

Effect of Factor V Leiden on Thrombosis in Childhood Leukemia

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ABSTRACT

Thromboembolism is an important complication in children undergoing therapy for ALL as it has the potential to impact adversely on both their survival and quality of life. The incidence of thrombosis in children with ALL varies between 1.1% and 36.7% and the actual mean is 3.2%. The aim of our study is to review the available reported data on the effect of FVL on thrombotic risk in pediatric patients with acute leukemia.

Keywords: Thrombosis; Acute Leukemia; Childhood; Factor V Leiden

1. Introduction

Pediatric patients with acute leukemia are at high risk of both hemorrhage and thromboembolic events (TEs) [1]. Thromboembolic events are among the more frequent and serious complications of acute lymphoblastic leukemia (ALL) and its treatment [2]. Thromboembolic events are thought to result from the interaction of various factors, including effects of disease itself, central venous line, catheterization, infections, dehydration, chemotherapeutic agents such as steroids and L-asparaginase (L-Asp), and acquired or inherited prothrombotic defects (IPDs). However, the risk factors for ALL associated TE are not yet clearly understood [3,4].

Vascular insults reported in children with ALL are discussed mainly in association with acquired quantitative deficiencies of protein C, protein S, or antithrombin associated with enhanced thrombin generation [2,5,6].

Chemotherapy can influence the haemostatic system either through direct effect of the chemotherapeutic agent or through complications such as infections. Corticosteroids activate platelet function, asparaginase reduces the synthesis of natural anticoagulants and in combination they increase the risk of TE in children with ALL. Some studies have shown increased thrombin activation at diagnosis in children with ALL [7,8].

The etiology of thromboembolism is thought to be multifactorial and caused by congenital and acquired risk factors. Common inherited factors are factor V (FV)

1691 G-A and Prothrombin (PT) 20210 G-A mutations [9,10]. Factor V Leiden (FVL) is the leading cause of constitutional thrombophilia. This gene defect includes G-A transition at nucleotide 1691 in exon 10 of the Factor V gene causing APC resistance yielding to a hypercoagulation disorder. The risk of developing thrombotic episodes for persons heterozygous for the FVL mutation is about 5 - 10 folds and for those homozygous is 80 - 100 folds higher than the general population [11].

The association between cancer and thromboembolic disease has been discussed in many reported studies. Many studies suggest that thromboembolism in association with childhood leukemia is a multifactorial entity resulting from the interaction of the disease. Previous reported data on the effect of FVL on leukemia-related thrombosis is controversial [1,12-22].

The aim of the present study is to compile the available data on the thrombotic risk of FVL in pediatric patients with ALL. The data in this review was compiled from PubMed and Science Citation Index databases. "Factor V, Factor V Leiden, FVL, pediatric leukemia, thrombosis" were used as key words. Published studies with their country, number of patients, genotype distribution of FVL and references are given in **Table 1**.

2. Conclusion

Thromboembolism is a well recognized complication of malignancy. However, the risk factors for ALL associated TE are unclear. The pathogenesis of the cancer-re-

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Table 1. The genotype distribution of FVL mutation in children with Leukemia and healthy individuals from different country.

<i>Patients with leukemia n:</i>	<i>Leukemia patients with FVL n (%):</i>	<i>FVL frequency of the healthy population % (ref)</i>	<i>Thrombosis in FVL carriers n:</i>	<i>Country</i>	<i>References</i>
289	32 (3)	7, 1 - 12 (26, 27)	1	Germany	13
27	5 (18, 5)	4, 3 (28)	none	Israel	20
60	2 (3, 3)	3, 2 - 6,0 (29, 30)	none	Canada	2
280	20 (7, 1)	7, 1-12 (26, 27)	1	Germany	8
92	7 (7,8)	2, 0 - 10, 6 (34, 35)	none	Iran	21
135	11 (8, 0)*	7, 9 (9)	none	Turkey	17
64	10 (15, 6)	7, 9 (9)	6	Turkey	16
82	16 (8, 5)	7, 9 (9)		Turkey	22

