Original Scientific Article
Acta Medica Academica 2023;52(3):161-168
DOI: 10.5644/ama2006-124.430

Inherited Thrombophilia and Risk of Thrombosis in Children with Cancer: a Single-center Experience[a]

Ana Đordević[1, 2], Blaženka Grahovac[3], Silvije Šegulja[4], Lidija Bilić Zulle[5, 6], Jelena Roganović[7, 8]

[1]Department of Chemical and Pharmaceutical Sciences, University of Trieste, Trieste, Italy, [2]Jadran-galenski laboratorij d.d., Rijeka, Croatia, [3]Department of Pathology, Faculty of Medicine, University of Rijeka, Rijeka, Croatia, [4]Faculty of Health Studies, University of Rijeka, Rijeka, Croatia, [5]Department of Medical Informatics, Faculty of Medicine, University of Rijeka, Rijeka, Croatia, [6]Clinical Institute for Laboratory Diagnostics, Clinical Hospital Center Rijeka, Rijeka, Croatia, [7]Department of Pediatrics, Faculty of Medicine, University of Rijeka, Rijeka, Croatia, [8]Division of Hematology and Oncology, Department of Pediatrics, Clinical Hospital Center Rijeka, Rijeka, Croatia

Correspondence: *jelena.roganovic@medri.uniri.hr*; *roganovic.kbcri@gmail.com*; Tel.: + 385 51 659214

Received: 21 November 2023; Accepted: 29 December 2023

Abstract

Objectives. Thrombosis is an increasingly recognized complication of childhood malignancy and its treatment. The incidence and etiology of pediatric cancer-related thrombosis is still not well understood. The aim of this study was to evaluate the prevalence of common prothrombotic genetic conditions in children with cancer, the frequency of thrombosis, and the role of inherited thrombophilia in the development of thrombosis in a pediatric oncology population. **Patients and Methods.** Forty-seven children (36 treated for hematological malignancies and 11 for solid tumors) with a median age of 8.8. years (range 0.4 – 19.3 years) were included in the study. Genetic polymorphisms of Factor V Leiden (G1691A), prothrombin G20210A, and methylenetetrahydrofolate reductase (MTHFR) C677T were determined by real-time polymerase chain reaction-based DNA analysis. **Results.** Four (8.5%) patients were heterozygous for Factor V Leiden, 3 (6.4%) were heterozygous for prothrombin G20210A mutation, and 3 (6.4%) were homozygous for MTHFR C677T mutation. All patients had implanted central venous catheters. Four (8.5%) children had documented thrombosis, three of which were in the upper venous system. Two of the four patients with thrombosis had Factor V Leiden heterozygosity. **Conclusions.** Thrombosis is an important complication of childhood cancer. The risk of thrombosis may be increased in patients with Factor V Leiden. In the absence of consensus guidelines, our results support the recommendation for thrombophilia screening in children with cancer.

Key Words: Inherited Thrombophilia ▪ Cancer ▪ Thrombosis ▪ Children,

Introduction

Thrombosis is a well-recognized complication of malignancy. It is estimated that up to 20% of all cancer patients develop thrombosis throughout the course of the disease, with an annual incidence rate of 0.5% compared to 0.1% in the general population (1, 2). There is substantially less knowledge about thrombosis in the pediatric cancer population, with reported rates varying from 2% to 16%, depending on the type of malignancy (3). Children with cancer and thrombosis have an increased risk of mortality, higher rates of recurrent thrombosis and thrombosis-related morbidity, and decreased quality of life (4, 5). The pathophysiology of pediatric cancer-related thrombosis is multifactorial, and may reflect prothrombotic genetic factors, and tumor-related and treatment-related factors (6). The role of inherited thrombophilia in the development of thrombosis in children with cancer is poorly investigated and still unclear.

[a] The name of the department and institution to which the work should be attributed: Division of Hematology and Oncology, Department of Pediatrics, Clinical Hospital Centre Rijeka, Istarska 43, HR-51000 Rijeka, Croatia

This study was undertaken to determine the prevalence of Factor V Leiden, prothrombin G20210A and methylenetetrahydrofolate reductase (MTHFR) C677T gene polymorphisms in children with hematological malignancies and malignant solid tumors, the frequency of cancer-associated thrombosis, and the role of inherited thrombophilic alterations in thrombotic events.

Patients and Methods

Patients

Forty-seven children (34 boys and 13 girls) with primary cancer consecutively admitted from January 1st, 2010 to December 31st, 2015 to the Division of Hematology and Oncology, Department of Pediatrics, Clinical Hospital Centre Rijeka, Croatia, were included in the study. The following data were collected from medical records: gender, age at diagnosis, the type of cancer, previous and family history of thrombosis, insertion/type of a central venous catheter (CVC), and the presence/developmental time/site of thrombosis. Ethical approval was obtained from the institutional ethics board. Informed written consent was obtained from the parents of all patients.

