Letter to the Editor

What can hide a neonatal sepsis with subsequent foot amputation?

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Portal vein thrombosis (PVT) is defined as a partial or complete obstruction of the extrahepatic portal vein, due to the presence of a thrombus in the vessel lumen and documented by radiological imaging [1, 2]. It is one of the most common vascular disorders of the liver. Large cohort studies have reported a global prevalence of 1%, but in some risk groups it can be up to 26%. The most frequent causes are cirrhosis, hepatobiliary malignancy, abdominal infectious, inflammatory diseases and myeloproliferative disorders (MPD) [3]. Myeloproliferative disorders are recognized to be among the principal causes of PVT in non-cirrhotic patients [1]. The natural history of PVT results in portal hypertension leading to splenomegaly and formation of portosystemic collateral blood vessels and esophageal, gastric, duodenal, and jejunal varices [3]. Portal vein thrombosis is the leading cause of variceal bleeding in children [4]. Diagnosis of PVT is made by imaging, mainly Doppler ultrasonography [3].

A 10-year-old child attended our Pediatric Department in October 2014 for recurrent vomiting from about 3 months; the child had vomiting 1–2 days/week (10–15 episodes/day). The episodes were not associated with abdominal pain or fever or other symptoms. His mother reported weight loss of 1 kg in the last month, but the child continued to feed regularly, without rejection of particular foods.

His past medical history was characterized by foot amputation during the neonatal period because of a sepsis and consequent disseminated intravascular coagulation. The patient had no history of hematemesis, jaundice, abdominal distension or abdominal pain. There was no family history for coagulation disorders.

At admission the complete blood count was normal and the inflammatory markers were negative. Metabolic parameters were within normal limits (Table I). Aminoacidemia and aminoaciduria were normal. Celiac disease, food allergy and acute gastroenteritis were excluded.

A neurological study was performed to exclude a central cause of vomiting: the electroencephalogram was normal, and the brain magnetic resonance imaging (MRI) documented no encephalic abnormalities.

The child was also evaluated in the gastroenterological field. Abdominal ultrasound was performed, revealing: liver left lobe mild atrophy; thrombosis of the portal vein left branch with left hepatic artery hypertrophy (Figures 1 A and 1 B); perihepatic and perigastric collateral circulation supported by the left gastric vein; increased spleen size in relation to the age of the patient (longitudinal diameter 13.3 cm) with

Table I. Blood test and urinalysis

Parameter	Results	Normal value
Complete blood count and inflammation:		
Erythrocyte sedimentation rate [mm/h]	1	1–12
C-reactive protein [mg/dl]	< 0.290	0–0.5
Leukocytes [× 10^{-3}/µl]	9.30	4.00–10.00
Erythrocytes [× 10^{-6}/µl]	5.51	4.50–6.00
Platelets [× 10^{-3}/µl]	211	150–450
Metabolic parameters:		
Aspartate aminotransferase [U/l]	33	15–46
Alanine aminotransferase [U/l]	15	11–66
Glycemia [mg/dl]	87	75–110
Ammonia [µg/dl]	29	0–75
Total bilirubin [mg/dl]	0.50	0.20–1.30
Ceruloplasmin [mg/dl]	22	20–60
Uricemia [mg/dl]	4.4	3.5–8.5
Triglycerides [mg/dl]	61	0–200
Other causes of vomiting:		
Anti-transglutaminase IgA [UA/ml]	2.1	0.8–9.9 negative
Anti-transglutaminase IgG [UA/ml]	0.2	< 10 negative
Anti-endomysium	Negative	Negative
Coproculture for viruses and bacteria	Negative	Negative
Total IgE [kU/l]	206.0	0.0–155.0
Specific IgE *Dermatophagoides pteronyssinus* [kUA/l]	3.92	Positive > 0.35 kUA/l
Lactic dehydrogenase [U/l]	500	313–618
Hormonal parameters:		
Growth hormone [ng/ml]	0.4	0.0–4.7
Cortisol [µg/dl]	9.7	Morning 8.0–25.0
Insulin [µU/ml]	0.8	0.0–24.5
Coagulation parameters:		
D-dimer [ng/ml]	70	0–255
Prothrombin time (%)	93	> 70
INR	1.05	0.90–1.15
Activated partial thromboplastin time (aPTT) [s]	51.0	26.0–38.0
Fibrinogen [mg/dl]	194	220–450
Homocysteine [µmol/l]	7.60	0.00–15.00
Anti-cardiolipin IgM [GPL-U/ml]	< 2.0	0–13
Anti-cardiolipin IgG [GPL-U/ml]	< 2.0	0–20
Anti-B2 glycoprotein IgM [UA/ml]	0.1	0.0–10.0

Table I. Cont.