lated prothrombotic state is complex and reflects the action of different mechanisms, including activation of blood coagulation via procoagulant substances, impairment of fibrinolytic pathways, alterations of endothelium toward a thrombogenic state detectable in the large majority of patients with cancer. The reported incidence of DVT in children with ALL ranges between 1% and 73%. Several studies on genetic risk factors for thrombosis excluded those patients with cancer-related thrombosis. Although surgery, chemotherapy, central venous catheters, and systemic hypercoagulability were associated with venous thromboembolism (VTE) in cancer, previous reports on the association of FVL and/or prothrombin 20210A with cancer associated VTE were few and present conflicting results [13,23,24].

Nowak-Gottl *et al.* reported in a prospective multicenter study which focused on the role of prothrombotic risk factors in consecutively admitted newly diagnosed children with ALL carrying prothrombotic risk factors. In this study 32 of 289 consecutively admitted leukemic children (11%) treated according to the ALL-BFM 90/95 study suffered venous thromboembolism [25]. 5 (1.73%) of them carried thrombosis relevant disease. One of them was heterozygous for the FV 1691 G-A mutation with venous sinus thromboembolism.

Rahimi *et al.* indicated that the frequency of FVL mutation was higher in ALL patients compared to healthy individuals. The frequency of FVL G1691A polymorphism was 7.8% in patients compared to 3.2% in controls ($p = 0.052$) [21]. None of them carried thrombosis relevant disease.

Caruso *et al.* demonstrated that inherited thrombophilia increased the risk of VTE in pediatric ALL patients by approximately 8.5 folds (4.4 - 17.4). They indicated that a meta-analysis of prospective studies in childhood ALL and VTE found that symptomatic VTE was diagnosed in the central nervous system (CNS) in

50% of cases, venous VTE in 31%, and cerebral infarction or stroke in 18% [1].

Sivashoglu *et al.* reported that the thrombosis risk was significantly high in cases which had heterozygote FVL mutation. They reported that the screening for FVL mutation would be helpful in children with ALL during the diagnosis period. However they demonstrated that no significant correlation between thrombosis development and increased Lp-a levels, frequencies of MTHFR and PT 20210 A mutations [16].

In our recent study we genotyped 135 pediatric leukemia patients for these mutations. Eleven (8%) of the 135 patients were heterozygous for the FV 1691 G-A mutation. Seven (5.1%) of the patients carried the PT 20210 G-A heterozygous mutation. We suggested, that the FV 1691A and the Prothrombin 20210A mutations are not associated with TE in pediatric leukemias [17]. Akar reported that the frequency of FVL is about 8% in our healthy population [9].

Torun *et al.* showed that of the eighty two leukemic children, sixteen (8.5%) were carriers of FV mutation [22]. Five (6.0%) of the 82 patients had thromboembolism. One had cerebrovascular thrombosis, the other one with carotids internal thrombosis and other three had Deep Vein Thrombosis.

Elhasid *et al.* reported that 5 (18.5%) of the 27 pediatric leukemia patients were carried FV 1691 G-A mutation. None of them carried thrombosis relevant disease [20].

A study by Mitchell *et al.* reported that none of the 22 children with TEs were positive for Factor V Leiden or prothrombin gene 20201A but 22 of 60 children had TEs, a prevalence of 36.7% without this mutation [2,18]. The North American Prophylactic Antithrombin Replacement in Kids with Acute Lymphoblastic Leukemia Treated with Asparaginase (PARKAA) study failed to show any correlation between the presence of the PT 20210A

variant or the FV G1691A mutation and development of asymptomatic VTE [2].

Meta-analysis of 5 studies showed that the presence of at least one genetic prothrombotic factor was associated with an 8 folds increase in the risk of thrombosis in children with ALL [1]. Accurate identification of children with cancer who carry a baseline increased risk of thrombosis could have important therapeutic implications. For example, some drugs which are important components of modern chemotherapy regimens, such as asparaginase, are also known to increase the risk of thrombotic [18].

In conclusion, we believe that FVL mutation does not significantly increase thrombosis risk in leukemic children.

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