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THROMBOTIC COMPLICATIONS DURING CANCER TREATMENT IN CHILDREN

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Aim: **To determine the hereditary risk factors contributing to the development of thrombosis in children with cancer.** ***Methods:*** **Sensitive PCR- restriction fragment length polymorphism assay.** ***Results:*** **There has been shown significant prevalence of factor V leiden (FVL) in the group of 19 patients with thrombosis ($P = 0.0004$). The prothrombin G20210A mutation was not detected in 19 cases and 80 controls, indicating low frequency of this mutation among Belarusian population. The MTHFR C677T mutation was found in both cases and controls and has approximately the same frequencies in both groups (47.4% and 55.0% accordingly).** ***Conclusion:*** **Clinical condition, coagulation status, volume of haemostatic therapy and clinical evidence of sepsis, as well as duration of catheterization were not significant as predisposing to thrombosis factors. We have shown that the leading risk factors for venous tromboembolism (VTE) in children with cancer are mutation FVL, prolonged immobilization or both immobilization and indwelling femoral venous catheter. Cancer patients affected with VTE during treatment are potential candidates for genotyping assay for FVL mutation, as the former may determine duration of anticoagulation therapy and administration of secondary prophylaxis.**
Key Words: **venous thromboembolism, cancer, children, Factor V Leiden, prothrombin G20210A, MTHFR C677T.**

It is well known that cancer patients have significantly increased risk of developing venous thromboembolism (VTE). The most strongly thrombosis-associated tumors are mucin-producing adenocarcinomas, cancer of pancreas, brain, ovary, colon [1–2]. In fact, about 15% of all cancer patients develop thrombosis during course of the malignant disease [3]. Moreover, the incidence of deep vein thrombosis may increase in some type of cancer, thus it ranges from 20% to 40% for patients with urological or gynecological malignancies in postoperative periods [4].

The clinical VTE is associated with worse outcomes in cancer patients, including increased mortality [5–6]. Among non-cancer causes of death in patients with malignancy. Thrombosis takes leading place. A.A. Khorana et al. [7] had estimated the annualized death rate for VTE in population of cancer patients, which represented a 47-fold elevation over the general population.

Although R. Virchow originally described a triad of causes of thrombosis (stasis, vessel wall injury and hypercoagulability) more than a century ago, the mechanism by which tumors may alter haemostasis is still not completely understood. It is known that cancer cells can activate the clotting system directly, which leads to thrombin formation, or indirectly by stimulating endothelial cells to produce procoagulants. Moreover, pathogenetic mechanisms of hypercoagulation realized through additive risk factors in case of cancer patients: treatment with some antineoplastic agents, immobilization, central venous line (CVL), infectious complications, surgical interventions, — all of them are acquired.

In recent years many inherited thrombophilia traits have been described [8–9]. Most common of them are resistance to activated protein C, which is caused by mutation of the factor V (Factor V Leiden or FVL), prothrombin G20210A mutation and MTHFR C677T variant of methylene-tetrahydrofolate reductase gene [10]. All of these mutations are point mutation, resulted from a single nucleotide substitution in DNA. They differ from each other by pathological mechanism but all of them alter haemostatic system and disrupt regulatory pathways that limit the coagulation cascade.

The role of hereditary thrombophilia in cancer patients with thrombosis is still unclear. Moreover, a lot of literature data show the association of cancer and thrombosis in adult patients but little is known about etiology of VTE in children with cancer. One of the possible reasons for that is higher frequency of VTE in adult than in children [11–13]. That is why the purpose of our study was to determine the hereditary risk factors that contribute to the development of thrombosis in pediatric cancer patients.

MATHERIALS AND METHODS

Patients. Ninety-nine patients aged neonate to 21 years with malignant disorders were analyzed in this study retrospectively. All patients were admitted in Belorusian Center for Pediatric Oncology and Hematology, Minsk, Belarus for diagnosis and treatment. Cases (19 patients) were identified if patients were diagnosed with episode of VTE during treatment. Others (80 patients) were identified as controls. The study was approved by Ethic Committee of the Center.

Patients from both groups were evaluated for congenital and acquired risk factors for thrombosis, and patients were screened for FVL, prothrombin G20210A, MTHFR C677T mutations, ATIII, presence of anti-phospholipid antibodies (APA).

