World Journal of Gastroenterology

Online Submissions: http://www.wjgnet.com/1007-9327office
wjg@wjgnet.com
doi:10.3748/wjg.v16.i48.6123

World J Gastroenterol 2010 December 28; 16(48): 6123-6127
ISSN 1007-9327 (print) ISSN 2219-2840 (online)

BRIEF ARTICLE

Extrahepatic portal vein thrombosis in children and adolescents: Influence of genetic thrombophilic disorders

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Received: January 26, 2010 Revised: March 10, 2010
Accepted: March 17, 2010
Published online: December 28, 2010

Abstract

AIM: To explore the prevalence of local and genetic thrombophilic disorders as risk factors for portal vein thrombosis (PVT) in our series, the largest ever published in pediatric literature.

METHODS: We conducted a case-control study enrolling 31 children with PVT and 26 age-matched controls. All were screened for thrombophilia, including genetic disorders, protein C, protein S and homocysteine deficiencies. All coagulation parameters were studied at least 3 mo after the diagnosis of portal vein obstruction.

RESULTS: In our study we showed that most pediatric patients with PVT have local prothrombotic risk factors, which are probably the most important factors leading to PVT. However, there is a clear association between the presence of prothrombotic disorders and PVT, suggesting that these increase the risk of thrombosis in patients with local factors such as perinatal umbilical vein catheterization or sepsis.

CONCLUSION: Patients with PVT should be screened for inherited prothrombotic disorders regardless of a history of an obvious local risk factor.

Key words: Portal vein thrombosis; Children; Thrombophilic disorders; Protein C; Protein S

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Pietrobattista A, Luciani M, Abraldes JG, Candusso M, Pancotti S, Soldati M, Monti L, Torre G, Nobili V. Extrahepatic portal vein thrombosis in children and adolescents: Influence of genetic thrombophilic disorders. *World J Gastroenterol* 2010; 16(48): 6123-6127 Available from: URL: http://www.wjgnet.com/1007-9327/full/v16/i48/6123.htm DOI: http://dx.doi.org/10.3748/wjg.v16.i48.6123

INTRODUCTION

Portal vein thrombosis (PVT) is a common cause of portal hypertension. To date, the pathogenesis of PVT in children still remains unexplained, yet it is the major cause of portal hypertension in children and adolescents.

Variceal bleeding due to PVT is a recognized cause of upper gastrointestinal bleeding in children in developing countries[1,2]. Hereditary thrombophilias that are known to predispose to venous thrombosis and PVT include certain mutations of the prothrombin (*PTHR*), factor V Leiden (*FVL*) or methylenetetrahydrofolate reductase (*MTHFR*) genes or deficiency of one of the natural anticoagulant proteins C and S[3-6].

Some neonatal events such as abdominal surgery, sepsis or umbilical vein catheterization (UVC) are typically identified in patients with PVT[7], with an incidence of thrombosis complicating UVC reported in the literature as high as 44%[8-10]. Moreover, other factors, such as dehydration, also have been suggested to play a part in PVT development[11].

Finally, despite all efforts, the cause of the blocked portal vein remains obscure in 50% to 90% of children[12]. Unlike in adults, studies of thrombophilic disorders in children are scant, and to date only a few studies have evaluated the prevalence of hereditary thrombophilic disorders in children and adolescents with PVT[1,2,13,14].

The aim of our study was to explore the prevalence of local and genetic thrombophilic disorders as risk factors in PVT in our series, the larger ever published.

MATERIALS AND METHODS

A 2-year prospective case-control study (December 2006 to December 2008) was carried out at Bambino Gesù Children's Hospital in Rome, Italy. The study was conducted according to the principles of the Declaration of Helsinki, informed consent was obtained, and the authors' institutional review board approved the study.

We enrolled two groups of subjects for the study. Group 1 included 31 (20 male) Caucasian patients with PVT; mean age, 7 yr 8 mo (range: 11 mo - 18 yr 2 mo). Group 2 comprised 26 children (15 male) free of liver disease and thrombotic events, age matched with group 1, who were inpatient in our hospital during the study. Upper endoscopy was performed in all patients of Group 1 and showed signs of portal hypertension but not always the presence of varices.

PVT was diagnosed by Doppler ultrasound scan or angiography [14 patients underwent both these procedures and we found a very high concordance (98%)]; both procedures were performed by the same radiologist. Normal liver function tests or no other sign of liver disease was an inclusion criteria, as well as the absence of histological abnormalities on liver biopsy examination when performed.

