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Etiology, presenting features and outcome of children with non-cirrhotic portal vein thrombosis: A multicentre national study

Angelo Di Giorgio[a], Paola De Angelis[b], Maurizio Cheli[c], Pietro Vajro[d], Raffaele Iorio[e], Mara Cananzi[f], Silvia Riva[g], Giuseppe Maggiore[h], Giuseppe Indolfi[i], Pier Luigi Calvo[j], Emanuele Nicastro[a], Lorenzo D'Antiga[a,*]

[a] Paediatric Liver, GI and Transplantation, Hospital Papa Giovanni XXIII Bergamo, Bergamo, Italy
[b] Paediatric Surgery and Endoscopy, Ospedale Pediatrico Bambino Gesù, Roma, Italy
[c] Paediatric Surgery, Hospital Papa Giovanni XXIII Bergamo, Bergamo, Italy
[d] Department of Medicine, Surgery and Dentistry "Scuola Medica Salernitana" Section of Pediatrics, University of Salerno, Baronissi (Salerno), Italy
[e] Paediatric Liver Unit, Department of Translational Medical Science, University of Naples Federico II, Naples, Italy
[f] Unit of Pediatric Gastroenterology and Hepatology, Dpt. of Women's and Children's Health, University Hospital of Padova, Italy
[g] Paediatric department and transplantation, Ismett, Palermo, Italy
[h] Paediatric Section of the Department of Medical Sciences, University of Ferrara, Ferrara, Italy
[i] Paediatric Liver, Ospedale Pediatrico Meyer, Firenze, Italy
[j] Paediatric Gastroenterology, Department of Pediatrics, Azienda Ospedaliera–Universitaria Cittadella Salute e della Scienza di Torino, University of Torino, Torino, Italy

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ABSTRACT

Objectives: Non-cirrhotic portal vein thrombosis (PVT) is a main cause of portal hypertension in children. We describe the characteristics at presentation and outcome of a cohort of patients with PVT to determine clinical features and predictors of outcome.
Methods: We recorded: (1) Associated factors: prematurity, congenital malformations, neonatal illnesses, umbilical vein catheterization (UVC), deep infections, surgery; (2) congenital and acquired prothrombotic disorders; (3) features at last follow up including survival rate and need for surgery.
Results: 187 patients, mean age at diagnosis 4 ± 3.7 years, had a history of prematurity (61%); UVC (65%); neonatal illnesses (79%). The diagnosis followed the detection of splenomegaly (40%), gastrointestinal bleeding (36%), hypersplenism (6%), or was incidental (18%). Of 71 patients who had endoscopy at presentation 62 (87%) had oesophageal varices. After 11.3 years' follow up 63 (34%) required surgery or TIPS. Ten-year survival rate was 98%, with 90% shunt patency. Spleen size, variceal bleeding and hypersplenism at presentation were predictors of surgery or TIPS ($p < 0.05$).
Conclusion: PVT is associated with congenital and acquired co-morbidities. History of prematurity, neonatal illnesses and UVC should lead to rule out PVT. Large spleen, variceal bleeding and hypersplenism at presentation predict the need for eventual surgery in a third of cases.

1. Introduction

Extrahepatic portal vein obstruction (EHPVO) is defined by the obstruction of the extrahepatic portal vein (PV) with or without the involvement of the intrahepatic portal branches. Portal vein thrombosis (PVT) is the most prevalent cause of EHPVO, whereas congenital abnormalities, such as PV stenosis, atresia, or agenesis, are uncommon [1]. PVT is the most common cause of non-cirrhotic, presinusoidal, and prehepatic portal hypertension (PH) in children in low income countries, accounting for 60% of cases of PH compared to 20% in the western world [2,3].

Children with PVT develop complications of PH at different ages, from infancy to adulthood, and are referred to liver centres with varied manifestations, including gastrointestinal (GI) haemorrhage from variceal bleeding, splenomegaly and hypersplenism, and less commonly with ascites [4].

Pathogenetic mechanisms leading to PH are mainly related to the increased vascular resistance in the portal venous system due

* Corresponding author at: Paediatric Hepatology, Gastroenterology and Transplantation, Hospital Papa Giovanni XXIII di Bergamo, Piazza OMS1, 24127 Bergamo, Italy.
E-mail address: ldantiga@asst-pg23.it (L. D'Antiga).

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to thrombus formation; a so-called "cavernous transformation" of the PV represents a tentative to bypass the thrombus and replace a physiological portal venous flow or, more commonly, establish a spontaneous porto-systemic shunt [5].