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Abbrevations used: VTE – venous thromboembolism; FVL – Factor V Leiden; MTHFR – methylene-tetrahydrofolate reductase; APA – antiphospholipid antibodies;CVL – central venous line; FDP – fibrin/fibrinogen degradation products; SFMC – soluble fibrin monomer complexes; SIRS – systemic inflammatory response syndrom.

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Diagnosis of VTE was confirmed by Doppler-ultrasonography.

The presence of risk factors provoking thrombosis was recorded. These were: 1 — placement of central vein catheter (CVC), 2 — haemostatic therapy, 3 — prolonged immobilization (> 1 week), 4 — surgery, 5 — administration of L-Asparaginase Medac with prednisolone in the ALL patients, 6 — clinical symptoms of Systemic Infammatory Response Syndrom (SIRS), 7 — presence of APA, 8-inhereted thrombophilia.

Sensitive PCR- restriction fragment length polymorphism assay. DNA from leucocytes of peripheral blood samples was isolated by standard phenol-chloroform method [14]. DNA analysis for FVL, prothrombin G20210A, MTHFR C677T was performed according previously described methods with some modifications [15–18]. Briefly, DNA was amplified with primers (Table 1) in reaction mix with final volume 25 µl. In each PCR reaction 80–150 ng DNA template, 300 nM of each primer, 1.5 mM $MgCl_2$, 0.2 mM dNTP, 1U Tag-polymerase (Promega) were used. PCR conditions were: initial denaturation at 94 °C for 2 min, followed by 35 cycles of amplification at 94 °C for 30 s, (60 °C for FVL, 57 °C for G20210A, 58 °C for MTHFR C677T) for 40 s, 72 °C for 1 min and a final extension at 72 °C for 5 min. Five units of (MnlI for FVL, HindIII for G20201A, Hinf1 for MTHFR C677T) restriction endonuclease were incubated with 10 µl of amplified DNA at 37 °C for 1.5 h. The digested products were electrophoresed on 3.5% agarose gel to detect wild, homozygous and heterozygous types.

Table 1. Oligonucleotide primers used in PCR analysis of FVL, G20210A, MTHFR C677T mutations

Gene	Primer	Sequence
Factor V		
	Forward	5'-TGC CCA GTC CTT AAC AAG AAC-3'
	Reverse	5'-CTT GAA GGA AAT GCC CCA TTA-3'
Factor II		
	Forward	5'-TCT AGA AAC AGT TGC TGC CTG GC-3'
	Reverse	5'-ATA GCA CTG GGA GCA TTG AAG C-3'
MTHFR		
	Forward	5'-TGA AGG AGA AGG TGT CTG CGG GA-3'
	Reverse	5'-AGG ACG GTG CGG TGA GAG TG-3'

Clotting parameters (APTT, PTT, TT, Fibrinogen, D-dimer) were measured on ACL-9000 (IL, USA). Hemoglobin, platelet and WBC count were measured on ABX Micros-60 (ABX Diagnostics, France). Plasma level of SFMC and FDP were measured using special kit (Roche, France). Anti-phospholipid antibodies (IgG and IgM) were measured with the help of the Asserachrom APA kit (Diagnostica Stago, France)

Statistical analysis was performed using program Statistica 6.0. Data is depicted as mean and 25th and 75th percentiles or as mean ± standard deviation in the case of normal distribution. Between-group allelic frequencies and differences in the position of catheter were compared using χ^2-test. In other cases two groups were compared by the Mann — Whitney U-test. *P* value < 0,05 were considered significant.

RESULTS AND DISCUSSION

Thromboses have been revealed in a group of 19 children with median age of 15 years (11–17) (Table 2). Five out of 19 were affected by acute lymphoblastic leukemia, 4 — by acute myeloid leukemia, 4 — by Non-Hodgkin's lymphoma, 6 — by solid tumors (2 cases of Ewing's sarcoma, 2 cases of CNS tumor, desmoid tumor and teratoma). Thromboses in this group occurred equally frequent in boys (9) and girls (10). None of children had VTE before treatment. All of them had only one episode of VTE during observation.

