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Research Article

Deep Venous Thrombosis in Children with Cancer: A Single-Centre Experience

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Abstract

Background: Deep venous thrombosis (DVT) is becoming increasingly diagnosed in children with malignancies. The etiology is multifactorial and includes congenital and acquired prothrombotic factors. The aim of this study was to investigate prothrombotic risk factors, characteristics of DVT, and therapeutic approach in children with malignant diseases, and to compare the obtained results with available literature.

Procedure: Eight oncology patients (5 boys and 3 girls) with DVT treated at the Department of Pediatrics, Clinical Hospital Center Rijeka, Croatia, between January 1, 2006, and December 31, 2021, were included in the study. All patients had implanted central venous catheters (CVC).

Results: The mean age of patients was 10.4 years (range 3 months - 17.5 years). DVT was the most frequent in children with acute lymphoblastic leukemia. The most common risk factors for DVT were the presence of CVC (100% of patients), inherited thrombophilia (62.5%), and concomitant use of multiple prothrombotic drugs (62.5%). Four (50%) patients had CVC-related thrombosis. The therapy of choice was low molecular weight heparin (LMWH), with achieved complete venous recanalization in 75% of patients. In 2 cases of therapeutic failure, mechanical thrombectomy was performed. Two patients had post-thrombotic syndrome, and recurrent thrombosis was observed in 2 patients.

Conclusion: Treatment-related outcomes, adverse effects, and post-thrombotic complications in our study are mainly consistent with published data. Given an increased risk and the multifactorial etiology of DVT in children with malignant diseases, individual and careful assessment for risk factors, timely diagnosis and early intervention are essential.

Keywords: *Child; Cancer; Pediatrics; Venous Thromboembolism*

Abbreviations

BMI: Body Mass Index; CVC: Central Venous Catheter; DVT: Deep Venous Thrombosis; G-CSF: Granulocyte-Colony Stimulating Factor; LMWH: Low Molecular Weight Heparin; MTHFR: Methylenetetrahydrofolate Reductase; N: Number

Introduction

Deep venous thrombosis (DVT) is very rare in pediatric population but has become an increasingly recognized complication of childhood malignancy and its treatment. The etiology of pediatric cancer-related thrombosis is multifactorial, and may reflect congenital factors, factors related to the disease and to the therapy.

Patient-related risk factors for thrombosis include inherited thrombophilia, age younger than 2 years and older than 10 years, A and/or B blood group, and obesity [1]. The incidence is also higher in children with particular types of malignant tumors and co-existing intrathoracic or pulmonary disease [2]. The use of certain cytotoxic agents, antibiotics, and/or granulocyte-colony stimulating factor (G-CSF) heightens the risk of thrombosis. In addition to drugs, blood vessel damage during central venous catheter placement, surgery, radiotherapy, immobilization, and infection are also treatment-related risk factors [1].

During the last decades, more aggressive chemotherapy and new treatment modalities have significantly increased the cure rates of children with cancer. Considering the intensity and prolonged duration of antitumor treatment, complications including DVT are more common.

Aim of the Study

The aim of the study was to investigate risk factors for thrombosis, DVT characteristics, and therapeutic approach in children with cancer, and to compare our results with published data.

Patients and Methods

Eight children with DVT treated for malignant diseases at the Department of Pediatrics, Clinical Hospital Center Rijeka, Croatia, between January 1, 2006, and December 31, 2021, were included in the study. DVT was diagnosed by Doppler ultrasound of the extremities (4 patients), transthoracic echocardiography (2 patients), magnetic resonance of the brain and of the abdomen (1 patient each).

The following data were collected from medical records:

1. Patients characteristics: Gender, age and nutritional status of the patient, the type of cancer, blood group, thrombophilia markers (factor II, factor V Leiden, methylenetetrahydrofolate reductase [MTHFR], homocysteine, protein C, protein S, lipoprotein A), type of CVC, and family history for thrombosis.
2. Informations related to DVT: Time from diagnosis to thrombotic event, symptoms, site; coexistence of documented severe infection, febrile neutropenia or positive blood cultures; medications at the time of thrombosis (anthracyclines, asparaginase, cisplatin, corticosteroids, systemic antibiotics, G-CSF), values of fibrinogen, antithrombin III and D dimer.
3. Data related to the treatment of DVT: Administered therapy, dosage and duration of administration, anti-Xa activity during therapy with low molecular weight heparin (LMWH), other therapeutic interventions (thrombolytics, thrombectomy), complications (thrombocytopenia, bleeding, post-thrombotic syndrome), recurrent thrombosis, outcome.