All patients were screened for thrombophilia including genetic disorders (*MTHFR C677T, FVL, PTHR G20210A*) protein C (PC), protein S (PS) and homocysteine. All coagulation parameters were studied at least 3 mo after the diagnosis of portal vein obstruction to avoid falsely low levels related to active thrombosis. Abnormal values of coagulation factors might be observed in patients with PVT due to impaired liver synthesis. Due to the lack of standards to define PC or PS deficiency in this setting, we used a ratio of these levels to prothrombin rate lower than 0.7 as a working definition for these deficits. This definition should exclude those patients with low PC and PS levels related to impaired liver synthesis, which would also affect prothrombin rate.

None of the patients were on anticoagulant or antiplatelet therapy at the time of the study. Detailed history was obtained with special emphasis on history of umbilical catheterization (50%), umbilical sepsis (6%), admission to neonatal intensive care unit (72%), severe gastroenteritis and dehydration (6%), history of thromboembolism in the patients and their family members (3%), and history of parental consanguinity (1%).

Genetic and specific analysis

Genomic DNA was isolated from white blood cells by standard procedures. A 222 bp fragment of the Factor V gene, a 165 bp fragment of the Factor Ⅱ gene and a fragment of the MTHFR gene are amplified from human genomic DNA using specific primers and the amplicon is detected by fluorescence using a specific pair of probes consisting of two different oligonucleotides that hybridize to an internal sequence of the amplified fragment during the annealing phase of a PCR cycle. The same specific probes are also used to determine the genotype by performing a melting curve analysis.

PC and PS activity was measured by coagulometric assay. PC activity was measured using a specific activator extracted from southern copperhead snake venom (*Agkistrodon c. contortrix;* STA protein C, Roche). PS activity was determined based on the principle of activated factor V inhibition (STA protein S, Roche). Protein activity was expressed as a percentage of a reference plasma pool.

Statistical analysis

Continuous variables were compared with unpaired *t*-test. Categorical variables were compared with the Fisher exact test. The association between the presence of an abnormality and PVT was assessed with odds ratios and their 95% confidence intervals (CI). All analyses were performed with SPSS version 15 (Chicago, IL, USA).

RESULTS

The characteristics of the patients and controls are summarized in Table 1. In patients, the first manifestation of portal vein thrombosis occurred at a mean age of 4 year 9 mo (range: 6 mo to 16 year 2 mo). This was upper gastrointestinal (GI) bleeding in 87% of patients followed by splenomegaly in 13%. Eighty-one percent of the patients had varices at presentation, while 74% had splenomegaly. Sixty-eight percent of the patients had a history of a local prothrombotic factor (neonatal sepsis or umbilical vein catheterization). Only 1 patient with a local prothrombotic factor was present in the controls.

Congenital thrombophilic disorders

FVL mutation was found in 2 (7%) patients and heterozygous *G20210A* mutation was found in 3 (10%), while

Table 1 Characteristics of the patients (mean ± SD)

	Controls	Patients
Age	6 yr 9 mo	7 yr 8 mo
Sex	15 males	20 males
INR (%)	1.05 ± 0.09	1.35 ± 0.21
ALT (UI/L)	31.15 ± 13.83	25.45 ± 14.71
AST (UI/L)	37.23 ± 11.86	31.42 ± 11.90
GGT (UI/L)	16.46 ± 16.89	17.68 ± 18.40
Albumin (g/dL)	4.16 ± 0.48	3.88 ± 0.37
Bil/tot (mg/dL)	0.78 ± 0.13	0.81 ± 0.27
Bil/dir (mg/dL)	0.12 ± 0.11	0.18 ± 0.14
ALP (UI/L)	404.09 ± 154.90	515.97 ± 180.44

INR: International normalized ratio; ALT: Aspartate aminotransferase; AST: Alanine aminotransferase; GGT: γ-glutamyl transpeptidase; Bil/tot: Bilirubin/total; Bil/dir: Bilirubin/direct; ALP: Alkaline phosphatase.

homozygosity for these two mutations was not found in any patient. No control patient had mutations in these two genes.

MTHFR-C667T mutation was found in 16 (68%) patients, and 4 (13%) were homozygous for this mutation. The corresponding figures in the control group were 6 (23%) and 0 patients, respectively (Table 2). Therefore, the odds ratio for having at least an allele with the *MTHFR-C677T* polymorphism in patients with portal vein thrombosis was 7.00 (95% CI: 2.15-22.85), suggesting that this polymorphism could increase the risk of PVT. However, intriguingly enough, levels of homocysteine in controls were similar to that found in cases ($P = 0.28$), and all subjects had normal values.

