Theme Issue Article

Total tissue factor pathway inhibitor is an independent risk factor for symptomatic paediatric venous thromboembolism and stroke

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Summary

Tissue factor pathway inhibitor (TFPI) plays an important role in inhibiting tissue factor-induced coagulation by a factor Xa-dependent pathway of the activated tissue-factor VIIa complex. Decreased values of the latter inhibitor have been recently reported in adult patients with venous thrombosis (VT) or ischaemic stroke (IS). The present case-control study was therefore performed to evaluate whether a decreased TFPI concentration is also involved in paediatric symptomatic thromboembolism (ST). Total TFPI concentrations were measured along with established prothrombotic risk factors six to twelve months after the acute thrombotic onset in 144 Caucasian children aged 0.6 to 18 years (VT: n=80; IS: n=64). The cut-off values defined as age-dependent 10th percentiles were obtained from 244 healthy controls. Median (range) values of TFPI were significantly lower in patients compared with control subjects [50.0(20.0-132.3) ng/ml vs. 59.5(25.4-117.4) ng/ml; p-value < 0.0001]. In addition, 42 of the 144 patients (29.2%) compared with 25 of the 244 controls (10.2%) showed TFPI concentrations below the 10th age-dependent percentiles. Compared to baseline values 78.6% of children with total TFPI Ag < 10th percentiles showed a low response to enoxaparin administration, whereas in children with normal baseline TFPI values 30% show a low TFPI release (p= 0.007). Multivariate analysis adjusted for the presence of established prothrombotic risk factors showed a significantly increased odds ratio (OR) and 95% confidence interval (CI) for patients with ST [OR/CI: 3.8/2.2-6.6; p< 0.0001]. Data shown here give evidence that total TFPI concentrations below the 10th age-dependent percentiles independently increase the risk of ST in Caucasian children 3.8-fold.

Keywords

TFPI, factor V G1691A, lipoprotein (a), paediatric thromboembolism

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Introduction

Venous and arterial thrombosis are rare diseases that are being increasingly diagnosed and recognised also in infancy and childhood. Due to the special properties of the haemostatic system during infancy and childhood, symptomatic thrombotic manifestation occurs in 0.07/10,000 children, 5.3/10,000 admissions of children, and 2.4/1000 admissions of newborns to intensive care units (1-4). Within the entire childhood population, possibly due to the lower concentrations of antithrombin, heparin cofactor II and protein C along with a reduced fibrinolytic capacity, neonates are at a greater risk of thromboembolic

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complications than older children. The incidence of vascular accidents decreases significantly after the first year of life, with a second peak during puberty and adolescence again associated with reduced fibrinolytic activity (1, 2). Numerous clinical and environmental conditions, such as peripartal asphyxia, neonatal infections, foetal diabetes, the use of central lines, trauma or surgery, dehydration, malignant diseases, renal diseases, autoimmune diseases, or the intake of oral contraceptives by adolescent girls resulted in elevated thrombin generation with subsequent thrombus formation in infancy and childhood (2-7). In addition to the stated underlying clinical conditions, various genetic prothrombotic defects, particularly those affecting the physiological anticoagulant systems, i.e. antithrombin, protein C and protein S deficiency, the mutation of coagulation factor V (G1691A), and the prothrombin gene variant (G20210A), have been well established as risk factors for thrombotic events (8). In addition, metabolic diseases, such as homozygous homocystinuria and moderate hyperhomocysteinemia as well as increased concentrations of lipoprotein (a), have recently been shown to significantly enhance the risk of thromboembolic arterial and venous thrombosis in paediatric and adult patients (9-13). The association of multiple haemostatic prothrombotic defects or the combination of established prothrombotic risk factors with acquired environmental or clinical conditions greatly increases the risk of thrombosis, not only in adults but also in infants and children (11).

Tissue factor and tissue factor pathway inhibitor (TFPI) play a key role in triggering thrombin generation (14). TFPI acts as an important regulator of the extrinsic pathway of blood coagulation through its ability to interact with blood coagulation factor VIIa/tissue factor complex and activated factor X via its Kunitz-type domains. TFPI plays an important role in inhibiting tissue factor-induced coagulation by a factor Xa-dependent pathway of the activated tissue-factor VIIa complex (14, 15). Decreased values of the latter inhibitor have been recently reported in adult patients with venous thrombosis, ischaemic stroke or peripheral artery disease (16-21). The present study was therefore performed to evaluate whether a decreased TFPI concentration is also involved in paediatric symptomatic thromboembolism.