Parameter	Results	Normal value
Anti-B2 glycoprotein IgG [UA/ml]	0.0	0.0–10.0
Lupus anticoagulant LAC	Absent	Absent
Protein C anticoagulant (%)	74	> 70
Protein S anticoagulant (%)	64	> 70
Antithrombin III (%)	106	> 70
aPC Resistance	2.89	> 2.20
Urinalysis:		
pH	6.0	5.5–6.5
Glucose [mg/dl]	0	0–10
Protein [mg/dl]	20	0–20
Hemoglobin [mg/dl]	0.00	0
Ketones [mg/dl]	0.00	0
Bilirubin [mg/dl]	0.00	0
Urobilinogen [mg/dl]	0.2	0.2–1.0
Nitrites	Absent	Absent
Leukocyte esterase [Leu/µl]	0	0
Appearance	Opalescent	
Color	Straw yellow	
Specific weight	1.029	1.015–1.028
Sodium 24 h [mmol/day]	192.75	40.00–220.00
Potassium 24 h [mmol/day]	31.50	25.00–125.00
Chlorine 24 h [mmol/day]	165.00	110.00–250.00
Calcium 24h [mmol/day]	7.13	2.50–7.50

a homogeneous structure; venous splenic hilum slightly dilated (Figure 1 C). The esophagogastroduodenoscopy excluded the presence of esophageal varices.

We started looking for a possible cause of thrombosis. An extensive coagulation work-up was done. The first-level laboratory tests were normal (Table I). Genetic testing for factor V Leiden mutation was negative; genetic testing for MPL and JAK2 gene mutation excluded an MPD.

Combined presence of homozygous C>T mutation at position 677 (C677T) in the MTHFR gene and heterozygous G1691A mutation in the factor II gene was found.

The hematologist consultant considered it unnecessary to undertake thrombosis prophylaxis, because of the normal blood levels of homocysteine and D-dimer and the current lack of signs and/or symptoms referable to PVT. But he recommended homocysteine, vitamin B_{12} and folic acid annual assessment and thrombosis prophylaxis in case of surgery and prolonged immobilization.

The surgeon consultant advised performing abdominal ultrasound every year to monitor the spleen size.

Portal vein thrombosis is more common in developing countries (20% of all cases of portal hypertension compared to 5% in western countries) because of the poor standard of living, lack of medical care, and the different impact of infectious and inflammatory causes [5].

Portal vein thrombosis can be classified as acute or chronic depending on clinical and radiological presentation. Abdominal pain, nausea and fever within 2 months prior to hospital admission are signs of an acute PVT. Asymptomatic patients or those who present with signs and symptoms of portal hypertension (portal cavernoma, ascites, bleeding from gastroesophageal or ectopic varices) give evidence of a long-stand-