The study was approved by the Institutional Ethics Committee. Descriptive statistics was used to summarize data.

Results

Five boys (62.5%) and 3 girls (37.5%) with the mean age of 10.4 years (range 3 months - 17.5 years) were included in the study. Four patients had hematological malignancies (acute lymphoblastic leukemia = 3, non-Hodgkin lymphoma = 1) and 4 patients had solid tumors (osteosarcoma = 2, medulloblastoma = 1, undifferentiated sarcoma = 1). Nutritional status was assessed in 7 children older than 2 years, and according to the percentile charts of the body mass index (BMI) for age; 6 (86%) had normal weight, and 1 (14%) was overweight.

Mean time from diagnosis to DVT was 7 months (range 1 - 42 months). All patients had inserted CVC: 6 (75%) patients had subcutaneous (implanted) port (Port-a-Cath®) and 2 (25%) had tunneled central catheters (Broviac®). Two patients each had DVT of the upper extremities (both axillar, brachial, and cubital vein), lower extremities (external iliac and popliteal vein, respectively), and

right atrium, one patient had cerebral venous sinus thrombosis, and one patient had portal vein thrombosis. Four (50%) patients had CVC-related thrombosis. Seven (87.5%) patients had symptoms of DVT. Four patients with DVT of the extremities had tenderness along the vein, redness, soreness and/or swelling distal of the thrombosis; a patient with right atrial thrombosis had arrythmia, a patient with cerebral venous sinus thrombosis had a headache and blurred vision and a patient with portal vein thrombosis had painful abdomen, enlarged spleen and blood vomiting. Family history for thrombosis was positive in 2 (25%) of patients.

All patients underwent testing for inherited thrombophilia. Pathological prothrombotic variants were observed in 5 (62.5%) patients (MTHFR homozygosity in 3 patients and Factor V Leiden in 2 patients). Homocysteine values were measured in four patients and in all of them were within normal limits. In five patients, the values of protein C and protein S were also measured, which were also normal. Three patients had blood group A, 2 patients each blood group B and 0, and one patient blood group AB.

The most common risk factors for DVT were the presence of CVC (100%), inherited thrombophilia (62.5%), and concomitant use of multiple prothrombotic drugs (62.5%). Prothrombotic drugs included systemic antibiotics in 6 (75%) patients, corticosteroids in 4 (50%) patients, anthracyclines in 4 (50%), asparaginase in 3 (37.5%), and cisplatin in 1 (12.5%) patient. Five (62.5%) patients were simultaneously receiving two or more prothrombotic drugs. No patient received G-CSF at the time of DVT. Seven (87.5%) patients were in the active phase of malignant disease at the time of DVT diagnosis. Concomitant severe infection was present in 3 (37.5%) patients.

Increased fibrinogen and decreased antithrombin III were present in 37.5% of subjects, and D dimer was elevated in 75% of cases.

The therapy of choice was LMWH, administered in an initial therapeutic dose of 1 mg/kg of body weight twice a day subcutaneously. The mean duration of the treatment was 18 days (range 6 - 44 days). Anti-Xa activity was regularly (once weekly) measured in all patients and LMWH dose adjusted. Thrombocytopenia with platelet count < 20 x 109/L was observed in 2 (25%) of patients, but no bleeding occurred during LMWH therapy. No patient received primary thromboprophylaxis. In 6 patients LMWH was used for secondary prophylaxis in a dose of 1 mg/kg of body weight once a day subcutaneously for a mean duration of 4.2 months (range 1.5 - 8 months). Edoxaban was used for secondary prophylaxis in another 2 patients for a mean duration of 6.5 months (range 3 - 10 months). Complete venous recanalization was achieved in 6 (75%) patients. In two cases of therapeutic failure, mechanical thrombectomy was performed with partial recanalization.

Two patients had post-thrombotic syndrome, and recurrent thrombosis was observed in another 2 patients. In both cases of recurrent thrombosis, the thrombus was located at the primary site and patients had pathological prothrombotic variant, one patient MTHFR homozygosity and another Factor V Leiden.

Summary characteristics of oncology patients with DVT are shown in table 1.