Complications of PH are principally managed by a conservative strategy based on medical and endoscopic therapy. However, if these fail, more aggressive strategies are required to control the bleeding, including radiological and surgical procedures [6]. Transjugular intrahepatic portosystemic shunt (TIPS) is a radiological procedure that can be technically feasible even in children with PVT if there is a large collateral vessel of the portal cavernoma [7,8]. However, the meso-portal bypass (MPB) represents the best option to restore a physiological flow through the intrahepatic portal venous system [9].

The aetiology of PVT is considered multifactorial, but commonly associated with hereditary prothrombotic conditions and predisposing local factors which may cause a procoagulable state and vessel damage respectively, leading to thrombus formation. However, no etiological factors can be identified in up to 50% of cases [10,11].

In this study we aim to report the characteristics at diagnosis, the prevalence of prothrombotic disorders and possible risk factors, as well as data on long-term outcome of a large cohort of Italian children with PVT.

2. Methods

2.1. Study population

A questionnaire was sent to 11 major pediatric hepatology centres in Italy to collect data of children with PVT managed in the last 20 years.

The questionnaire comprised 36 questions referring to patient demographic features (n = 3 questions), neonatal history (n = 8), characteristics at diagnosis of PVT (n = 16), and data at last follow up (n = 9). The questions were expressed in a simple way (possible answer: "yes or not") in order to achieve a high level of completeness. Further details were required when the answer was "yes" (see Supplementary document 1). The overall survey response rate was defined as: the number of centres who responded to the survey; the percentage of received answer (PRA) as a percentage ratio between the number of received answers for each question; the total number of patients.

Inclusion criteria to enter the patients' data were: diagnosis of PVT based on Doppler ultrasonography (US), computerised tomography (CT), or magnetic resonance imaging (MRI) scans, demonstrating portal vein obstruction, presence of intraluminal material, or portal vein cavernoma. Children who had also an occlusion of the splenic, superior mesenteric, and coronary veins were included in the study. Conversely, the patients with an isolated splenic vein thrombosis (known as left-side portal hypertension) or an underlying chronic liver disease were excluded from the study.

We collected data on clinical features at birth and at diagnosis, including: age, gender, type of presentation (defined by signs or symptoms that brought the patient to medical attention), physical examination, laboratory investigations (blood count and liver function tests), radiological investigations, endoscopy.

We hypothesised the following characteristics may represent risk factors for PVT:

- Inherited prothrombotic disorders including factor V gene G1691A mutation (factor V Leiden), prothrombin gene G20210A mutation, methylenetetrahydrofolate reductase (MTHFR) gene C677T mutation and primary deficiencies of coagulation inhibitor proteins (proteins C, S, and antithrombin) [12].
- Acquired prothrombotic disorders including myeloproliferative neoplasms, the antiphospholipid antibody syndrome (APS), paroxysmal nocturnal haemoglobinuria [13].
- Clinical factors possibly involved in the pathogenesis of PVT including history of umbilical venous catheterization (UVC), omphalitis, deep infections (e.g. sepsis), associated neonatal illnesses (jaundice, respiratory distress, TORCH infections, haematological diseases, pneumonia, urinary infections, failure to thrive), congenital malformations, splenectomy, sickle cell anaemia, trauma, abdominal surgery [14,15].

Lastly, we collected data of the last follow up to have information on survival and the type of treatment required to control variceal bleeding: "conservative treatment" (endoscopy and medical therapy) vs "surgery or TIPS".

2.2. Management of PH complications

The protocol used for managing the complications of PH in children with PVT in the study period was extensively reported in a previous study [6].

Shortly, children with PVT underwent surveillance endoscopies when features of PH arose (e.g. splenomegaly and hypersplenism). "Conservative management" including non-selective beta blockers (NSBBs) and endoscopic variceal obliteration (EVO) was used when large (or Grade 3) varices (=oesophageal varices occupying more than one third of the lumen) were detected [1]. In case of persistent large varices despite medical and endoscopic treatment, a retrograde portogram and a contrast enhanced computerised tomography angiogram was carried out and, if a patent Rex recessus was documented, the patients underwent meso-portal bypass (MPB). Those with an obliterated Rex recessus were considered for shunt surgery or transjugular intrahepatic portosystemic shunt (TIPS). Surgery was considered also in children with severe hypersplenism (platelet count below 30000/mm^3, white cell count below 2000/mm^3, or transfusion dependent anaemia).

2.3. Prognostic indicators and statistical analysis

In order to identify predicting factors for different type of treatments ("conservative" vs "surgery or TIPS") the patients were divided into two groups:

- Group 1 (G1): patients managed by conservative treatment (B-blockers and/or endoscopy).
- Group 2 (G2): patients who underwent surgery or TIPS.

The protocol adopted within the group G2 considered a patient eligible for surgery in case of: (1) Refractory oesophageal varices despite endoscopic eradication; (2) Severe hypersplenism (platelet count <30000/mm^3, white cell count below 2000/mm^3, or transfusion dependent anaemia).

