



Two years experience of a multidisciplinary approach for pediatric thrombosis in a tertiary referral center*

Pediyatrik tromboza multidisipliner yaklaşım, üçüncü basamak referans merkezin 2 yıllık deneyimi

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ABSTRACT

Pediatric thrombosis has unique characteristics due to its epidemiology, pathophysiology and treatment considerations. Children diagnosed with thrombosis should be evaluated by a multidisciplinary team at the level of diagnosis, treatment, and follow-up. Here we present our 2 years experience of pediatric thrombosis patients with a multidisciplinary thrombosis council management. We retrospectively reviewed case presentations and recommendations of monthly thrombosis council for 61 children (95 admissions) between November 2017 and August 2019. The male/female ratio was 1.54 and children and adolescents were the majority of evaluated 61 patients. Based on patients' clinical and radiological status, treatment and prophylaxis periods were determined. Cerebral arterial and sinovenous thrombosis were more common in our pediatric thrombosis council cases. Acquired risk factors for thrombosis were more common than congenital thrombophilia. Infection and elevated Factor VIII were commonest, respectively. Thirty-nine patients (64%) received primary or secondary prophylaxis with vitamin K antagonists, aspirin or LMVH for different periods. Further studies on treatment and prophylaxis management are needed for the improvement of evidence-based guidelines in pediatric thrombosis. Multidisciplinary councils may improve patient care for pediatric patients with complicated thrombosis.

Keywords: Pediatric thrombosis, treatment, prophylaxis, multidisciplinary management

ÖZ

Pediyatrik tromboz epidemiyolojisi, patofizyolojisi ve tedavi öncelikleri nedeniyle erişkin tromboz yönetiminden çok farklı özelliklere sahiptir. Tromboz teşhisi konan çocuklar, multidisipliner bir ekip tarafından tanı, tedavi ve takip süresince değerlendirilmelidir. Burada pediyatrik tromboz hastalarımızın yönetildiği 2 yıllık multidisipliner tromboz konseyi deneyimimizi sunuyoruz. Kasım 2017-Ağustos 2019 tarihleri arasında 61 çocuk (95 başvuru) için tromboz konseyi olgu sunumlarını ve konsey sonuçlarını geriye dönük olarak inceledik. Değerlendirilen hastalarda erkek/kadın oranı 1,54 saptandı, çocuklar ve adolesanlar çoğunlukta idi. Hastaların klinik ve radyolojik durumlarına göre tedavi ve profilaksi süreleri belirlendi. Olgularımız içinde serebral arteriyel ve sinovenöz tromboz olguları daha fazla idi. Kazanılmış risk faktörleri, kalıtsal olanlardan daha fazla olup, enfeksiyon ve Faktör VIII yüksekliği sık idi. Otuz dokuz hastaya (%64) farklı süreler boyunca K vitamini antagonistleri, aspirin veya LMVH ile primer veya sekonder profilaksi uygulandı. Pediyatrik trombozda kanıta dayalı kılavuzların iyileştirilmesi için tedavi ve profilaksi yönetimi üzerine daha fazla çalışmaya ihtiyaç vardır. Multidisipliner tromboz konseyi komplike pediyatrik trombozlu çocuk hastalarda hasta bakımını iyileştirebilir.

Anahtar Kelimeler: Pediyatrik tromboz, tedavi, profilaksi, multidisipliner yönetim

INTRODUCTION

Pediatric thrombosis has unique characteristics due to its epidemiology, pathophysiology and treatment considerations. Venous thromboembolism (VTE) incidence in children is 0.07 to 0.14 per 10000 children (1). Although it is rare in the general population, 100-1000 times higher rates in hospitalized children are seen. Especially 2 risky age groups are determined; newborns due to their immature coagulation systems and interventions such as umbilical vein catheterization and adolescents for hormonal changes, obesity and trauma (2). The most common causative factors are central venous catheters in newborns and older children. Evidence-based guidelines are mostly extrapolated from adult studies (1). Recommendations on optimal drug choice, treatment duration and risk assessment in children have evidence gaps. Pediatric thrombosis management requires expertise and a multidisciplinary approach. The risk and benefits of anticoagulation for the treatment or prophylaxis of thrombosis in children should be evaluated on a patient-specific basis. We present our 2 years' experience of a multidisciplinary pediatric thrombosis council in a tertiary referral center.

METHOD

Complicated pediatric thrombosis cases were evaluated in a monthly multidisciplinary council in Istanbul University Faculty of Medicine. Members were from pediatric hematology-oncology, pediatric radiology, and neuroradiology in addition to other pediatric subspecialties (pediatric rheumatology, pediatric nephrology, neonatology, pediatric neurology, pediatric cardiology, pediatric endocrinology, pediatric intensive care, and pediatric gastroenterology).

We retrospectively reviewed case presentations and recommendations of the council for 61 children (95 admissions) between November 2017 and August 2019. Evaluated cases in thrombosis council included; cerebral thrombosis, unprovoked thrombosis of different sites, provoked thrombosis of any site in case of comorbidities or persistent risk factors, patients in risky situations with family history without a personal history of

thromboembolism. All patients were re-evaluated by the radiologist at the multidisciplinary council for primary diagnosis and/or ongoing management. All patients were examined for hereditary and acquired thrombophilia factors (3,4). Multidisciplinary council determined treatment, prophylaxis and monitoring periods based on patients' clinical and radiological status.