Materials and methods

Ethics

The present study was performed in accordance with the ethical standards laid down in the updated relevant version of the Declaration of Helsinki and approved by the medical ethics committee at the Westfälische Wilhelms-University, Münster, Germany.

Study period

In total, 971 paediatric patients aged neonate to 18 years with a first symptomatic thromboembolic event were consecutively recruited and screened for hereditary prothrombotic risk factors between January 1995 and June 2003 by the following participating centres in the catchment areas of Hamburg, Kiel, Lübeck, Münster, Bielefeld, Düsseldorf, Berlin, Magdeburg, Halle and Munich (9, 11, 12).

Inclusion criteria

Inclusion criteria were a thromboembolic event confirmed objectively by standard imaging methods, i.e. duplex sonography, venography, CT or MR imaging for the diagnosis of venous thromboembolism, and cerebral CT scanning, MR imaging, MR angiography, or transcranial Doppler ultrasonography for the diagnosis of thromboembolic ischaemic stroke.

Exclusion criteria

Patients older than 18 years at onset, children not of Caucasian origin, patients with incomplete clinical or laboratory work-up (established prothrombotic risk factors), and subjects lost for follow-up or without parental consent were not enrolled in the present study.

In addition, children during the acute thromboembolic phase, patients with renal insufficiency, liver disease or malignancies, subjects on heparin therapy, and adolescent girls taking oral contraceptives were excluded (14, 22).

Final study population

From the ongoing multicentre study, a subgroup of 144 white patients with a median (range) age of 6.4 (0.6 to 18) years was analysed. Thromboembolic manifestation included venous thrombosis (n=80) and thromboembolic ischaemic stroke (n=64). As a standard anticoagulant/antithrombotic therapy of care, children with venous thrombosis received LMWH (enoxaparin: adjusted to a 4-hour anti factor Xa activity of 0.3 to 0.5 IU/ml) alone, followed by warfarin (INR 2.2-3-0) in selected cases, and children with thromboembolic stroke were treated with LMWH (enoxaparin) or aspirin (3-5 mg/kg bodyweight) respectively.

Control group

Patients were compared with 244 white infants from different geographic areas of Germany, recruited between January 1996 and June 2003. These control infants, who had no history of chronic disease or of thromboembolic events, and were not on medication at the time of recruitment, had presented as out patients for evaluation before minor surgery (planned circum cisions and hernias) or bone marrow donation (9, 11, 12).

Laboratory tests

With informed parental consent, the factor V G1691A (FV) and factor II G20210A (FII) mutations, concentration of lipoprotein (Lp) (a), protein C (PC), protein S (PS), antithrombin (AT) and total fasting plasma homocysteine levels were investigated in

patients and controls 6-12 months after the acute event, using standard laboratory techniques (9, 11, 12). Total TFPI was investigated with a commercially available ELISA (total TFPI, IMUBIND®, American Diagnostica Inc.). This assay, using a sandwich ELISA employing a rabbit anti-human TFPI native polyclonal antibody as the capture antibody and a monoclonal antibody specific for the Kunitz domain 1 of TFPI, detects both intact and truncal forms of TFPI as well as complexes with tissue factor and factor VIIa. Since data on normal values for total TFPI in children are sparse (22, 23), TFPI concentrations < age-dependent 10th percentiles derived from the healthy control children were used as cut-off values. To evaluate the endothelial TFPI release in children under heparin treatment in a subgroup of 40 children receiving LMWH for standard care at least three months [TFPI < 10th percentile n = 14; TFPI > 10th percentile n=23)] total TFPI ag were measured immediately before withdrawal of LMWH. TFPI values under heparin treatment were compared to baseline values obtained 6 months later. A low TFPI response under LMWH administration was defined as an endothelial TFPI release < 1.5-fold compared to baseline (24). A type I deficiency (antithrombin, protein C) was diagnosed when functional plasma activity and immunological antigen concentrations of a protein were repeatedly shown to be below 50% of the normal age-related limit. A type II deficiency (antithrombin, protein C) was diagnosed in patients with repeatedly low functional activity along with normal antigen concentrations. The diagnosis of protein S deficiency was based on reduced free protein S antigen levels combined with decreased or normal total protein S antigen concentrations respectively. Criteria for the hereditary nature of a haemostatic defect were its presence in at least one first degree family member, or the identification of a causative gene mutation, or both.