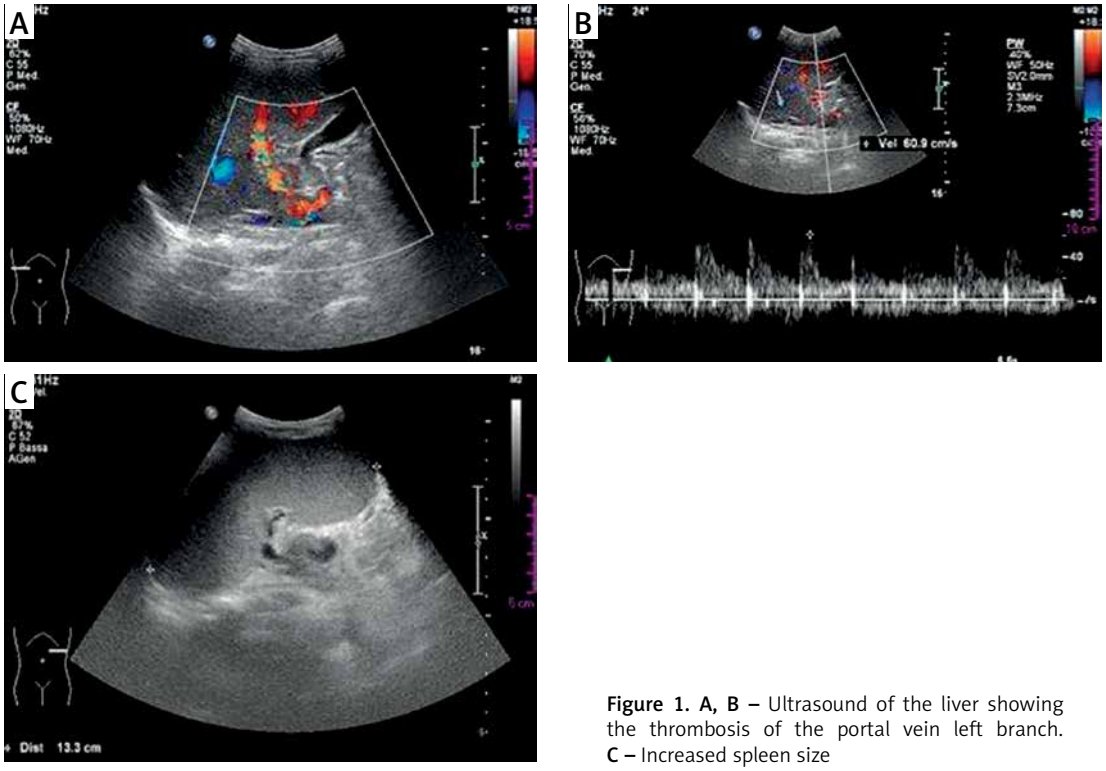

Figure 1. A, B – Ultrasound of the liver showing the thrombosis of the portal vein left branch. **C –** Increased spleen size

ing PVT [1, 2]. The present patient seems to have had a chronic PVT, discovered occasionally, because at the time of diagnosis he was asymptomatic. There was no evidence of ectopic varices, but early signs of portal hypertension were highlighted by the abdominal ultrasound, e.g. perihepatic and perigastric collateral circulation, increased spleen size and a slightly dilated venous splenic hilum.

The etiology of PVT in children has not been comprehensively studied like in adults. Studies in children are sparse and are affected by the small population size, but the limited evidence supports the hypothesis that the prevalence of inherited or acquired thrombophilia in children with PVT is lower than in adults [5].

A deep investigation can identify one or more systemic prothrombotic risk factor (PRF) in approximately 60% of patients with PVT and further local triggering factors in as many as 40% of cases [5]. The prevalence of the mutation in position 20210 in the prothrombin gene seems to be increased among subjects with PVT, compared with controls [6]. C677T homozygous mutation of the MTHFR gene is associated with an increased risk of venous thrombosis [7], but it has recently been shown that the prevalence of C677T homozygosis among patients with PVT is no higher than that observed in healthy European populations (~10%) [8], and it is possible that this mutation does not increase the risk of PVT [2]. Our patient had a normal homocysteine blood level at the time of diagnosis, and it is unclear whether this mutation had contributed to the development of PVT.

A remarkable finding of the present case report is the coexistence of two inherited PRFs and no clinical features of PVT or the consequent portal hypertension. In nearly 50% of patients two, and in 16% even three PRFs were found at presentation [9]. Maybe prothrombotic mutations in one or more genes create an inherited predisposition for PVT, and clinical thrombosis might then manifest in the presence of thrombotic stimuli such as oral contraceptives, pregnancy, MPD, or abdominal surgery [10].

Myeloproliferative disorders are responsible of 21% of PVT [8]. We excluded the presence of an MPD thanks to the research on the $JAK_2V6_{17}F$ mutation, whose discovery has changed the diagnostic strategy of MPD. $JAK_2V6_{17}F$ screening in abdominal vein thrombosis patients without typical hematological MPD features identified MPD in 15.4% of screened PVT patients [9].

Portal vein thrombosis has been associated with umbilical venous catheterization. The most important risk factor for thromboembolic events in neonates is placement of central catheters and some perinatal prothrombotic conditions [11].

In the neonatal period, the ductus venosus connects the umbilical to the hepatic veins, so 60% of the umbilical blood flow bypasses the liver. The ductus venosus is also connected to the left branch of the portal vein. Umbilical vein catheters (UVC) use the ductus venosus pathway to reach the right atrium [12].