RESULTS

The male/female ratio was 1.54 of evaluated 61 patients. Twenty-two patients were re-evaluated at follow-up for treatment management or reporting outcome. Five of the patients (8%) were newborns (0-1 month), 10 (16%) were infants (1 month to 2 years), 23 (37%) were children (2 to 12 years), 22 (36%) were adolescents (12 to 18 years) and 2 (3%) were young adults (22 and 26 years, respectively) at diagnosis. All patients were re-evaluated by the radiologist at the multidisciplinary council for primary diagnosis or ongoing management. Eight of the 61 patients had thrombosis of more than one site. Cerebral arterial infarction and cerebral sinovenous thrombosis were the most common diagnoses (Table 1). Six patients were evaluated for anticoagulation prophylaxis without a personal history of the previous thrombosis; 5 for pre-hormone replacement therapy (HRT) evaluation and 1 for strong family history, respectively. Fifty patients had concomitant diseases which increased the risk of thrombosis. Infection, rheumatologic disease, and catheterization were common concomitant diseases (Table 2). High factor VIII and homocysteine levels were commonest underlying thrombophilia factors, respectively (Table 3). Based on patients' clinical and radiological status, treatment and prophylaxis periods were determined. Thirty-nine patients (64%) received primary or secondary prophylaxis with vitamin K antagonists (VKA), Aspirin or low molecular weight heparin (LMWH) for different periods.

None of the patients had bleeding or thrombosis related mortality except the patient with hepatic cirrhosis. She developed hepatic vein and IVC (inferior vena cava) thrombosis. Lupus anticoagulant and homozygous Factor V Leiden mutation were detected. She died due to cirrhosis related systemic complications.

Table 1. Patients' Diagnosis

Patient's Diagnosis	Patient Number (Percentage)
Cerebral arterial infarction	22 (36%)
Cerebral sinovenous thrombosis	20 (32%)
Portal vein thrombosis	5 (8%)
Renal vein thrombosis	4 (6.5%)
Extremity deep vein thrombosis	4 (6.5%)
Cardiac thrombosis	3 (5%)
Hepatic vein thrombosis	2 (3%)
Recurrent catheter thrombosis	2 (3%)
Peripheral arterial thrombosis	2 (3%)
Pulmonary Embolism	1 (1.5%)

Table 2. Patients with concomitant diseases

Concomitant Diseases	Patient Number (Percentage)
Infection	17 (27%)
Trauma	5 (8%)
Rheumatologic disease	6 (10%)
Congenital heart disease	5 (8%)
Catheterization	6 (10%)
Kidney disease	4 (6.5%)
Malignancy	3 (5%)
Hemoglobinopathy	2 (3%)
Dehydration	2 (3%)

Table 3. Underlying congenital and acquired thrombophilia factors*

Thrombophilia Factors	Patient Number (Percentage)
High Factor VIII level	17 (27%)
High Homocysteine level	14 (23%)
High Fibrinogen level	9 (14%)
Factor V leiden mutation	10 (16%) (1/9: homozygous/heterozygous)
Prothrombin 20210A mutation	4 (6.5%) (all heterozygous)
Protein C deficiency (Mild)	6 (10%)
Protein S deficiency (Mild)	8 (13%)
Antithrombin III deficiency (Mild)	4 (6.5%)
Hyperlipidemia	6 (10%)
Lupus anticoagulant	2 (3.25%)

*Lipoprotein (a) levels can not be measured in our center

DISCUSSION

Cerebral arterial and sinovenous thrombosis were more common in our pediatric thrombosis council cases. It was associated with difficulties that

pediatricians should face in the treatment of cerebral thrombosis and our center's crucial position as a tertiary referral center where complicated cases were referred. The most common age groups were children and adolescents in our council cases which was different from the general population. Even though thrombosis incidence is higher in newborns and adolescents (2), neonates did not form the majority in our council cases as most of the neonatal thrombosis could be solved without anticoagulation therapy with the displacement of umbilical vein catheters. In our council cases, acquired risk factors for thrombosis were more common than congenital ones, which was consistent with the literature (5,6).

Besides its rarity, some call VTE "an epidemic of tertiary pediatrics" (7). Treatment strategies should be individualized as the course of VTE varies according to the underlying diseases and risk factors in children of different age groups (8). Patients with unprovoked VTE or provoked VTE and persistent risk factors, have more than 10% recurrent VTE per year (8,9). The presence of single strong or combined inherited thrombophilia in pediatric patients has an association with VTE onset and recurrences (4,10). Contributing thrombophilia factors like hyperhomocysteinemia, increased lipoprotein (a) and elevated plasma factor VIII at diagnosis should be reassessed during prophylaxis. The decision for prolonged anticoagulation to prevent recurrent VTE in children is an extremely challenging question considering bleeding or other complications. Preferred agents for prophylaxis in children are LMWH for short term, Aspirin or VKA for long term (3,8).

CONCLUSION

Assessment of risk factors and multidisciplinary evaluation from a wider aspect can improve physicians' understanding and practice for better care of pediatric patients with complicated thrombosis. Clinical studies are needed to clarify the clinical importance of laboratory and imaging studies and the risk&benefits of long term anticoagulation of pediatric patients with thrombosis.

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