years along with the advances in diagnostic imaging and the increase in the survival rate of children with chronic diseases [4], these vascular incidents remain rare in pediatrics as shown in our results.

This rarity is related to a high antithrombotic power and a state of hypocoagulability predominating till adulthood [4,5]. Furthermore, the clinical presentations are non-specific, confusing with other pathologies especially infectious.

Our series was heterogenous which allows a global vision of the question; it included vena cava thrombosis which is extremely rare in both adults and children [6]. Furthermore, our etiological investigations were positive in all cases. However, our sample was small which is partly related to the rarity of the pathology, the establishment of a Tunisian register would be more contributive. In addition to that, our study includes a selection bias for patients in oncology which we tried to mitigate by recruiting more patients of general pediatrics.

Through our study, we found a greater frequency of venous thromboses which is in agreement with literature since arterial thromboses are mostly related to atherosclerosis that develops with age [7]. Furthermore, unlike adults in whom DVTs sit in the lower limbs in 90-95% of cases [8], we noted a predominance of DVT in the upper venous system. This is due to CVAD's that are placed at the superior venous system both in our patients and in the literature [9-11].

A painful swelling was the main circumstance of discovery of DVT of the limbs in our patients as well as in the literature [11,12]. However, unlike our reported cases, thromboses on CVAD's are often asymptomatic and sub-acute [13]. The suggestive sign is CVAD dysfunction according to a Cochrane pediatric study [12].

Only one patient presented an acute asymptomatic PT in our series. Indeed, clinical signs of acute PT may vary from simple abdominal pain observed in nearly 80% of cases to peritonitis and multiple organ failure according to a recent review of the literature [14]. In some cases, these manifestations overlap with those of the triggering factor, such as recent surgery in our patient. Gastrointestinal haemorrhage due to oesophageal varices revealed chronic PT in our patients. This circoumstance is inaugural in 50 to 60% of the cases of chronic PT according to Guo [15] and Ferri [16].

PE is underestimated in children since there is often underlying chronic pathology and practitioners rarely mention the diagnosis. In our study, as well as Biss results [17], chest pain, dyspnea and tachycardia on examination were the most common signs and the diagnosis was made in time since the context was alarming.

Radiological investigations depend on the thrombosis location and the device availability. Doppler sonography was sensitive to all DVT of the limbs in our study even though non-compressibility is the major sign of vascular thromboses which is technically more difficult in young patients [18].That's why, a complement by angio-MRI is recommended in case of suspicion of femoral extension of the DVT [19].

Doppler ULS was the first-line radiological investigation for PT because of its availability in our patients. However, CT angiography is more sensitive showing a vascular enhancement defect with increased hepatic enhancement [10].

During PE, CT's sensitivity is 83% and its specificity is 94% when two risk factors are present according to the largest prospective multicenter study involving 824 patients [20]. Ventilation-perfusion scintigraphy performed in one case in our series is more beneficial in terms of sensitivity and invasiveness [17]. Therefore, it is recommended as first-line investigation if there is suspicion of PE in the absence of a pathological lung [19].

Etiologies were dominated by tumor causes, thrombophilias, vascular catheterization and more rarely metabolic or autoimmune diseases.

Cancer is a major and independent risk factor for childhood thromboembolism. It's prothrombotic risk increases with age, the stage of the disease, treatment with asparaginase, high doses of corticosteroids and especially when combined therapies, the systemic inflammatory response to cancer and immobilization [11,18, 21].

In patients with thromboembolic disease, the indications for thrombophilia assessment in children with thrombosis diverge. It should not be practiced [22,23] neither in the acute phase of the thrombotic accident, nor during the anticoagulant therapy nor when the thrombotic event was caused by a major risk factor.

CVAD is a predominant thromboembolic factor in pediatrics. In an international study of children in seven different countries, more than half of critically ill children with thromboses had catheters [24]. According to another recent study on non-critically ill children [25], the presence of a catheter is associated with thromboses with an OR of 27.67.

The other promoting factors identified in our patients were Behçet, surgery and trauma. In fact, DVT during Behçet's disease sit electively in the lower limbs as reported [26]. Surgeries and especially those in an emergency context and severe trauma are also recognized prothrombotic factors.

As far as the management of non cerebral thromboembolic disease is concerned, the treatment is based on anticoagulants. Despite the absence of galenic forms of anticoagulants adapted to children, all our patients were treated and our global prognosis was favorable. UFH is recommended in the initial phase of PE treatment. LMWH or UFH may be prescribed at other locations [27]. In case of prescription of VKA, the initial anticoagulant treatment must be started from the first day, the overlap must last for at least 6 days [28].

The randomized Kids-DOTT (Kids Duration of Therapy for Thrombosis) clinical trial conducted in 2015 showed that imaging data are a major breakthrough in the duration of anticoagulant therapy [29]. Guidelines are summarized in Table III.

Table 3 : Recommendations for duration of anticoagulation in Thromboembolic non cerebral disease

American College for Chest Physicians [34]	British Committee for Standards in Haematology [22]
LMWH -Secondary thrombosis: 3 months Idiopathic thrombosis: 6 to 12 months. -Reverse risk factor: until disappearance of the factor. Recurrent idiopathic thrombosis or venous malformation: for life. - Treatment should be maintained for 3 more months if thrombus persistence at control imaging.	<1 year old: LMWH > 1 year old: VKA -Secondary thrombosis: 3 months -Idiopathic thrombosis: 6 months -Recurrent thrombosis or APS: for life -The control imaging is recommended before stopping anticoagulation in symptomatic patients, it is not required in asymptomatic patients.

LMWH: low molecular weight heparin; VKA: vitamin K antagonist; APS: phosphopholipid antibody syndrome

As far as thromboses on CVADs are concerned, preventive treatment is based on a suitable choice of CVAD material and the daily administration of “flushs” of physiological salt solution or heparin. Curative doses of LMWH are recommended for a minimum duration of 3 months and removal of the CVAD is recommended if it is unnecessary or not functional [28,30].

Anticoagulation started as early as possible is also the basis of the treatment of acute PT since spontaneous recanalization is extremely rare. LMWHs are as effective as UFHs in this location [10]. Although anticoagulant therapy does not seem to increase the risk of gastrointestinal bleeding when adequate endoscopic treatment has been performed, its prescription in chronic PT remains controversial [10].

The clinical consequences of DVT in children are heavier in the literature compared to our results given the small size of our sample; a PTS with chronic venous insufficiency occurs in 25% to 70% of cases according to the studies [10,25]. It can develop sometimes several years after the initial event. In PT, recurrent digestive hematemesis was reported in portal cavernoma in our patients. In fact, the risk of recurrence of gastrointestinal bleeding in PT depends on the age of the thrombosis, the severity of oesophageal varices and the pressure in the portal vein [15].

After an average follow-up of 27 months, no patient has recurred, the risk of recurrence is indeed more important that the follow-up is long [31].

CONCLUSIONS

Vascular non cerebral thromboses are rare in children. They often complicate underlying conditions, and occur more frequently in critically ill children with chronic diseases and central catheters. They are mainly venous.

The clinical presentation is polymorphic depending on the thrombus location and the etiological context. The systematic search for thrombophilia in pediatric is not recommended, since intercurrent situations are often associated. LMWH are well tolerated by children and their prescription should benefit from more experimental studies.

Conflicts of interest: None

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