Table 2. Characteristics of cases and controls

	Cases n = 19	Controls n = 80
Age at enter, years	15 (11–17)	10 (6–14)
Male/Female	1.1/1	2.8/1
Cancer type:		
ALL	5	30
AML	4	30
NHL	4	10
Solid tumors	6	10
Genotype for MTHFR C677T, %		
Wild type	52.6	45.0
Heterozygous	47.4	45.0
Homozygous	0.0	10.0
Genotype for prothrombin G20210A, %		
Wild type	0.0	0.0
Heterozygous	0.0	0.0
Homozygous	0.0	0.0
Genotype for FV L, %		
Wild type	79.0	98.75
Heterozygous	21.0	1.25
Homozygous	0.0	0.0
Number of risk factors for thrombosis	3,0 (2,0–4,0)	3,0 (2,0–4,0)

As for genetic analysis, our study showed significant prevalence of FVL in the group of patients with thrombosis (*P* = 0.0004). Four out of 19 cases (21%) were heterozygous for FVL. Only one patient from 80 controls was FVL positive (1.25%). This FVL positive patient with acute myeloid leukemia remained asymptomatic for VTE during 3-years' observation period. Nevertheless these findings suggest an association of FVL with increased risk of VTE. There are controversial and limited data about VTE in children with malignancy. Thus some authors confirm the association between thrombosis and inherited prothrombotic state [19–20], although the opposite opinions can be found in literature as well [21–22].

The prothrombin G20210A mutation was not detected in all 99 patients, indicating low frequency of this abnormality among Belarusian population. The MTHFR C677T mutation was found in cases and controls and has approximately the same frequencies in both groups (47.4% for cases and 55.0% for controls). Thus, like other researchers, in this work we demonstrate that there is no association between MTHFR C677T and VTE [23].

The clinic manifestation of Systemic Inflammatory Response Syndrome (SIRS) among children with thromboses was reported in 4 out of 19 cases. In the second group symptoms of SIRS were reported for 37 patients and 43 children had no clinical evidence of sepsis. Statistical analysis of the data revealed an association between the fact of thrombosis and absence of clinical evidence of SIRS (*P* = 0,045). However, this interlinking becomes non-significant with the approximation of the Chi-square by Yates' correction (*P* = 0,08). This fact allows us to state that the development of thrombosis in children and clinical evidence of

sepsis has no essential value as predisposing factor. This observation contrasts with the data presented by others, e. g. Gurgey A. et al. [24] indicated that the most frequent underlying disorder in children with non-catheter-related thrombosis is infection.

The clinical condition of patients in compared groups was different. Among children without clinical evidence of thrombosis septic complications occurred more often than among children with thromboses. For maintenance of homeostatic indices the patients of the control group required more intensive therapy, although this trend was non-significant ($P > 0,05$).

The evaluation of the haemostatic status of patients in compared to groups did not reveal significant differences in the majority of parameters (Table 3). As it was mentioned above half of controls had clinical evidence of SIRS as a result of cytopenia. In connection with that, patients of the control group had higher level of fibrinogen than cases (4.7 ± 0.2 g/l vs. 3.4 ± 0.4 g/l, $P = 0.008$). For the same reasons the count of platelets and WBC of peripheral blood were lower among controls: 87.0 ± 11.3 x 10^9/l and 1.6 ± 0.3 x 10^9/l respectively in controls compared to 188.5 ± 22.8 x 10^9/l and 4.98 ± 2.8 x 10^9/l respectively in cases ($P = 0.001$). At the same time the extent of haemostatic therapy in controls was greater then in cases.