Gender	**N (%)**
Female	3 (37.5%)
Male	5 (62.5%)
Age (years)	**Mean (range)**
Female	5 (4 - 7 years)
Male	13.1 (0.3 - 17 years)
Type of cancer	**N (%)**
Hematological malignancy	4 (50%)
Solid tumor	4 (50%)

CVC type	**N (%)**
Subcutaneous port	6 (75%)
Tunneled	2 (25%)
Inherited thrombophilia	**N (%)**
Yes	5 (62.5%)
No	3 (37.5%)
Blood group	**N (%)**
A	3 (37.5%)
B	2 (25%)
0	2 (25%)
AB	1 (12.5%)
Concomitant use of prothrombotic drugs	**N (%)**
Yes	5 (62.5%)
No	3 (37.5%)
Concomitant severe infection	**N (%)**
Yes	3 (37.5%)
No	5 (62.5%)
Site of thrombosis	**N (%)**
Upper extremities	2 (25%)
Lower extremities	2 (25%)
Right Atrium	2 (25%)
Other	2 (25%)
Symptomatic DVT	**N (%)**
Yes	7 (87.5%)
No	1 (12.5%)
LMWH	**N (%)**
Yes	8 (100%)
No	0 (0%)
LMWH + thrombectomy	2 (25%)
Complete recanalization	**N (%)**
Yes	6 (75%)
No	2 (25%)
Family history of DVT	**N (%)**
Yes	2 (25%)
No	6 (75%)

Table 1: *The characteristics of patients with deep venous thrombosis.*

Discussion

Our study showed a higher incidence of DVT in children with inherited thrombophilia (62.5%), of which homozygosity of MTHFR gene mutation (3 patients) or heterozygosity of factor V Leiden gene mutation (2 patients) was proven. Mutations of the prothrombin gene have not been proven. Other risk factors that were mostly not present in our patients are age more than 10 years, blood type A or B, obesity, and a family history of thrombosis [1].

The diagnosis of DVT was most often made within 6 months of the diagnosis of cancer, which is in accordance with the data in the literature [3]. Five (62.5%) patients were simultaneously taking multiple prothrombotic drugs, which, along with CVC and the malignant disease itself, are considered the most important risk factors for the development of DVT in children with malignant diseases.

In our study, 87.5% of subjects had symptoms. The ratio of symptomatic and asymptomatic DVT in research is highly variable, which can be explained by the fact that asymptomatic DVT is most often diagnosed by an incidental radiological finding [4]. Besides, symptoms greatly vary depending on the site. Venous thrombosis of the extremities is presented with tenderness along the affected vein, redness, pain and/or swelling of the extremities. Thrombosis of cerebral veins and venous sinuses can cause headache, hemiparesis, epileptic seizures, or different state of consciousness.

In half of the subjects, the thrombosis was related to the CVC with localization of the thrombus in the upper extremity veins (2 patients) or the right atrium (2 patients). In a Dutch prospective study, one third of subjects had CVC-related DVT [5]. Our finding, although mostly in accordance with available literature, leaves space for improvement mainly through the precise positioning of the tip of CVC at the proximity of the cavo-atrial junction [6].

Children with a tunneled central catheter developed CVC-related thrombosis more often compared to those with an implanted port, 2 out of 2 versus 2 out of 6 patients. These results, despite the small sample, coincide with data available from the literature [7].

In our research, the therapeutic approach with LMWH was in accordance with the guidelines, and frequency of complications was consistent with the published data [8]. In 75% of subjects, complete recanalization was achieved. In the meta-analysis by Klaasen and colleagues, 63.5% of children who received a therapeutic dose of LMWH had a complete resolution [9].

Marked thrombocytopenia was recorded in 2 patients who underwent chemotherapy at the same time, and thrombocytopenia is more likely related to anticancer treatment toxicity. No patient had bleeding. According to Monagle and Newall, the risk of major bleeding in children receiving LMWH therapy ranges between 0% and 19% [8]. Our results showed that achieving complete recanalization with LMWH carries a low risk of complications. These included cases of post-thrombotic syndrome (25%) and recurrent thrombosis (25%). The frequency of post-thrombotic syndrome in studies varies between 10 and 60%. Patients have a risk of recurrent thrombosis of 10 to 15%, which is lower than the results obtained in our research [9].

Conclusion

Despite a limited number of patients, our study contributes to the existing body of knowledge. Obtained treatment-related outcomes, adverse effects, and long-term complications are consistent with published data. Given an increased risk and the multifactorial etiology of DVT in children with cancer, individual and careful assessment for risk factors, and timely diagnosis and therapeutic intervention are essential.

Conflict of Interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

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