Coagulation inhibitor protein deficiency

Four patients presented PC levels compatible with prot C deficiency and 4 had PS levels compatible with prot S deficiency. We also investigated their parents to show any prot C alteration. Moreover, none of the controls had prot C deficiency while one had values consistent with prot S deficiency.

The overall frequency of inherited thrombophilic abnormalities (excluding mutations in *MTHFR*) in cases was 32% (8 patients had only one factor, one patient had two factors and one patient had three factors). This prevalence was significantly lower in controls (1/26, 4%) (Table 3). Thus, the OR of having any inherited prothrombotic disorder (excluding *MTHFR* polymorphism) in patients with portal vein thrombosis as compared to controls was 11.91 (95% CI: 1.41-100.77).

Eight patients (26%) had neither a thrombophilic nor a local factor (idiopathic portal vein thrombosis). This figure is in keeping with previously published series of adult portal vein thrombosis. Thirteen patients (42%) had only local factors, eight (26%) had both local and thrombophilic factors and only 2 patients (6%) had isolated inherited thrombophilic factors with no history of a local factor.

There were no associations between the presence of an inherited prothombotic disorder and the manner of initial presentation of PVT (splenomegaly or GI bleeding). However, patients with inherited thrombophilic factors were less likely to have varices at the time of presentation (6 out of 10 patients) as compared with patients without (19 out of 21; $P = 0.045$).

No recurrent thrombotic events were recorded in a 24 mo long follow-up, both in patients with and without prothrombotic disorders.

Table 2 Distribution of type and prevalence of mutations in study subjects *n* (%)

Type of mutations	Prevalence of mutations		
	Control (26)	Case (31)	Total (57)
Normal	20 (76.9)	10 (32.3)	30 (52.6)
Abnormal *MTHFRC677T*			
Heterozygous	6 (23.1)	17 (54.8)	23 (40.4)
Homozygous	0 (0)	4 (12.9)	4 (7.0)

$P = 0.001$. *MTHFR*: Methylenetetrahydrofolate reductase.

Table 3 Frequency of inherited thrombophilic abnormalities *n* (%)

Any thrombophilic factor	Control	Case	Total
No	25 (96.2)	21 (67.7)	46 (80.7)
Yes	1 (3.8)	10 (32.3)	11 (19.3)
Total	26 (100)	31 (100)	57 (100)

$P = 0.008$ (Fisher's exact test).

DISCUSSION

In this study we show that most patients with pediatric portal vein thrombosis have a history of a local prothrombotic factor, such as sepsis or umbilical vein catheterization, a figure much higher than that reported for adult portal vein thrombosis (around 30%)[15]. Therefore, and distinctly from adult PVT, local factors seem clearly to be the major players implicated in the development of PVT in children. However, a major finding of this study is that inherited disorders of coagulation are also frequently found in these patients (38%, as compared with 4% in controls), though most times in association with a local factor. This suggests, on one hand, that inherited thrombophilic disorders might facilitate the development of PVT thrombosis after a "local" event. On the other hand, since the presence of a thrombophilic disorder might have an impact on the management and follow-up of these patients, our data support the notion that children with PVT should be thoroughly investigated for the presence of a thrombophilic factor, even if an obvious history of a local factor is present.

The most frequent thrombophilic disorder was a deficit in naturally occurring anticoagulants (proteins C or S). It is possible, however, that the prevalence of coagulation inhibitor protein deficiency might be overestimated, since these factors might decrease due to altered liver synthesis and decreased hepatic blood flow secondary to the thrombosis, as already suggested in literature[6,16]. Notably, some

Table 4 Frequency of thrombophilic disorders in children and adolescents with portal vein thrombosis *n* (%)

Study	Coagulation inhibitor protein deficit		Gene mutations		
	PC	PS	*FVL*	*PTHR*	*MTHFR*
Dubuisson *et al*[13] (*n* = 20)	9 (45)	13 (65)	NP	NP	NP
Uttenreuther-Fischer *et al*[2] (*n* = 23)	NP	NP	2 (9)	NP	NP
Heller *et al*[1] (*n* = 24)	NP	NP	4 (17)	0	1 (4)
Pinto *et al*[12] (*n* = 14)	6 (43)	3 (21)	0	1 (7)	3 (21)
Current study (*n* = 31)	4 (13)	4 (13)	2 (6.5)	3 (9.7)	16 (67.7)

PC: Protein C; PS: Protein S; *FVL*: Factor V Leiden; *PTHR*: Prothrombin; *MTHFR*: Methylenetetrahydrofolate reductase; NP: Not provided.

studies have already shown a rise in the concentration of coagulation inhibitor proteins after a surgical correction directly bypassing the venous obstruction[17,18], confirming this hypothesis. However, even with our restrictive working definition of prot C and S deficit (less than 0.7 × prothrombin rate), we have found a high prevalence of these disorders, suggesting that their role is more relevant in pediatric than in adult PVT. Larger numbers with detailed family history (difficult to recruit in this setting) would be required to gain further insight into this finding.