The following parameters were compared: gender, age at diagnosis, presence of prematurity, history of neonatal illnesses, UVC, symptoms of PH at diagnosis (at least one among episode of GI bleeding or splenomegaly), any grade of oesophageal varices at endoscopy performed at diagnosis, hypersplenism (defined by platelet count <150000/mm^3).

Data are reported as means and standard deviations. Univariate analysis was performed in Microsoft Excel and IBM-SPSS 13.0 for Windows. Pearson chi square and Mann–Whitney tests were used to compare the percentages between the two groups. A p value of 0.05 or less was assigned significance.

3. Results

We reported data from 9 out of 11 centres. Survey response rate was 82%, and the level of completeness of each question was high. We collected data on 187 children with a mean age at presentation of 4 years ± 3.7; 101 (54%) were male (Table 1).

All centres had managed children with PVT according to the protocol reported above.

3.1. Risk factors for the development of PVT

Inherited prothrombotic disorders: Pro-thrombotic screening was performed in 76/187 patients (41%); 15/76 patients (20% of those tested) had low serum anticoagulant protein C and S (protein C alone in 6 patients, protein alone S in 2 and a combined deficiency in 7), and 15/76 patients (20%) had a mutation in prothrombin gene (2 patients), Factor V Leiden (2 patients), MTHFR (11 patients) (Table 2). No patient had history of acquired prothrombotic disorders.

Clinical factors possibly involved in the pathogenesis of PVT: History of prematurity (data on 172 patients, PRA 92%) was reported in 105 neonates (61%), of whom 21 (20%) were extremely preterm (<28 weeks); 38 patients (36%) were very preterm (<32 > 28 weeks) and 46 (44%) were moderate or late preterm (<37 > 32 weeks). Associated neonatal illnesses (data on 156 patients, PRA 83%) were documented in 123 patients (79%) including respiratory complications of prematurity in 70 (53%), cardiac malformations in 12 (9%), non-cardiac malformations in 13 (11%), deep infections (sepsis and omphalitis) in 112 (8%), haematological disorders in 8 (6%) and other disorders in 9 (7%). History of umbilical-vein catheterisation (data on 165 patients; PRA 88%) was reported in 107 (65%) neonates (Table 1).

Table 1
Risk factors and clinical features at diagnosis of 187 Italian children with portal vein thrombosis

Risk factors	
Gender	
Female	86/187 (46%)
Male	101/187 (54%)
Gestational age	
Term	70/172 (41%)
Preterm	105/172 (61%)
Associated neonatal illnesses	
Complications of prematurity	123/156 (79%)
Cardiac malformations	70 (53%)
Non-cardiac malformations	12 (9%)
Infections (sepsis or omphalitis)	13 (11%)
Haematological disorders	11 (9%)
Miscellaneous	8 (6%) 9 (7%)
Umbilical catheterization	107/165 (65%)
Phenotype at diagnosis	
Age at diagnosis (yrs)	4.0 y (SD 3.7)
Type of presentation	
Detection of splenomegaly	68/172 (40%)
Gastrointestinal bleeding	63/172 (36%)
Detection of hypersplenism	10/172 (6%)
Incidental	31/172 (18%)
Laboratory features (mean values)	
WBC (mm/3)	6.074 (SD 3.342)
Haemoglobin (gr/dl)	10.4 (SD 2.4)
PLT (mm/3)	141.978 (SD 103.583)
INR	1.17 (SD 0.16)
Total bilirubin (mg/dl)	0.9 (SD 0.3)
Ascites	3/172 (2%)
Upper varices at first endoscopy	62/71(87%)

WBC: white blood cell count; PLT: platelet count; INR: International Normalised Ratio.

Table 2
Inherited prothrombotic disorders in 76 patients with EHPVO.

Parameters	All patients N = 76 (%)	G1 N = 53 (%)	G2 N = 23 (%)	P value
Protein C deficiency[a]	6 (20%)	5 (83%)	1 (17%)	0.04
Protein S deficiency[a]	2 (7%)	1 (50%)	1 (50%)	1.00
Protein C and S deficiency[a]	7 (23%)	5 (71%)	2 (28%)	0.14
Prothrombin (G20210A)	2 (7%)	2 (100%)	0 (0%)	0.16
Factor V leiden-M	2 (7%)	2 (100%)	0 (0%)	0.16
MTHFR (C677T and A1298C)	11 (37%)	8 (73%)	3 (27%)	0.04
Positive Pro-thrombotic screening	30 (39%)	23 (77%)	7 (23%)	0.21

MTHFR: methylenetetrahydrofolate reductase. G1 = patients managed conservatively; G2 = patients managed with surgery or TIPS.
[a] serum protein C and S below the normal values.