Methods

The samples were taken from the peripheral blood in tubes containing EDTA. The genomic DNA was prepared from the whole blood with a NucleoSpin Blood kit (Macherey-Nagel GmbH & Co. KG, Düren, Germany). Genetic polymorphisms of Factor V G1691A (Factor V Leiden), Factor II-Prothrombin G20210A and MTHFR C677T were screened by real-time polymerase chain reaction (RT-PCR) on a Light Cycler® 1.5 Instrument, Roche Diagnostics, Germany. Tests were performed by binding specific DNA probes marked with fluorescent colors during PCR and melting curve analysis of marked PCR products, according to the manufacturer's instructions. Plasma homocysteine levels were not routinely assessed.

Statistical Analyses

Descriptive statistics were used to summarize the data. The results were compared with the relative frequencies of heterozygous and homozygous variants of each polymorphism in the general population. Fisher's exact test was used to compare the prevalence of Factor II and Factor V Leiden polymorphism between boys and girls with cancer, between children with hematological malignancies and solid tumors, and between patients with and without thrombotic events. The Chi-squared test was used to describe MTHFR genotype distribution in boys and girls with cancer, and between patients with hematological malignancies and solid tumors. A P value of <0.05 was considered statistically significant.

Results

The median age of the patients was 8.8 years (range 0.4 – 19.3 years). Thirty-six patients had hematological malignancies (acute lymphoblastic leukemia [ALL] = 26, acute myeloid leukemia = 2, non-Hodgkin lymphoma = 7, Hodgkin lymphoma = 1) and 11 patients had solid tumors (malignant brain tumor = 3, soft tissue sarcoma = 3, osteosarcoma = 2, Ewing sarcoma = 1, neuroblastoma = 1, nasopharyngeal carcinoma = 1). All patients had implanted CVC: 33 patients had tunneled catheters (Broviac®) and 14 had implantable ports (Port-a-cath®).

Three (6.4%) patients (all boys) had heterozygous Factor II G20210A mutation, while no homozygosity was detected. Heterozygous Factor V Leiden was identified in 4 (8.5%) children (2 boys and 2 girls) with cancer, and no homozygous Factor V Leiden was found. MTHFR C677T heterozygosity was present in 21 (44.7%) patients, and homozygosity in 3 (6.4%). Six (46.2%) girls and 15 (44.1%) boys were heterozygous for MTHFR C677T, while 1 (7.7%) girl and 2 (5.9%) boys were homozygous. There was no statistical significance in the prevalence of FII G20210A mutation (Fisher's exact test, P=0.550), Factor V G1691A mutation (Fisher's exact test, P=0.304),

and MTHFR C677T mutation (Chi-squared test, P=0.928) between male and female patients.

Two (5.6%) patients with hematological malignancies and one (9.1%) with a solid tumor had heterozygosity for Factor II G20210A mutation. Factor V Leiden heterozygosity was identified in 3 (8.3%) children with hematological malignancies, and in 1 (9.1%) with a solid tumor. A heterozygous MTHFR C667T mutation was identified in 16 (44.4%) children with hematological malignancies and in 5 (45.5%) children with solid tumors, while 2 (5.6%) patients with hematological malignancies and 1 (9.1%) with a solid tumor had MTHFR C667T homozygosity. No statistical significance was found in the prevalence of Factor II G20210A mutation (Fisher's exact test, P=0.560), Factor V Leiden (Fisher's exact test, P=01.000) and MTHFR C667T mutation (Chi-squared test, P=0.936) between patients with hematological malignancies and solid tumors. The previous or family history of thrombosis was negative in all patients.

Four (8.5%) children (all boys) had a documented thrombotic event during treatment: right axillar and brachial vein thrombosis in a patient with non-Hodgkin lymphoma; right brachial vein thrombosis in a patient with neuroblastoma; right subclavian, axillary and brachial vein thrombosis in a patient with nasopharyngeal carcinoma, and right atrial thrombosis in a patient with osteosarcoma. No patient had any recurrent thrombosis. Two patients had heterozygous Factor V Leiden (both combined with heterozygous but no homozygous MTHFR C677T mutation), and one patient had a heterozygous MTHFR C677T mutation. Heterozygosity for Factor V Leiden was statistically more frequent among patients with thrombotic events than in patients without thrombosis (50% versus 5.3%, Fisher's exact test, P=0.039), while there was no statistical difference in the prevalence of MTHFR C677T mutation between cancer patients with and without thrombosis (Fisher's exact test, P=0.332). Homocysteine levels were normal in all patients. In one patient no thrombophilia gene alteration was detected.

The characteristics of patients with thrombosis are shown in Table 1.