Table 3. Clotting parameters and haemostatic therapy in the children with and without thrombosis

Parameter	Cases n = 19	Controls n = 80	Significance
Activated partial thromboplastin time, ratio	1.05 ± 0.04	1.04 ± 0.02	n. s.
Prothrombine time, INR	1.2 ± 0.05	1.29 ± 0.04	n. s.
Thrombin time, ratio	1.29 ± 0.05	1.24 ± 0.5	n. s.
Fibrinogen, g/l	3.4 ± 0.37	4.7 ± 0.23	$P = 0.008$
Soluble fibrin monomer complexes			n. s.
– positive	3	4	
– negative	16	76	
D-dimer, 10^{-3}g/l	2.8 ± 0.6	2.7 ± 0.5	n. s.
Fibrin /fibrinogen degradation products, 10^{-3}g/l	11.2 ± 2.4	15.2 ± 3.1	n. s.
Hemoglobin, g/l	104.5 ± 4.5	91.8 ± 2.3	n. s.
Platelets, 10^9/l	188.5 ± 22.8	87.0 ± 11.3	$P = 0.001$
WBC, 10^9/l	4.98 ± 2.8	1.6 ± 0.3	$P = 0.001$
Clinical manifestation of SIRS, %	21.0	46.0	$P = 0.045$
Blood components transfusion:	n = 6	n = 12	n. s.
Cryoprecipitate, ml/kg x day	12.0 ± 2.5	19.8 ± 6.0	
Platelets, ml/kg x day	n = 4	n = 40	n. s.
Red blood cell, ml/kg x day	7.3 ± 1.1 n = 4	9.1 ± 5.2 n = 18	n. s.
Factor VIII concentrate, ml/kg x day	11.7 ± 1.9 n = 3	9.0 ± 1.1 n = 2	n. s.
	40.0 ± 15.0	60.0 ± 11.0	

Interestingly, we have found that a higher D-dimer level in patients with VTE was indistinguishable from level of those without. This finding reflects the hypercoagulable state of cancer patient and is in agreement with other studies showing increased D-dimer concentration in those [25]. So D-dimer as laboratory test seems to be the indicator of hypercoagulable state of patient rather than predictor of VTE.

The number of predisposing to thrombosis risk factors in both groups was identical — 3,0 (2,0–4,0) (Table 4). Duration of immobilization in controls and cases was the same: 2,0 (0–3,0) and 2,0 (1,0–4,0) weeks respectively ($P > 0.05$). Surprisingly, duration of catheterization of central vein was shorter among cases: 3.0 (1.0–8.0) weeks compared to 8.0 (3.0–14.0) in controls ($P = 0.046$).

Table 4. Catheter placement and location and causes of VTE in children with cancer

	Patients		
	Cases n = 19	Controls n = 80	Significance
Position of catheter at time of VTE, (%):			
• v. cephalica, basilica dextr/sinistr	3 (16.0%)	16 (20.0%)	n. s.
• v. subclavia dextr/sinistr	11 (58.0%)	63 (78.7%)	n. s.
• v. jugularis dextr/sinistr	1 (5,0%)	0	n. s.
• v. femoralis	4 (21.0%)	1 (1.3%)	$P = 0.0004$
Location of VTE			
• cephalica, basilica dextr/sinistr	5	0	
• v. brachialis	1	0	
• v. subclavia dextr/sinistr	2	0	
• v. jugularis	2	0	
• v. cava superior	1	0	
• v. femoralis dextr/sinistr	4	0	
• v. ileofemoralis	2	0	
• v. poplitea	2	0	
Cause of VTE:			
• catheter-related VTE	4 + 2	0	
• ulcer of soft tissue	1	0	
• vein compression by tumor mass	1	0	
• prolonged immobilization (> 3 weeks)	3	0	
• both prolonged immobilization and indwelling femoral venous catheter	3	0	
• unknown	1	0	
• FVL and presence of antiphospholipid antibodies	2	0	
• FVL and catheterization	2	0	
Duration of catheter placement, week	3 (1–8)	8 (3–14)	$P = 0.046$
Duration of immobilization, week	2 (0–3)	2 (1–4)	n. s.
Predisposing to VTE factors, number	3.0 (2.0–4.0)	3.0 (2.0–4.0)	n. s.

Catheterization of v. subclavia dominated as a choice of venous access for patients of both groups. Also v. v. cephalica and basilica in compared groups were catheterized equally frequently. We did not reveal any association between the thrombosis and catheterization of above veins.

The facts of thrombosis located in the pool of v. cava inferior after catheterization of femoral vein (3 patients) and subclavian vein (1 patient) were reported. In control group femoral catheter was used only for 1 patient. The association between catheterization of femoral vein and the development of thrombosis was revealed for compared groups ($P = 0.0004$).