3.2. Presenting features

The clinical manifestations that led to the diagnosis (data on 172 patients, PRA 92%) were the detection of splenomegaly in 68 (40%), gastrointestinal bleeding in 63 (36%), hypersplenism in 10 (6%), incidental in 31 patients (18%) (mostly in correspondence of the follow up of prematurity).

On full blood count the mean values were white blood cells (WBC) 6070/mm^3 (±3342); Hb 10.4 gr/dl (±2.4); platelet count 141978/mm^3 (±103583); mean INR was 1.17 (±0.16); total bilirubin 0.9 mg/dl (±0.3). Hypersplenism (platelet count < 150000/mm^3) was reported in 69% (58 patients, data available in 84, PRA 45%); 41% of patients (35/84 patients) had a platelet count < 100000/mm^3.

In 15 patients (8%) the data on presenting features were unknown.

Among 71 patients who had the first endoscopy at the time of diagnosis (data on 121 patients, PRA 65%), 62 (87%) had oesophageal varices, of whom 56 had already large varices requiring endoscopic treatment. Ascites (data on 172 patients, PRA 92%) was documented on liver ultrasound only in 3 patients (Table 1).

3.3. Data at last follow up

After a mean follow up of 11.2 years (±4.8) 185 patients (99%) survived (data on 187%, PRA 100%), 2 patients (1%, aged 2 and 6 years, both with bronchopulmonary dysplasia and chronic lung disease due to prematurity) died from pneumonia (Table 3).

At last follow up (data on 187 patients, PRA 100%), 124 patients (66%) were treated conservatively and 63 (34%) had undergone sur-

Table 3
Data at last follow up in 187 children with EHPVO.

Mean follow up	11.2 years (SD 4.8)
Survived	185/187 (99%)
Died	2/187 (1%)
Conservative treatment	124/187 (66%)
Surgery or TIPS	63/187 (34%)
Meso-Rex bypass[a]	30 (48%)
Distal spleno-renal shunt	16 (25%)
Proximal spleno-renal shunt[b]	7 (11%)
Meso-caval shunt[c]	4 (6%)
Isolated splenectomy	2 (3%)
Porto-caval shunt	1 (2%)
Liver Tx	1 (2%)
TIPS	2 (3%)
Patent Shunts at last FU	54/60 (90%)

TIPS: transjugular intra-hepatic porto-systemic shunt; TX: liver transplantation; FU: follow up.
[a] n. 1 shunt was obstructed at last follow up.
[b] n. 4 shunts were obstructed at last FU.
[c] n. 1 shunt obstructed at last FU.

Table 4
Comparison of features at presentation between the two groups (G1 vs G2).

Features at presentation	All patients n = 187	Group 1 n = 124 (%)	Group 2 n = 63 (%)	OR (95% C.I)	*P* value
Sex					
F	86/187 (46%)	57/124 (46%)	29/63 (46%)		
M	101/187 (54%)	67/124 (54%)	34/63 (54%)	1.00 (0.54–1.84)	0.993[b]
Age	2.98 (0.1–16.9)	3.17 (0.1–16.9)	2.85 (0.2–15.5)	0.99 (0.91–1.07)	0.91[b]
Prematurity	105/172(61%)	70/114 (61%)	35/58 (55%)	0.77 (0.41–1.47)	0.432[c]
Neonatal associated illnesses	123/156 (79%)	84/104 (81%)	39/52 (75%)	0.71 (0.32–1.58)	0.406[b]
UV-Cathether	107/165 (65%)	74/108 (68%)	33/57 (58%)	0.63 (0.32–1.23)	0.174[b]
Complications of PH[a]	145/173 (84%)	92/115 (80%)	53/58 (91%)	2.65 (0.95–7.38)	0.055[b]
Varices (grade 1–3)	62/71 (87%)	41/49 (84%)	21/22 (95%)	4.40 (0.51–37.50)	0.144[b]
Hypersplenism	58/84 (69%)	35/58 (60%)	23/26 (88%)	5.03 (1.35–18.73)	0.010[b]

Group 1 = children managed conservatively; Group 2 = patients managed with surgery or TIPS. UV: umbilical-vein; PH: portal hypertension.
[a] At least one feature among GI bleeding from varices and splenomegaly.
[b] Pearson chi square test was used to compare the percentages between the two groups.
[c] Mann–Whitney test was used to compare the age between the two groups.

gical or radiological procedures including meso-portal bypass in 30 (48%), distal spleno-renal shunt in 16 (25%), proximal spleno-renal shunt in 7 (11%), meso-caval shunt in 4 (6%), isolated splenectomy in 2 (3%), TIPS in 2 (3%), porto-caval shunt in 1 (2%), and liver transplantation in 1, because of development of hepatopulmonary syndrome.

