VENOUS THROMBOEMBOLISM IN ADOLESCENTS

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Summary: The incidence of venous thromboembolism (VTE) during childhood is low with two peaks – neonatal and adolescent age. This retrospective study is focused on clinical characteristics of VTE during adolescence. The main goals are to assess the most frequent inherited and acquired risk factors and to evaluate the benefit of D-dimers in diagnostics of venous thromboemblism. The data of 18 adolescents were analysed – 16 girls (88.9%), 2 boys (11.1%). In 9 patients (50%) thrombosis of the lower limb deep veins was diagnosed, six patients (33.3%) suffered from symptomatic pulmonary embolism (PE) and 3 patients (16.7%) from thrombosis at unusual sites. One patient had an idiopathic VTE, the mean number of the inherited and acquired risk factors was 2.6. The most frequent inherited risk factor was Leiden mutation of factor V (27.8%). The most frequent acquired risk factor was oral contraception (OC) in 12 out of 16 girls (75%). All of our patients on oral contraception had one or more additional risk factors. 10 out of 18 (55.6%) patients with VTE had elevated activity of factor VIII. The sensitivity of D-dimers was low (50%) in patients with distal lower limb thrombosis, but very high (100%) in patients with PE.

Key words: *Venous thromboembolism; Adolescence; D-dimer, Risk factors; Thrombosis; Thrombophilia*

Introduction

The incidence of VTE during childhood is low (0.07 per 10,000) (1) compared to adulthood (1 per 1,000 per year) (13). Lower and delayed thrombin generation in children plasma and increased thrombin inhibition by alpha-2-makroglobulin (2) are among the known reasons of low incidence of VTE in childhood. VTE incidence during childhood has 2 peaks – neonatal age (14.5 per 10,000 per year) and adolescence (1.1 per 10,000 per year) (15). Central venous catheter (CVC) is the major risk factor increasing the incidence in the neonatal age. The highest risk is associated with neonates, especially premature ones, who require intensive care including CVC (7). The thrombosis later in childhood occures usually in children with other severe illness, after cumulation of more risk factors (CVC, malignancy, autoimmune disease, sepsis, drugs with prothrombotic influence – L-asparaginase, steroids) (5). The incidence of VTE is increasing with age (6). OC is substantial risk factor within the group of adolescent girls. This study is focused on VTE characteristics in adolescent patients in Eastern Bohemia.

The goals of this study are: 1. To assess the most frequent risk factors contributing to genesis of thromboembolism during adolescence in this setting. 2. To evaluate the benefit of testing of D-dimers.

Material and methods

We retrospectively analysed the data of consecutive adolescent patients, who were admitted to the Department of Paediatrics of University Hospital Hradec Králové during the period 1. 4. 2006 – 31. 3. 2011.

All patients between the age of 14 to 18 with symptomatic deep venous thrombosis (DVT) and/or PE as primar diagnosis were included. Diagnosis of DVT was based on specific symptoms (unilateral limb oedema and pain) and Doppler ultrasonography with compression. Diagnosis of PE was based on clinical signs (dyspnea, chest pain and/or cardiovascular collapse) and echocardiography or spiral CT. The patients with thrombosis without pulmonal symptoms were not examined for possible asymptomatic minor PE. The group of distal lower limb thrombosis consisted of thrombosis of popliteal vein and calf vein thrombosis. Thrombotic events other than lower limb thrombosis and pulmonary embolism were grouped together as thrombosis at unusual sites. All the patients were tested for inherited risk factors (Protein C, Protein S, Antithrombin deficiency, Leiden mutation of factor V (FVL), G20210A mutation of factor II, lipoprotein (a), MTHFR polymorphism in case of elevated homocystein) and acquired or combined laboratory risk factors (antiphospholipid antibodies – anticardiolipin, anti-beta-2-glycoprotein I, homocystein, factor VIII). Other predisposing and provoking factors were evaluated: obesity, trauma, surgery, oral contraception, gestation and puerperium, sepsis and immobilisation incl. plaster cast. As positive family history we considered the occurence of VTE among first line relatives under the age of 45. The testing of inherited and acquired risk factors was performed at the beginning of therapy and selected tests further after 3–12 months. The blood samples were obtained