Statistical analysis

All statistical analyses were performed with the StatView 5 software package (SAS Institute) and the MedCalc software package (MedCalc, Mariakerke, Belgium). Prevalence rates of prothrombotic risk factors in patients and control subjects were calculated by χ^2-analysis or by Fisher's exact test. To compare the overall rate of prothrombotic risk factors between patients and controls and to evaluate the interaction between decreased TFPI concentrations and established prothrombotic risk factors, odds ratios (ORs) together with 95% confidence intervals (CIs) were estimated from a multivariate analysis using a logistic regression model. The significance level was set at 0.05. For variables with a non-Gaussian frequency distribution, data were presented as medians and ranges. All evaluations and comparisons between patients and controls were conducted using the Mann-Whitney test (p-values < 0.05 were considered significant). In addition, Spearman's rank test was used to evaluate the correlation between total TFPI levels and age.

Results

Age-dependent distribution of total TFPI

Lower age-specific 10th percentiles of TFPI levels in the 244 healthy paediatric controls showed a significantly negative correlation with age (rho = -0.31; p< 0.0001: Figure). The lower 10th percentile was 46 ng/ml in children aged 6-12 months, 43 ng/ml in children from 1.1 to 9 years, and 40 ng/ml in subjects aged 9.1 to 18 years.

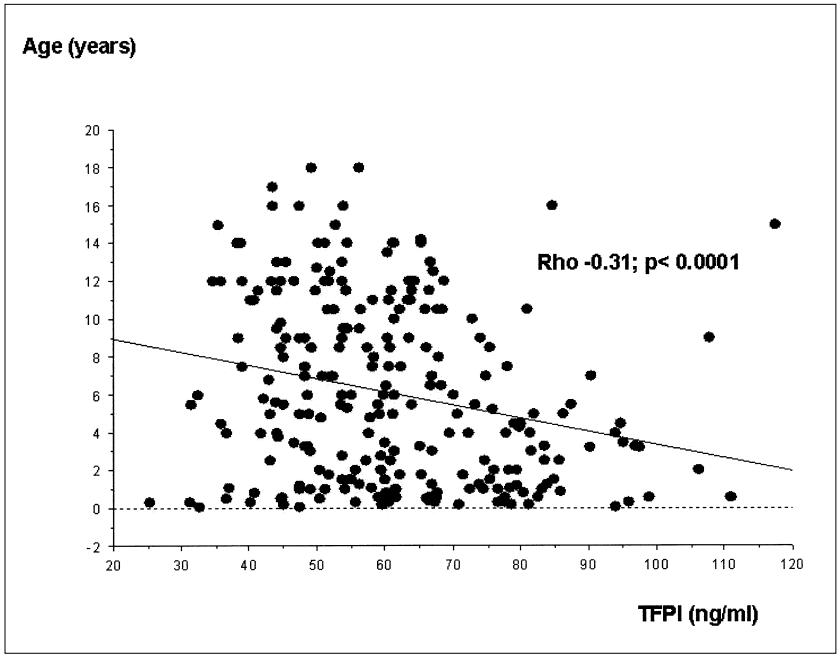

Figure: Total age-dependent TFPI concentration in 244 healthy control children.

Table 1: Distribution of single and combined prothrombotic risk factors in patients and controls.

Prothrombotic risk factor	Patients n=144	Controls n=244	P-value
Total TFPI < 10th percentiles			
Single	**16/144 (11.0%)**	**11/244 (4.5%)**	**0.02**
Combined	**26/144 (18.1%)**	**14/244 (5.7%)**	**<0.0001**
& factor V G1691A	12	10	
& factor II G20210A	3	0	
& lipoprotein (a) >30 mg/dl	8	4	
& protein C type I deficiency	1	0	
& protein S type I deficiency	1	0	
& antithrombin type I deficiency	1	0	
Σ single and combined	**42/144 (29.2%)**	**25/244 (10.2%)**	**<0.0001**

Median/range total TFPI concentration in patients and controls

The median (range) level of total TFPI was 50.0 ng/ml (20.0-132.3) in the 144 patients with symptomatic thromboembolism compared with 59.5 ng/ml (25.4-117.4: p< 0.0001) in the controls: venous thrombosis group 46.9 ng/ml (20.5-132.3:p< 0.0001), stroke population 53.3 ng/ml (27.1-116.2; p= 0.0049).