All patients were on stable conditions at the time of surgical operation. No major complications were reported after surgery. However, two children who underwent surgical meso-caval shunt developed a slight increase in serum ammonia (2 × ULN) in absence of overt encephalopathy; both patients were treated with oral lactulose and rifaximin successfully.

Two patients (both male, aged 14 and 17 years, the first one who had already undergone splenectomy as a treatment of hereditary spherocytosis) were not considered for MPB procedure due to Rex recessus closure. Both had a large collateral vessel of the portal cavernoma which could be utilised for TIPS placement. Therefore, in view of favourable anatomy and in presence of a local expertise, both patients underwent TIPS placement successfully (details are reported in our previous study) [7].

The surgical or radiological shunt (total n = 60) was patent in 54 patients (90%) and obstructed in 6 (10%, 4 with proximal spleno-renal shunt, 1 with meso-portal bypass, and 1 with meso-caval shunt).

Propranolol was utilised in 6 out of 9 centres (67%), and overall it was given for the secondary prophylaxis of variceal bleeding in 47 patients (36%, data on 129 patients, PRA 69%).

3.4. Predicting factors of surgery or TIPS

Comparing by univariate analysis the patients treated conservatively (Group 1) with those who underwent invasive procedures (Group 2), we found that gender, age at diagnosis, history of UVC, associated neonatal illnesses, and presence of any grade of varices at first endoscopy were not associated, while spleen size, variceal bleeding and severe hypersplenism at diagnosis predicted the severity of portal hypertension, and therefore the need for surgery or TIPS ($p < 0.05$) (Table 4).

On multivariate analysis, the presence of PH complications increased the risk of invasive approaches but without a statistical significance [OR: 2.01 (95%CI: 0.19–21.09); $p = 0.560$].

Conversely, hypersplenism resulted to be independently associated with the need of surgical treatment [OR: 4.06 (95%CI: 0.95–17.23); $p = 0.057$].

4. Discussion

This is a large multicentre survey carried out in Italy on clinical features and outcome of children with PVT. We identified a possible causative factor in the majority of patients (85%), and failed in 15% of them. This percentage is higher than that reported in the literature which refers of approximately 50% of cases of PVT which remain without a defined etiology [16,17]. Umbilical vein catheterization is a well-recognised associated factor in PVT [18,19]. We reported a history of UVC in 65% of cases, while in the literature the incidence of PVT-related catheter ranges from 0 to 43% [20]. In this study, the high rate of UVC is likely related to the high percentage of preterm babies in whom the UVC is very commonly inserted to gain a central venous access and manage the complications of prematurity [21].

Other factors associated with the initiation and propagation of thrombosis may include patient characteristics, such as low birth weight, hypercoagulability, sepsis, and congenital malformations [22,23]. The high rate of prematurity (61%) and of neonatal associated illnesses (79%) among our patients certainly represented contributing factors to thrombus formation. The most common neonatal illness were the respiratory complications of prematurity (53%) and congenital malformations (20%), while sepsis was documented in only 9% of cases. In the literature the prevalence of sepsis is quite variable [18–23]; in Shakka's study, among 17 neonates with PVT, the percentage of patients who experienced sepsis was 65% of cases [24].

The most common type of presentation included the detection of splenomegaly and hypersplenism and an episode of GI bleeding. Similarly, Ferri et al. reported upper GI bleeding and splenomegaly as the initial clinical manifestation in 50% and 37.5% of children with PVT respectively [15]. The same results are reported by other authors [3,4,25,26]. This confirms that PVT diagnosis is often delayed, and strengthens what reported in the literature suggesting that, since PVTs rarely causes clinical problems during the neonatal period, the majority of cases may remain unrecognised and are discovered later in childhood [16]. PVT should always be in the differential diagnosis of children with afebrile palpable spleen [2].

Hereditary conditions that are known to predispose to venous thrombosis and PVT include mutations of prothrombin (PTHR), factor V Leiden (FVL) or methylenetetrahydrofolate reductase (MTHFR) genes, or deficiency of one of the natural anticoagulant proteins C and S [27,28]. The association between venous thrombosis and these defects has been well defined [29]. Conversely, the association between heritable thrombophilias and the development of PVT is still debated. In our study a prothrombotic genetic disorder was documented in 39% of patients, similarly to a previous study [30]. A deficit of proteins C and S was documented in 50% of the our patients. Conversely Seixas et al. found that hereditary protein C or protein S deficiency was not an etiological factor for PVT in children [31]. In adults, isolated protein C and protein S deficiency have been detected in approximately 30% of patients with PVT [28,30,31]. Remarkably, low values of protein C and S could

be a reflection of impaired liver synthetic function due to chronic ischemia, rather than being genetically determined [30,31].