by venipuncture. The sterile tube with 1 ml of 0.106 mol/l sodium citrate was filled with 9 ml of blood for coagulation assays. Another sterile tube with 1 ml of 0.5 mol/l sodium ethylenediamine tetraacetic acid was filled with 9 ml of blood for DNA extraction. Coagulation tests were performed with STA-R and STA-Compact (Diagnostica Stago S.A.S., Asnières sur Seine, France) with following reagents: aPTT – PTT Automate 10 (Diagnostica Stago), PT – DG-PT (Grifols, S.A., Sant Cugat del Vallčs, Barcelona – Spain), D dimers – STA-LIATEST D-DI (Diagnostica Stago), factor VIII – DG-FVIII (Grifols), C.K. Prest 5 (Diagnostica Stago), Protein C – STACLOT PROTEIN C (Diagnostiga Stago), Protein S – STACLOT PROTEIN S (Diagnostica Stago), Antitrombin – STACHROM AT KIT (Diagnostica Stago). The polymerase chain method was used for F V Leiden and F II20210A determination. Genomic DNA was isolated from peripheral blood leukocytes using High Pure PCR Template Preparation Kit (Roche Diagnostics, Mannheim, Germany). The presence of factor V Leiden and prothrombin G20210A mutation was determined by the LightCycler 1.5 instrument using commercially available Factor F V Leiden Mutation Detection Kit and Prothrombin (G20210A) Mutation Detection Kit (Roche Diagnostics, Mannheim,Germany). The level of homocystein was determined immunoanalytically after 12 h. fasting with DPC Immulite 2000 analyzer. Lipoprotein (a) was determined immunoturbidimetric with analyser Modular (Roche). Beta-2glykoprotein and cardiolipin antibodies were detected by ELISA (Orgentec Diagnostica, Mainz, Germany). Obesity was evaluated according to percentile chart for BMI in children. We have used retrospectively collected and anonymous data from clinical records. In accordance with state legal requirements, no approval from an ethics committee was needed nor requested.

Results

In this period 18 adolescents fullfiling the criteria of VTE and/or PE were hospitalised in our paediatric department – 16 girls (88.9%), 2 boys (11.1%) with age 14 to 18 (mean age 16 years). The follow-up was 8–67 months with median 28 months.

Localization of thromboembolism

In 9 patients (50%) lower limb VTE was diagnosed – in 6 patients distal thrombosis, in 3 patients proximal thrombosis. Six patients (33.3%) suffered from PE, the primary thrombus (calf VTE) was detected in only two patients from those six. In 3 patients (16.7%) thrombosis occured at unusual sites – in 2 patients thrombosis of upper limb vein was present, 1 girl had thrombosis of vena mesenterica superior and vena portae.

Tab. 1

	Sex	Age	VTE type	Thrombophilia	Risk factors
1	F	16	PE	FVIII	OC, obesity
2	F	15	PE	FVIII	OC
3	F	16	PE, DVT-dist	FVIII	OC, knee arthroscopy, immobilisation
4	F	17	PE	FVL-htz, APL	OC
5	F	16	PE	FVIII	OC, obesity
6	F	16	PE, DVT-dist	FVL-hoz	OC
7	M	18	DVT-prox	FVIII	trauma, immobilisation
8	M	17	DVT-dist		obesity, immobilisation – plaster cast
9	F	14	DVT-upper	FVIII	
10	F	17	DVT-dist		surgery, immobilisation, obesity
11	F	14	VT-port	FVL-htz	sepsis
12	F	16	DVT-dist	Lp(a)	OC
13	F	15	DVT-dist	FVL-htz	OC
14	F	15	DVT-dist	FVIII	OC

	Sex	Age	VTE type	Thrombophilia	Risk factors
15	F	17	DVT-upper		OC, hemithyreoidectomy
16	F	17	DVT-prox	FVL-htz, FVIII	OC
17	F	15	DVT-dist	FVIII	OC-gest, pelvic laparoscopy
18	F	17	DVT-prox	FVIII, Lp(a), Homo	puerperium, cesarean section

F – female, M – male, PE – pulmonal embolism, DVT-prox – proximal DVT, DVT dist – distal DVT, DVT-upper – upper limb, VT-port – thrombosis of vena mesenterica superior and vena portae, OC – oral contraception, OC-gest – gestagen only OC, FVIII – elevation of factor VIII, FVL-htz – factor V Leiden mutation – heterozygous, FVLhoz – homozygous, APL – antiphospholipid antibodies, Lp(a) – hyperlipoproteinemia (a), Homo – hyperhomocysteinemia