Its anatomic location explains the complications of local trauma by UVC and the left lobe atrophy after ipsilateral PVT. The incidence of this complication after umbilical vein catheterization is not known. In some cases, portal vein repermeabilization occurs. However, how and when this occurs needs further study. Some risk factors contribute to the development of portal vein thrombosis. In the neonatal period, placement of an umbilical vein catheterization, sepsis and local infections or other medical conditions may play major roles [12].

A Korean study found that statistically significant risk factors were catheterization for more than 6 days and transfusion [13]. In another study, catheter-associated portal venous thrombosis was uncommon (3.04% of 164 infants received UVC), and the duration of catheter placement was not longer in patients with PVT than those without it [14].

It is possible that the patient's inherited predisposition for thrombosis manifested itself in the presence of thrombotic stimuli such as the neonatal UVC and the sepsis.

Abdominal vein thrombosis is not described well in the literature, particularly in children, and pediatric providers and researchers often rely on data from adults to inform management decisions [15].

Acute PVT in previously healthy patients must be treated as early as possible with anticoagulants, because spontaneous recanalization is very rare, compared to an approximately 40% recanalization rate in patients receiving early anticoagulation [5].

There are few available data and no guidelines about therapy for chronic PVT. No data from clinical studies or guidelines exist about chronic therapy in subjects with a recognized prothrombotic disorder [5]. It remains unclear when anticoagulant therapy should be given in patients with non-cirrhotic PVT, and the decision is made on a case-by-case basis. This is an important problem in patients with non-cirrhotic PVT with an underlying prothrombotic disorder (PTD), like in our case, because in this population recurrent thrombosis is more frequent. It was found that patients with PVT and PTD had a three-fold increased risk of developing a recurrent thrombotic event [1].

We decided not to start anticoagulant therapy because the clinical presentation was at the chronic stage, as most often occurs in pediatric cases, and anticoagulation has rarely been considered at this stage [5]. According to the few available data from retrospective studies, anticoagulation is not contraindicated in patients with portal cavernoma and esophageal or gastric varices: it can prevent recurrent thrombosis without increasing the risk of severity of gastrointestinal bleeding. However, the strength of this recommendation depends on the clinical setting: it is high in the presence of one or more identified prothrombotic factor, a personal or familial history of venous thromboembolism, or recurrent abdominal pain due to extensive thrombosis in the portal venous system [5]. But there are no guidelines on the pediatric population, and decisions are often made based on expert opinion. We decided not to start the anticoagulation continuous prophylaxis because it seems that hyperhomocysteinemia but not C677T MTHFR mutation is associated with increased risk of splanchnic vein thrombosis [16]. The genetic contribution to the variance in plasma homocysteine was estimated to be 9%, compared with approximately 35% that could be attributed to vitamin B_{12} and folate [17].

Therefore, we have not documented a case of hyperhomocysteinemia, and the child did not have a history of venous thromboembolism or recurrent abdominal pain. Anyway, it is very important that the child undertakes prophylaxis if acquired risk factors occur.

Despite the lack of knowledge on the most appropriate therapeutic strategy, 5- and 10-year survival rates of patients with non-cirrhotic, non-malignant PVT are 90% and 80%, respectively [9].

In conclusions, this case report describes an accidental diagnosis of portal vein thrombosis made at pediatric age in a patient with combined presence of a C677T homozygous mutation in the MTHFR gene and a heterozygous G1691A mutation in the factor II gene, affected by neonatal sepsis, disseminated intravascular coagulation and subsequent foot amputation at neonatal age.

In conclusion, pediatricians should specifically consider the possibility of PVT and portal hypertension in infants needing neonatal intensive care. Moreover, the presence of a massive thrombosis in the neonatal period and PVT at pediatric age should always lead clinicians to perform investigations for thrombophilia, especially to make an early diagnosis in infants with a history of a pathological neonatal feature.

In fact, this case report shows the importance of performing thrombophilic screening in patients who have had neonatal sepsis that causes thrombosis so serious as to cause amputation. Moreover, the frequent coexistence of different thrombophilic factors in the same patient with PVT justifies the need to perform complete thrombophilic screening in all patients affected by PVT; this does not reflect the real current situation, which shows that most of the studies performed on PVT pathogenesis are limited by the lack of complete thrombophilic testing.

Finally, the duration of umbilical catheter placement should be minimized, and we need indications for ultrasound examination in newborns who underwent UVC; a prospective study would be useful.

Conflict of interest

The authors declare no conflict of interest.

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