Discussion

In our study, thrombosis was documented in 4 of 47 (8.5%) children with cancer, which is substantially higher than in the general pediatric population. The incidence of thrombosis ranges from 0.14 to 0.21 per 10,000 children per year, and 0.2 to 0.6% among hospitalized pediatric patients (7). The majority of affected children have at least one underlying condition or trigger for thrombosis, the most common being CVC, inherited thrombophilia, malignancy, congenital heart disease, chronic neuromuscular disease, surgery, major trauma, immobility, estrogen-containing contraceptives, obesity, and severe infection (8-11).

Table 1. The Characteristics of Patients with Thrombosis

Patient number	Sex/Age at diagnosis (years)	Type of malignancy	Site of thrombosis	Time of thrombosis	CVC* type	CVC* duration (days)	Inherited thrombophilic factors
1	Male / 16.5	Non-Hodgkin lymphoma	Right axillar and brachial vein	During therapy	Broviac	52	Factor V Leiden heterozygous (MTHFR† C677T heterozygous)
2	Male / 15.6	Osteosarcoma	Right atrium	During therapy	Port-a-Cath	96	Factor V Leiden heterozygous (MTHFR† C677T heterozygous)
3	Male / 17.2	Nasopharyngeal carcinoma	Right subclavian, axillary and brachial vein	During therapy	Port-a-Cath	209	(MTHFR† C677 heterozygous)
4	Male / 2.4	Neuroblastoma	Right brachial vein	During therapy	Port-a-Cath	491	None

*Central venous catheter; †Methylenetetrahydrofolate reductase.

The association between thrombosis and pediatric cancer is well established, and overall, 25% of children with thrombosis have an underlying diagnosis of cancer (12). The reported prevalence of thrombosis in children with cancer ranges from 2 to 16%, while the occurrence of asymptomatic events is approximately 40% (13-19). The risk is highest in children with ALL, followed by sarcoma and lymphoma, and the lowest risk is in children with brain tumors (4, 20, 21). The occurrence of thrombosis in the current study is in agreement with the published data, although thrombosis was more frequent in children with solid tumors (3/11) compared to hematological malignancies (1/36).

The etiology of thrombosis in children with cancer is multifactorial and includes patient-related (inherited thrombophilia), disease-related and treatment-related factors. Cancer may be considered a hypercoagulable state. Tumor cells express tissue factor, procoagulant proteins, metalloproteases, and molecules that can induce direct and indirect activation of coagulation. Several additional mechanisms, such as inflammatory, immune, and angiogenic responses, are involved (22, 23). Major risk factors for thrombosis in children with hematological malignancies include the presence of CVC, older age, prothrombotic genetic defects, non-O blood group, obesity, and medications (asparaginase, concomitant use of steroids, anthracyclines) (4, 24-26). Proposed prothrombotic risk factors in children with solid tumors include the presence of CVC, age > 10 years, certain tumor types and sites, metastatic disease, thrombophilia, obesity, and type of treatment (surgery, radiation, anthracyclines, and platinum) (4, 17, 27). CVC is the most important risk factor (28). Reported rates of symptomatic catheter-related thrombosis range from 2.6 to 36.7%, and rates of asymptomatic catheter-related thrombosis range from 5.9 to 43% (3, 29). The pathogenesis of catheter-related thrombosis is not well characterized, and it may involve endothelial damage and local activation of blood coagulation (30). The most common sites are the upper venous system, and the lower extremities for non-catheter-related thrombosis (28, 31). Central nervous system thrombosis is more common in children with ALL, with approximately half of patients having sinus venous thrombosis (19, 28). The incidence of cerebral sinus venous thrombosis in pediatric ALL patients varies from 1.4 to 10.5% (32-35). Right atrial thrombosis is reported in 2% of patients with symptomatic thrombosis (36).

In our study, all patients had CVC in place, and all thrombotic events occurred during chemotherapy. All four patients were male, and three were adolescents. Three patients had upper extremity thrombosis, and one had right atrial thrombosis. Two patients (50%) had heterozygous Factor Leiden (combined with MTHFR C677T heterozygosity).

The contribution of inherited thrombophilia to the occurrence of thrombosis in cancer patients has been documented. The two most common genetic causes of thrombophilia identified to date are Factor V Leiden and prothrombin G20210A mutation (37, 38). MTHFR C677T heterozygosity is a very frequent polymorphism, but it only increases the risk of thrombosis when it results in hyperhomocysteinemia (39). A meta-analysis of 17 prospective studies comprising 1752 pediatric patients with ALL reported the overall thrombotic risk of 5.2%. Prothrombotic genetic defects were studied in 557 children. Thirty-one thrombotic events were observed in 113 children affected by at least one genetic alteration, pointing to an approximately 8-fold increased thrombotic risk (relative risk [RR]:8.5; 95% CI: 4.4-17.4) in patients with inherited thrombophilia (26). Similar results were reported by Nowak-Göttle et al., who documented venous thrombosis in 46.5% (27/58) of children with ALL carrying a prothrombotic defect, compared to 2.2% (5/131) of children with no identified prothrombotic defect ($P<0.0001$; chi-square 137.0). Homozygous MTHFR mutation with hyperhomocysteinemia was diagnosed in 12.5% (4/32) children with thrombosis, and in a further 9.4% (3/32) patients combined with Factor V Leiden or increased lipoprotein A concentrations. In addition, an increased risk of thrombotic complications was clearly demonstrated in leukemia patients with combined prothrombotic risk factors, compared to patients with single