Univariate analysis

In the entire study cohort, 42 of the 144 (29.2%) symptomatic patients investigated had TFPI concentrations < age-dependent 10th percentiles versus 25 of the 244 controls (OR/CI 3.0/2.0-6.2; p<0.0001). Whereas 11% of the patients and 4.5% of the healthy controls showed a single decrease of total TFPI (OR/CI 2.6/1.2-5.9; p=0.02), TFPI < 10th percentiles combined with established prothrombotic risks were found in 18.1% of patients versus 5.7% of control subjects (OR/CI 3.6/1.2-7.0; p<0.0001). The distribution of decreased total TFPI concentrations with established prothrombotic risk factors is shown in the Table.

In the subgroup analysis 26 of the 80 children with venous thrombosis (32.5%) versus 25 of the 244 controls (10.2%) had TFPI levels below the age-specific 10th percentile (OR/CI 3.8/2.0-6.9; p<0.0001), and 16 of the 64 stroke children (25.0%) had decreased TFPI concentrations (OR/CI 2.6/1.3-5.2; p=0.008).

Logistic regression analysis

In the multivariate analysis, including the overall rate of established prothrombotic risk factors known to be significantly associated with symptomatic thromboembolism in paediatric patients in Germany, e.g. the FV G1691A mutation, the FII G20210A variant, deficiency states of protein C, S or antithrombin, or elevated Lp(a) concentrations, decreased TFPI levels < the age-specific 10th percentiles retained their statistically significant and independent association (OR/CI 3.8/2.2-6.6; p<0.0001). In the 42 children with decreased TFPI levels the inheritance of low concentrations was confirmed in at least one family member.

Endothelial TFPI release

To evaluate the endothelial TFPI release under a stable 3-month period of LMWH administration a subgroup analysis was performed in 40 children (TFPI < 10th percentile n=14; TFPI > 10th percentile n=23). In children with normal total TFPI values the median (range) TFPI increase was 1.9 (1.3-3.0) compared to 1.26 (1.0-2.7) in patients with baseline TFPI values < 10th age-dependent percentiles (p=0.005). Compared to baseline values obtained 6 months after cessation of LMWH 11 out of 14 children (78.6%) with total TFPI ag < 10th age dependent percentiles showed a low response to enoxaparin administration, whereas in children with normal baseline TFPI values only 7 out of 23 patients (30%) demonstrated a low TFPI release under LMWH (p= 0.007).

TFPI values in children with recurrent thromboembolism

During the follow-up period, four out of 80 children with venous thrombosis (5.0%) suffered a second thromboembolic event. Interestingly three out of the four children affected with recurrent venous thrombosis showed decreased TFPI values prior to rethrombosis.

Discussion

The importance of various hereditary haemostatic abnormalities in contributing to the risk of paediatric thromboembolism is well established (8). To date, the rate of single or combined prothrombotic risk factors detected in Caucasian children is approximately 50%, while no thrombophilia has been found in the remaining subjects (9-12). Data presented here provide evidence that decreased total TFPI concentrations < age dependent 10th percentiles further contribute as a significant and independent risk factor to symptomatic thromboembolism in Caucasian children, in 11% of cases not combined with one of the established risk factors. The OR found was 3.8 for children with venous thrombosis and 2.6 for subjects with thromboembolic stroke, i.e. clearly within the range reported for further inherited thrombophilic risk factors in white children, e.g. the heterozygous FV G1691A mutation, the FII G20210A variant and elevated lipoprotein (a) levels.

TFPI is a multivalent Kunitz-type protease inhibitor of 276 amino acids and approximately 42 kDa that has three domains (14). It is synthesised mainly by the vascular endothelium (80-

85%) and has also been detected in at least four intravascular pools, e.g. bound to the endothelial surface, associated with lipoproteins (10%), carrier-free within the plasma, and sequestered in platelets (3%). TFPI interacts with blood coagulation factor VIIa/tissue factor complex and activated factor X via its Kunitz-type domains. Furthermore, it plays an important role in inhibiting tissue factor-induced coagulation by a factor Xa-dependent pathway of the activated tissue-factor VIIa complex (14, 15). TFPI is cleared from the circulation primarily by the liver and the kidneys (14). On the one hand, increased TFPI levels have been reported in subjects prone to thromboembolic diseases, e.g. diabetes, nephrotic proteinuria, as well as in patients suffering from cancer or ischaemic heart disease (25-28). On the other hand, decreased TFPI values have been found in small case series of adult patients with objectively confirmed venous thrombosis or ischaemic stroke as well as in the coronary circulation of patients with acute coronary syndromes (16-21, 29, 30). Furthermore, the administration of exogenous recombinant TFPI has been claimed to protect against intravascular coagulation and venous thrombosis in animal models (14). However, the molecular basis for the prothrombotic action of low TFPI concentrations has not yet been elucidated (14, 31-32).