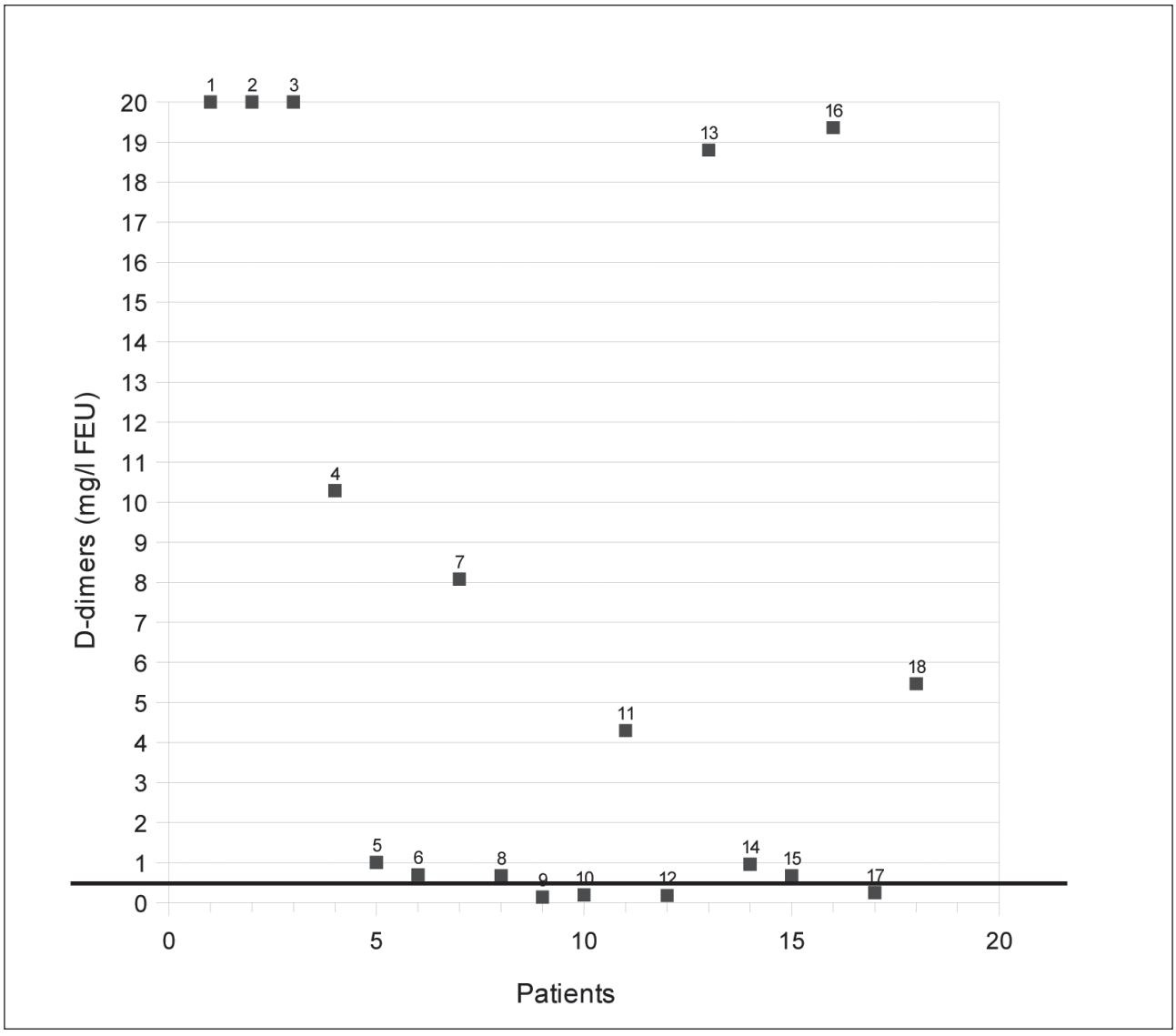

Fig. 1: The horizontal line represents the upper limit of reference range for D-dimers: 0.5 mg/l FEU

The causes of thromboembolism

One to five known risk factors contributed to the onset of VTE in our patients (mean 2.6, median 2.5). One patient (5.6%) had an idiopathic VTE.

Inherited thrombophilia

In 7 out of 18 patients (38.9%) inherited risk factor was detected. The most frequent inherited thrombophilia was Leiden mutation of factor V, in 5 girls (27.8%) – 4 heterozygous form, 1 homozygous. Two girls (11.1%) had hyperlipoproteinemia (a).