The other 50% of our tested patients had a genetic mutations in MTHFR gene (11 patients), prothrombin gene (2 patients), and Factor V leiden (2 patients). The association between the MTHFR mutation and thrombosis has not been fully clarified [32]. In Pietrobattista's study the MTHFR-C677T polymorphism was much more frequent in patients than in controls, suggesting that it might represent a risk factor for PVT. However, no difference in the levels of homocysteine between controls and patients was found [30]. Gurakan et al. and Seixas et al. failed to demonstrate an association between factor V Leiden mutation and PVT [33,34]. We do not have available data on JACK2-VS17 mutation in our cohort of patients. This gene is strongly implicated in the pathogenesis of myeloproliferative disorders and it may be associated with increased rates of thrombosis [35]. Primigani et al. and Kiladjian et al. have examined JAK2-V617F in adult patients with idiopathic PVT and Budd–Chiari syndrome, and found JAK2 mutation in 36% and 34% of patients with PVT and 40% and 45% of patients with Budd–Chiari syndrome, respectively [36,37]. Conversely, no JAK2-V617F mutation was found in two previous studies of 19 and 30 children with PVT, demonstrating that the role of this gene mutation in this setting is still unclear [11,38]. The high prevalence of risk factors and congenital prothrombotic disorders that we reported in this study suggest a crucial role of both conditions in the development of PVT. This association between system illnesses, local triggers and prothrombotic factors was demonstrated in a case-control study of 31 children with PVT and 26 age-matched controls.

The results from this study confirmed that PVT is a liver disorder associated with a low mortality rate [10,15,39]. The majority of patients were managed conservatively while one third required surgical procedures, and only a small percentage of patients (n = 13) underwent MPB. Propranolol was used in a small proportion of patients confirming that its use is still questionable [1].

MPB should be considered as the primary approach in children with PVT, even in absence of clinical complications of portal hypertension [1]. However this study collected data on patients managed in the last 20 years, during which MPB was considered indicated only after failure of medical and endoscopic management. Despite that, MPB was performed in nearly 50% of children who were candidate for surgery suggesting that, among the Italian centres, this procedure is considered the best surgical treatment option to restore a physiological intra-hepatic venous flow.

In Lautz's study the authors demonstrated the feasibility of MPB procedure in 65 out of 88 children [40]. However the need of favourable anatomy (e.g. patency of recess rex), the general medical condition and a surgical/institutional qualification may contribute to the reduced utilisation of this procedure. In our experience, in a study on 65 children with PVT, the Rex recessus resulted patent and MPB resulted feasible only in 44% of cases.

This was possibly related to the large number of patients having a history of UVC, considered at higher risk of intrahepatic extension of the thrombus [6].

In patients requiring surgery, but with anatomical features unsuitable for MPB or TIPS, a surgical porto-systemic shunt is the remaining option. Although the choice of shunt surgery may not be obvious, in general the meso-caval shunt has a high rate of success and patency in the long term, whereas a distal spleno-renal shunt may preserve from severe bouts of hyperammonemia. However, if there is a huge spleen and deep hypersplenism, a proximal spleno-renal shunt with splenectomy may be considered as the best option.

The limitation of this study is related to the fact that this is a survey, and therefore the large number of collected patients is not accompanied by the completeness of the records, such as the endoscopic features at diagnosis and the pro-thrombotic screening in all patients. Nevertheless, it includes information on the largest series of children with PVT published so far.

In conclusion, the development of PVT is associated with congenital and acquired etiological predisposing factors. The diagnosis of PVT is often overlooked, and made once the complications of portal hypertension are already established, therefore better awareness of this condition is advocated. History of prematurity, neonatal systemic illnesses and UVC insertion should lead to rule out PVT by a doppler ultrasound performed before discharge from the neonatal unit. Despite the good survival, a large spleen, variceal bleeding and hypersplenism at presentation predict the need for eventual surgery in a third of cases.

Conflict of interest

None declared.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.dld.2019.02.014.

References

[1] Shneider BL, de Ville de Goyet J, Leung DH, Srivastava A, Ling SC, Duché M, et al. Primary prophylaxis of variceal bleeding in children and the role of MesoRex Bypass: summary of the Baveno VI Pediatric Satellite Symposium. Hepatology 2016;63(April (4)):1368–80.

[2] Gugig R, Rosenthal P. Management of portal hypertension in children. World J Gastroenterol 2012;18(11):1176–84.

[3] Poddar U, Thapa BR, Rao KL, Singh K. Etiological spectrum of esophageal varices due to portal hypertension in Indian children: is it different from the West? J Gastroenterol Hepatol 2008;23:1354–7.