In our population the *MTHFR-C677T* polymorphism was much more frequent in patients than in controls, suggesting that it behaves as a risk factor for PVT. However, in our cohort no difference in the levels of homocysteine between controls and patients was found. Thus, this polymorphism is not always associated with high plasma levels of homocysteine[19,20], even in patients with documented thrombotic events and no other risk factor for thrombophilia. This raises the question of whether the *MTHFR* gene polymorphism, without hyperhomocysteinemia, may itself contribute to thrombophilia. On the other hand, intermittent hyperhomocysteinemia may occur, which is not easily detectable even if clinically significant. In addition, the interpretation of homocysteine levels in these patients is problematic. Dietary imbalances, such as an inadequate intake of folate and vitamin B12 which are needed to break down excess homocysteine or methionine overabundance from dietary protein, may play a critical role in homocysteine metabolism[21,22].

Although the association between the *MTHFR* mutation and thrombosis has not yet been fully clarified[6,23,24], anticoagulation may be indicated in patients with *MTHFR* mutation (either homozygous or heterozygous, with or without hyperhomocysteinemia)[25] with previous thrombotic events and other thrombotic risk factors (pregnancy, oral contraceptives, surgery, sepsis and immobilization). Therefore, our data suggest that the presence of *MTHFR* mutations should be investigated in all pediatric patients with PVT. In addition, if hyperhomocysteinemia is present, therapy with folic acid and B6 and B12 vitamins should be instituted.

Another finding of this study was the lower prevalence of GI varices in patients with prothrombotic disorders. This might be an association by chance, or could reflect that those patients with a thrombophilic factor were more likely to be diagnosed in a phase of "recent thrombosis", when varices still have not developed. At any rate, no differences were observed in the clinical evolution of PVT between patients with genetic anomaly and those without.

In summary, most pediatric patients with PVT have local prothrombotic factors, which are probably the most important factors leading to PVT (Table 4). However, there is a clear association between the presence of prothrombotic disorders and PVT, suggesting that these increase the risk of thrombosis in patients with local factors such as perinatal UVC or sepsis. Patients with PVT should be screened for inherited prothrombotic disorders regardless of a history of an obvious local risk factor. Future trials should evaluate the role of prophylactic low molecular weight heparins in children requiring UVC, especially in those with a family history of thrombotic events or other thrombotic risk factors.

COMMENTS

Background

Portal vein thrombosis (PVT) is a common cause of portal hypertension. To date, the pathogenesis of PVT in children still remains unexplained despite the fact that it is the major cause of portal hypertension in children and adolescents. Unlike in adults, studies of thrombophilic disorders in children are scant, and to date only a few studies have evaluated the prevalence of hereditary thrombophilic disorders in children and adolescents with PVT.

Research frontiers

To date, many pediatric patients with PVT have local prothrombotic factors, which are probably the most important factors leading to PVT. However, there is a clear association between the presence of prothrombotic disorders and PVT, suggesting that these increase the risk of thrombosis in patients with local factors such as perinatal umbilical vein catheterization (UVC) or sepsis. Patients with PVT should be screened for inherited prothrombotic disorders regardless of a history of an obvious local risk factor. Future studies should evaluate the role of prophylactic low molecular weight heparins in children requiring UVC.

Innovations and breakthroughs

This series is the larger ever published so far. In this study the authors show that most patients with pediatric PVT have a history of a local prothrombotic factor, a figure much higher than that reported for adult portal vein thrombosis (around 30%). The authors suggest extending the thrombophilic screening of three different genetic mutations to better analyze this population.

Applications

Patients with PVT should be screened for inherited prothrombotic disorders regardless of a history of an obvious local risk factor.

Peer review

This is a well written and important contribution to the pediatric literature. The paper describes the wider case series of patients with these conditions and few published series are present at the moment, the data could be of interest for the readers.

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