alterations (40). The study by Knöfler et al. included 77 children with malignancies and in 11 (14%) of them catheter-related thrombosis was detected. Prothrombotic genetic defects were found in 23% (17/77) patients, and in 7 of 11 (64%) patients had thrombosis. Three children had combined defects (heterozygous Factor V G1691A combined with heterozygous prothrombin G20210A mutation, protein S deficiency or hyperlipoproteinemia), and 4 had a single defect (heterozygous Factor V G1691A, heterozygous prothrombin G20210A mutation, hyperlipoproteinemia, and protein C deficiency type I) (41). Ünal et al. evaluated inherited and acquired prothrombotic risk factors in 37 children with malignancies and thrombosis. Congenital defects were detected in 15 (40%) patients: 8 had heterozygous Factor V G1691A, 1 had heterozygous prothrombin G20210A mutation, 4 had lipoprotein(a) elevation, 1 had decreased protein S level, and 1 had decreased protein C level. The risk of thrombosis increased when accompanied by additional prothrombotic risk factors (42). A large population-based study in Israel of 1191 children with ALL reported venous thromboembolism in 89 (7.5%) children. Thrombophilia screening was performed in 584 children, and findings were positive in 84 (14.4%). Patients with thrombophilia had significantly more thrombotic events compared to children without thrombophilia ($p < 0.001$) (43). Other studies failed to show any impact of thrombophilic gene mutations on thrombosis risk in patients with cancer (28, 44-47). Thus, the impact of inherited thrombophilic markers on the development of thrombosis in pediatric oncology patients has not been completely clarified. Our study confirms the higher occurrence of symptomatic thrombosis in children with cancer. Two out of 4 children with thrombosis had heterozygosity for Factor V Leiden as an inherited prothrombotic risk factor.

Limitation of Study

Our study has several limitations, including retrospective design, the small number of patients, heterogenous underlying malignancies, and the limited panel of genetic prothrombotic traits tested. Moreover, no investigations for asymptomatic vessel occlusion were performed. This could result in underestimation of thrombotic events, which in turn leads to an overestimation of the role of inherited prothrombotic risk factors. Larger multicenter prospective studies, development of guidelines for thrombophilia screening, identification of high-risk groups, individualized reevaluation of additional prothrombotic risk factors and appropriate measures might help in the prevention and early intervention of thrombotic events.

Conclusion

Children with cancer are at increased risk for developing thrombosis secondary to disease- and treatment-related factors, and other poorly characterized conditions. The prevalence of inherited thrombophilia in our patients was within the prevalence in the healthy population, but fact that two out of four patients with thrombosis had documented congenital prothrombotic risk factors should not be overlooked. There is still much to be learned regarding the risk factors, prevention, and treatment of thrombosis in children with cancer. In the absence of consensus guidelines, our results support a recommendation for thrombophilia screening in this population.

What Is Already Known on This Topic:

Children with cancer constitute the largest subset of patients who experience thrombosis. The pathophysiology of pediatric cancer-associated thrombosis is multifactorial, and the role that inherited thrombophilia plays in the pathogenesis is largely unknown. Thrombosis is a serious condition that can lead to significant long-term morbidity, as well as early mortality. With over 80% cure rates of childhood cancer, strategies for prevention, early diagnosis, and optimal intervention of cancer-related thrombosis in pediatric patients are of great importance.

What This Study Adds:

This is the first study in the Republic of Croatia to investigate the frequency of thrombosis and the prevalence of common prothrombotic genetic defects in children with cancer, as well as to evaluate the role of inherited thrombophilia in the development of pediatric cancer-related thrombosis. Our results confirm that children with cancer experience increased risk of thrombosis. To identify patients at increased risk for thrombosis better, we suggest thrombophilia screening in the routine clinical care of children with cancer.

Authors' Contributions: Conception and design: AĐ and BG; Acquisition, analysis, and interpretation of data: AĐ, SŠ, BG, LBZ and JR; Drafting the article: AĐ, SŠ, BG, LBZ and JR; Revising it critically for important intellectual content: AĐ, SŠ, BG, LBZ and JR; Approved final version of the manuscript: AĐ, BG and JR.

Conflict of Interest: The authors declare that they have no conflict of interest.

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