Location of venous thrombosis and position of catheter were the same among 9 of 19 patients. Thus our study, like others reports [26–27], confirmed association between presence of central venous line and thrombosis. Two of those 9 cases had thrombosis of upper extremities, in another two v. subclavia was affected, the thrombosis of v. internal jugularis had arisen as a result of incorrect catheter placement in yet another two children and three of the patients had thrombosis in femoral segment of venous system. These latter ones were immobilized for over 3 weeks. Compression of v. cava superior by tumor mass resulted in thrombosis in one child.

For 9 children venous access did not correlate with the place of formation of blood clot. All positive for FV

Leiden patients (4 out of 19 studied cases) belong to this group. Four patients had thrombosis of lower extremities (vv. poplitea, femoralis). Duration of immobilization for all 4 children had exceeded 3 weeks. The thromboses of vv. cephalica and basilica were registered in 4 cases (catheter was placed in v. subclavia). In one case the thrombosis of femoral vein occurred in patient with CVL located in v. subclavia. Two out of those 9 patients additionally had antiphospholipid syndrome, while other cases and all controls were APA-negative.

Although the specific combination of acquired and genetic risk factors differed between patients, detailed analysis of each episode of VTE allowed us to formulate leading cause of thrombotic complications for each studied case (see Table 4).

The listed facts allow us to speculate that the thrombosis in children with cancer does not depend on gender. Such factors as clinical condition, coagulation status, volume of haemostatic therapy and presence of clinical evidence of sepsis, as well as duration of catheterization are not significant as predisposing to thrombosis factors.

Overall, our study showed that the leading risk factors for VTE in children with cancer are prolonged immobilization or both immobilization and indwelling femoral venous catheter. Also mutation FV Leiden is associated with higher risk for VTE in children with cancer. Oncological patients affected with VTE during treatment are candidates for genotyping assay for Factor V Leiden, as the former may determine duration of anticoagulation therapy and administration of secondary prophylaxis. Mutation MTHFR C677T is a widespread polymorphism and is of little practical significance without plasma homocystein measurement. It is also in agreement with other reports. Nevertheless, authors believe that genetic background has real influence on blood coagulation processes and further studies may uncover new genes and genetic abnormalities underlying tendency to thrombosis.

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ТРОМБОЭМБОЛИЧЕСКИЕ ОСЛОЖНЕНИЯ ВО ВРЕМЯ ЛЕЧЕНИЯ У ПАЦИЕНТОВ ОНКОЛОГИЧЕСКОГО ПРОФИЛЯ ДЕТСКОГО ВОЗРАСТА

Цель: **оценить вклад наследственной предрасположенности к тромбозу в формировании венозной тромбоэмболии у пациентов онкологического профиля детского возраста.** ***Методы:*** **ПЦР с последующим рестрикционным анализом.** ***Результаты:*** **показано достоверное повышение частоты встречаемости мутации Лейдена в группе больных с тромбозами по сравнению с контрольной группой ($P = 0{,}0004$). Мутация гена протромбина *G20210A* не выявлена в ходе исследования ни у одного из 99 обследованных пациентов, что свидетельствует о низкой частоте встречаемости данной мутации в белорусской популяции. Мутация гена *MTHFR C677T* выявлена в группе больных и в контрольной с примерно одинаковой частотой (47,4 и 55,0% соответственно).** ***Выводы:*** **такие факторы как тяжесть состояния пациента, коагуляционный статус, объем заместительной гемостатической терапии, наличие симптомов сепсиса, равно как и длительность катетеризации вен, не являются существенными в прогнозировании риска возникновения тромбоза. Показано, что ведущими факторами риска в возникновении тромбоэмболических осложнений у пациентов онкологического профиля детского возраста являются длительная гиподинамия или сочетание длительной гиподинамии и катетеризации бедренной вены, а также наличие мутации Лейдена. Больным онкологического профиля с развившимся венозным тромбозом на фоне лечения основного заболевания необходимо определение мутации Лейдена, так как носительство последней позволяет определить на длительность антикоагулянтной терапии и проведение вторичной профилактики.**

Ключевые слова: **венозный тромбоз, рак, дети, фактор V Лейдена, протромбин G20210A, MTHFR C677T.**