[4] Schettino GC, Fagundes ED, Roquete ML, Ferreira AR, Penna FJ. Portal vein thrombosis in children and adolescents. J Pediatr (Rio J) 2006;82:171–8.

[5] Di Giorgio A, D'Antiga L. In: Guandalini Stefano, Dhawan Anil, Branski David, editors. Portal hypertension in children, textbook of pediatric gastroenterology, hepatology and nutrition. 2016. p. 791–817.

[6] Alberti D, Colusso M, Cheli M, Ravelli P, Indriolo A, Signorelli S, et al. Results of a stepwise approach to extrahepatic portal vein obstruction in children. J Pediatr Gastroenterol Nutr 2013;57(November (5)):619–26.

[7] Di Giorgio A, Agazzi R, Alberti D, Colledan M, D'Antiga L. Feasibility and efficacy of transjugular intrahepatic portosystemic shunt (TIPS) in children. J Pediatr Gastroenterol Nutr 2012;54(May (5)):594–600.

[8] Lv Y, He C, Guo W, Yin Z, Wang J, Zhang B, et al. Transjugular intrahepatic portosystemic shunt for extrahepatic portal venous obstruction in children. J Pediatr Gastroenterol Nutr 2016;62(February (2)):233–41.

[9] de Ville de Goyet J, D'Ambrosio G, Grimaldi C. Surgical management of portal hypertension in children. Semin Pediatr Surg 2012;21(August (3)):219–32.

[10] Khanna R, Sarin SK. Idiopathic portal hypertension and extrahepatic portal venous obstruction. Hepatol Int 2018;12(Feburary (Suppl. 1)):148–67.

[11] Abd El-Hamid N, Taylor RM, Marinello D, Mufti GJ, Patel R, Mieli-Vergani G, et al. Aetiology and management of extrahepatic portal vein obstruction in children: King's College Hospital experience. J Pediatr Gastroenterol Nutr 2008;47(November (5)):630–4.

[12] Heller C, Schobess R, Kurnik K, Junker R, Günther G, Kreuz W, et al. Abdominal venous thrombosis in neonates and infants: role of prothrombotic risk factors — a multicenter case-control study. For the Childhood Thrombophilia Study Group. Br J Haematol 2000;111:534–9.

[13] Levine RL, Wadleigh M, Cools J, Ebert BL, Wernig G, Huntly BJ, et al. Activating mutation in the tyrosine kinase JAK2 in polycythemia vera, essential thrombocythemia, and myeloid metaplasia with myelofibrosis. Cancer Cell 2005;7:387–97.

[14] Rees DC, Cox M, Clegg JB. World distribution of factor V Leiden. Lancet 1995;346:1133–4;
Weiss B, Shteyer E, Vivante A, et al. Etiology and long-term outcome of extrahepatic portal vein obstruction in children. World J Gastroenterol 2010;16:4968–72.

[15] Ferri PM, Rodrigues Ferreira A, Fagundes ED, Xavier SG, Dias Ribeiro D, Fernandes AP, et al. Evaluation of the presence of hereditary and acquired thrombophilias in Brazilian children and adolescents with diagnoses of portal vein thrombosis. J Pediatr Gastroenterol Nutr 2012;55(November (5)):599–604.

[16] Alvarez F, Bernard O, Brunelle F, Hadchouel P, Odièvre M, Alagille D. Portal obstruction in children. I. Clinical investigation and hemorrhage risk. J Pediatr 1983;103:696–702.

[17] Weiss B, Shteyer E, Vivante A, Berkowitz D, Reif S, Weizman Z, et al. Etiology and long-term outcome of extrahepatic portal vein obstruction in children. World J Gastroenterol 2010;16:4968–72.