Acquired and combined thrombophilia

Ten out of 18 (55.6%) patients with VTE had elevated activity of factor VIII (157–364%).

1 patient had positive antiphospholipid antibodies – anticardiolipin IgG, antibeta-2-glycoprotein IgG. In one patient hyperhomocysteinemia was detected without MTHFR gene polymorphism.

Predisposing and provoking factors

The most frequent risk factor was oral contraception (OC) in 12 out of 16 girls (75%). The OC was predominant in girls with thrombosis at usual sites (lower limb thrombosis) and PE, in 11 out of 13 (84.6%) and less frequent in patients with thrombosis at unusual sites 1 out of 3. One patient experienced proximal lower limb thrombosis during puerperium after premature cesarean section. Four out of 18 patients (22.2 %) were obese. Three patients (16.7%) had trauma and 4 patients had surgery before the unset of VTE. There was positive family history in 1 patient.

D-dimers

In 4 patients the level of D-dimers was initially normal. These patients had smaller size thrombosis – 3 had distal lower limb thrombosis, one suffered from thrombosis of subclavial vein. The sensitivity of D-dimers in our setting is 77.8% but in the group of pulmonal embolism and extensive proximal thrombosis the sensitivity is 100%, while only 50% in patients with distal lower limb thrombosis.

Discussion

Inherited risk factors

The most frequent inherited risk factor in our setting was factor V Leiden mutation, which is consistent with other studies in our region (8, 17). The mean number of risk factors was 2.6 in our patients, the multifactorial etiology of childhood VTE was observed in other studies (16). There is no evidence, that elevation of lipoprotein (a) is a significant risk factor for VTE in adulthood (12), but it is associated with occurrence of first VTE in childhood (14). The risk of reccurence of VTE is not increased in patients with elevated lipoprotein (a), therefore the testing does not seem to be crucial for anticoagulation managment (22).

Elevation of factor VIII

Ten out of 18 patients (55.6%) had elevated factor VIII upon the diagnosis of VTE. In five patients factor VIII was checked, when the oral anticoagulation was stopped, in 4 patients the FVIII level was not repeated or there are still on prophylaxis. In 2 out of 6 patients the elevation of FVIII persisted. One of these two patients with FVIII elevation upon the anticoagulation withdrawal, experienced VTE reccurence during surgery despite secondary prophylaxis with LMWH. The role of elevation of factor VIII is currently under investigation. According to several studies, elevation of factor VIII is an independent risk factor for venous and arterial thrombosis (3, 10, 18). Patients with high levels of factor VIII after the first episode of VTE after discontinuation of oral anticoagulation have an increased risk of reccurent thrombosis (11). The risk of VTE in adults with cancer and elevation of FVIII does not depend on a certain cut-off but increases continuously (21). It is not clear from which level of FVIII should prolonged anticoagulation be considered to outweigh the risk of bleeding during anticoagulation. But prolonged anticoagulation in adults with FVIII greater than 230 IU/dl was effective to decrease the reccurence of VTE (9). However the benefit was not maintained after the discontinuation of anticoagulation.

Oral contraception

The majority of patients on oral contraception were using combined OC, 1 patient used gestagen only OC. The using of modern low estrogen combined OC is associated with about a fourfold higher relative risk of VTE (20). The relation between gestagen only pills and the risk of VTE is not clear. It is considered, that the risk is slightly higher or equal as without OC (4). Our patient taking gestagen – only OC had also additional risk factors as surgery and factor VIII elevation, we can only speculate about the role of gestagen – only OC in the onset of her thrombosis. All of our patients on OC had one or more additional inherited or acquired risk factors. We did not observed any VTE solely due to OC.

D-dimers

According to literature, the sensitivity of D-dimers for VTE diagnosis is up to 97%, patients after clot organisation or patients with a small clot burden (isolated calf vein clot) may have falsely negative results (19). In our setting all D-dimer negative patients had a thrombus of small extent.

Conclusions

We conclude, that the etiology of VTE in our setting is mutifactorial, the mean number of risk factors is 2.6. The occurrence of inherited risk factors in our patients is significant, but all patients with inherited thrombophilia had additional risk factors, which contributed to the manifestation of VTE.

The low sensitivity of D-dimers in patients with distal lower limb thrombosis emphasize using Doppler ultrasound, when evaluating a patient with high clinical suspicion for distal limb thrombosis even with negative D-dimers.

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