Since the eighties more and more knowledge is available indicating that there are important physiologic differences between the haemostatic systems in children and adults (1). In contrast to lower levels of the natural anticoagulant inhibitors protein C and protein S in early childhood, α2macroglobulin and c1-inactivator are elevated until puberty (1, 33), and total TFPI ag derived from the healthy cohort investigated here are higher beyond the neonatal period in the first year of life compared with children in puberty. As a consequence, in the last 20 years the need for age-dependent normal values to correctly classify bleeding as well as thrombotic tendencies in neonates, infants and children has been increasingly accepted.

To the best of our knowledge, the first controlled study on decreased TFPI concentrations and their possible role in venous thrombosis was recently published by Dahm et al. (19). These authors evaluated TFPI in a case-control design with subjects enrolled from the Leiden Thrombophilia study population. They found low TFPI levels, e.g. free TFPI as well as total TFPI antigen and activity, to be a significant risk factor for venous thrombosis in the white cohort investigated. The data reported by us in a case-control setting enrolled from the multicentre German Childhood Thrombophilia Study are in agreement with the findings of Dahm et al. and Abumiya et al. that decreased total TFPI levels < age dependent 10^{th} percentiles are a risk factor for venous thrombosis as well as for ischaemic stroke in children (19, 20). The relation of reduced free TFPI levels was not studied in the present cohort due to the lack of adequate paediatric sample sizes. Whether, as suggested by Dahm et al., the relation of free TFPI in children with venous thromboembolism is even stronger than that reported for total TFPI is the subject of further ongoing analysis.

Paediatric thromboembolism is being treated increasingly with low molecular heparin, either as a first line therapy or following unfractionated heparin in a prophylactic regimen (34). Plasma levels of total TFPI are influenced not only by basic diseases but also by the various heparins available: Depending on the molecular weight of the heparin used, different levels of TFPI release from the vascular endothelium have been described (35-39). In addition, a release of TFPI from the endothelium is also observed during intermittent pneumatic compression (40). Thus, the use of heparin either unfractionated or as low molecular weight heparin as well as the protective use of compression stockings in patients with symptomatic thromboembolism also underlines this therapeutic option in children.

In the study presented here the endothelial TFPI release in a subgroup of children treated at least three months with the LMWH enoxaparin in prophylactic dosages adjusted to anti factor Xa-activity levels between 0.3 and 0.5 IU/ml was significantly lower in children with decreased baseline TFPI concentrations compared with children carrying age-dependent normal TFPI levels. The endothelial TFPI release observed by us in children with normal TFPI concentrations is in accordance with the TFPI release reported in 40 adult patients measured with the same TFPI ag assay and treated with the same LMWH enoxaparin for prophylaxis after orthopaedic surgery (24). Keeping in mind that in the present study TFPI ag levels were determined clearly beyond the acute thrombotic onset it seems to be unlikely that TFPI bound to TF-FVIIa-FXa complexes has an important impact on TFPI plasma levels, e.g. lower levels, which can be expected as a state of consumption during the acute thrombotic phase. Thus, the findings of low TFPI levels along with a poor endothelial release following LMWH administration, the observation that low TFPI levels precede recurrent venous thrombosis, and the fact that at least one first degree family member has a low total TFPI too, clearly underline the hypothesis that a lowered TFPI concentration serves as a candidate risk factor for thromboembolic diseases not only in adults, but also in children (17-19).

In summary, besides the established risk factors, a total TFPI concentration < 10^{th} age-dependent percentiles is another risk factor in Caucasian children, enhancing the laboratory rate of detecting risk factors not combined with established thrombophilic risks in 11% of children with symptomatic thromboembolism. However, the findings of the present study are restricted to white German patients, and further studies are recommended to clarify the role of decreased TFPI in paediatric populations not of Caucasian origin.

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