[18] Glimelius B, Busch C, Hook M. Binding of heparin on the surface of cultured human endothelial cells. Thromb Res 1978;12, 773e82.
[19] Pottecher T, Forrler M, Picardat P, Krause D, Bellocq JP, Otteni JC. Thrombogenicity of central venous catheters: prospective study of polyethylene, silicone and polyurethane catheters with phlebography or post-mortem examination. Eur J Anaesthesiol 1984;1, 361e5.
[20] Williams S, Chan AK. Neonatal portal vein thrombosis: diagnosis and management. Semin Fetal Neonatal Med 2011;16(Decembre (6)):329–39.
[21] Yadav S, Dutta AK, Sarin SK. Do umbilical vein catheterization and sepsis lead to portal vein thrombosis? A prospective, clinical, and sonographic evaluation. J Pediatr Gastroenterol Nutr 1993;17:392–6.
[22] Gharehbaghi MM, Nemati M, Hosseinpour SS, Taei R, Ghargharechi R. Umbilical vascular catheter associated portal vein thrombosis detected by ultrasound. Indian J Pediatr 2011;78, 161e4.
[23] Krafte-Jacobs B, Sivit CJ, Mejia R, Pollack MM. Catheter-related thrombosis in critically ill children: comparison of catheters with and without heparin bonding. J Pediatr 1995;126, 50e4.
[24] Sakha SH, Rafeey M, Tarzamani MK. Portal venous thrombosis after umbilical vein catheterization. Indian J Gastroenterol 2007;26, 283e4.
[25] Jain M, Jain J, Passi GR, Jain K, Jain S. Profile of extrahepatic portal venous obstruction among children in Central India. Clin Exp Hepatol 2017;3(Decembre (4)):209–11.
[26] El-Karaksy HM, El-Koofy N, Mohsen N, Helmy H, Nabil N, El-Shabrawi M. Extrahepatic portal vein obstruction in Egyptian children. J Pediatr Gastroenterol Nutr 2015;60(January (1)):105–9.
[27] Kosch A, Junker R, Kurnik K, Schobess R, Günther G, Koch H, et al. Prothrombotic risk factors in children with spontaneous venous thrombosis and their asymptomatic parents: a family study. Thromb Res 2000;99:531–7.
[28] Fisher NC, Wilde JT, Roper J, Elias E. Deficiency of natural anticoagulant proteins C, S, and antithrombin in portal vein thrombosis: a secondary phenomenon. Gut 2000;46:534–9.
[29] Gurgey A, Mesci L, Renda Y, Olcay L, Kocak N, Erdem G. Factor V Q 506 mutation in children with thrombosis. Am J Hematol 1996;53:37–9.
[30] Pietrobattista A, Luciani M, Abraldes JG, Candusso M, Pancotti S, Soldati M, et al. Extrahepatic portal vein thrombosis in children and adolescents: Influence of genetic thrombophilic disorders. World J Gastroenterol 2010;16(December (48)):6123–7.
[31] Seixas CA, Hessel G, Siqueira LH, Machado TF, Gallizoni AM, Annichino-Bizzacchi JM. Study of hemostasis in pediatric patients with portal vein thrombosis. Haematologica 1998;83:955.
[32] Seinost G, Renner W, Brodmann M, Winkler M, Köppel H, Pilger E. C677T mutation in the methylene tetrahydrofolate reductase gene as a risk factor for venous thrombotic disease in Austrian patients. Thromb Res 2000;100:405–7.
[33] Gürakan F, Gürgey A, Bakkaloğlu A, Koçak N. Homozygous factor V Leiden mutation in a child with Budd-Chiari syndrome. J Pediatr Gastroenterol Nutr 1999;28:516–7.
[34] Seixas CA, Hessel G, Ribeiro CC, Arruda VR, Annichino-Bizzacchi JM. Factor V Leiden is not common in children with portal vein thrombosis. Thromb Haemost 1997;77:258–61.
[35] Patel RK, Lea NC, Heneghan MA, Westwood NB, Milojkovic D, Thanigaikumar M, et al. Prevalence of the activating JAK2 tyrosine kinase mutation V617F in the Budd-Chiari syndrome. Gastroenterol 2006;130:2031–8.
[36] Primignani M, Barosi G, Bergamaschi G, Gianelli U, Fabris F, Reati R, et al. Role of the JAK2 mutation in the diagnosis of chronic myeloproliferative disorders in splanchnic vein thrombosis. Hepatology 2006;44:1528–34.
[37] Kiladjian J-J, Cervantes F, Leebeek FWG, Chevret S, Cazals-Hatem D, Plessier A, et al. Role of JAK2 mutation detection in Budd Chiari syndrome (BCS) and portal vein thrombosis (PVT) associated MPD [abstract]. Blood 2006;108:377.
[38] Caropreso M, Campanile R, Maddaluno S, Veropalumbo C, Piscopo C, Castaldo G, et al. Genetic prothrombotic risk factors in children with extrahepatic portal vein obstruction. J Pediatr Gastroenterol Nutr 2010;51:374.
[39] Maksoud-Filho JG, Gonçalves ME, Cardoso SR, Gibelli NE, Tannuri U. Long-term follow-up of children with extrahepatic portal vein obstruction: impact of an endoscopic sclerotherapy program on bleeding episodes, hepatic function, hypersplenism, and mortality. J Pediatr Surg 2009;44(October (10)):1877–83.
[40] Lautz TB, Keys LA, Melvin JC, Ito J, Superina RA. Advantages of the meso-Rex bypass compared with portosystemic shunts in the management of extrahepatic portal vein obstruction in children. J Am Coll Surg 2013;216(January (1)):83–9.