Unilateral Renal Vein Thrombosis and Adrenal Hemorrhage in A Newborn with Homozygous Factor V Leiden and Heterozygous Of MTHFR-677T, MTHFR-1298C Gene Mutations

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Abstract Renal vein thrombosis (RVT) occurs as an acute and life-threatening event in neonates. RVT is the most common non-catheter-related thrombosis in infancy and occurs primarily in the newborn period. Non-catheter-related abdominal thrombosis on neonates has a higher incidence of genetic prothrombotic risk factors. RVT and adrenal hemorrhage can both be encountered in the neonatal period and they may occur at the same time (Bokenkamp et al., *Eur J Pediatr* 159:44–8, 2000; Lau et al. *Pediatrics* 120:1278–84, 2007). We report a case of unilateral RVT and adrenal hemorrhage in a newborn with homozygous factor V Leiden mutation and heterozygous of the methylene tetrahydrofolate reductase (MTHFR) gene mutations.

Keywords Newborn · Renal vein thrombosis · Adrenal hemorrhage · Homozygous factor V Leiden mutation

Introduction

A recent study from Germany suggested that the incidence of symptomatic RVT in neonates was at least 2.2 per 100 000 live births [1]. Thrombus extension into the inferior vena was found in approximately 40 % of patients and 15 % of them may have adrenal hemorrhage [2]. Several inherited prothrombotic conditions have been reported in association with neonatal renal vein thrombosis (RVT). We report a case of unilateral RVT and adrenal hemorrhage in

a newborn who was a homozygous factor V Leiden mutation and heterozygous carrier of the methylene tetrahydrofolate reductase (MTHFR) gene mutations.

Case Report

A 2,930 gm full-term male infant was born after an uneventful pregnancy by cesarean section prompted by variable decelerations in fetal heart rate recordings to a gravida 4, para 2 with meconium stained amniotic fluid. Apgar score was 6/9 in the first, fifth minute, and arterial umbilical pH was normal range. Oxygen therapy performed for transient tachypnea. On postnatally second day; respiratory distress resolved. Infection was not found and no venous or arterial catheters were inserted.

On the third day, macroscopic hematuria were noted. Laboratory studies disclosed the following values: hemoglobin: 14 g/dL, hematocrit: 41,8 %, white blood cell: $23.5 \times 10^3/\mu\text{L}$, platelet, $96 \times 10^3/\mu\text{L}$, sodium, 146 mEq/L; blood urea nitrogen, 27 mg/dL; and creatinine of 0.8 mg/dL. Clotting studies were normal and his blood pressure was 74/45 mm Hg. Urinalysis showed red dark urine with +3 hemoglobin. Urine output at the time was 3 mL/kg/h.

Abdomen ultrasonography at age 3 days showed the right kidney to be 6.5×3.5 cm, the left kidney 4.7×2.4 cm in length (normal for age: 4.5×0.3 cm), the mean renal parenchymal thickness of right kidney was 9 mm, and the mean renal parenchymal thickness of left kidney was 7 mm. The right kidney parenchymal cortex echogenicity was Grade II, the left kidney parenchymal cortex echogenicity was Grade I. The both of the kidneys' collecting systems were normal. The complex cystic lesions (5.7×3.7 mm) within left adrenal gland. A finding consistent with adrenal hemorrhage (Fig. 1). Doppler

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Fig. 1 The abdomen USG show the complex cystic lesion (5.7 × 3.7 mm) within left adrenal gland

Fig. 2 Doppler ultrasound showed a large right kidney and absence of flow in the right renal vein branches

ultrasound showed a large *left* kidney and absence of flow in the *right* renal vein branches, a finding consistent with RVT (Fig. 2). ACTH and cortisol values were normal (35.9 pg/mL, 150.8 nmol/L, respectively).

Laboratory studies for congenital defects leading to venous thrombosis documented normal activities for anti-thrombin III (75 %, measured repeatedly by an amidolytic assay), protein C (58 % measured coagulometrically), and protein S (total protein S 106 %, immunologic assay). Mutation analysis of the factor V gene identified a homozygous FV Leiden mutation (G1691A) and implicated APC resistance as the origin of thrombophilia. MTHFR C677T and MTHFR A1298C heterozygous mutations founded. Low molecular weight heparin (LMWH), enoxaparin, was commenced at an initial dose of 1 mg/kg/dose via subcutaneous injection Q12 hourly. The patient was rehydrated. Following rehydration, the patient's creatinine returned to 0.4 mg/dL and macroscopic hematuria was improved. At the follow-up; the patient developed milder hypertension. The hypertension was treated with oral enalapril.

At the age of 3 months, renal scan showed non functioned right kidney and ultrasound showed a small right kidney. In view of the severe thrombotic manifestations, continuous oral anticoagulation (international normalized ratio approximately 2.3) despite the patient's young age was recommended. No relapse or other thrombotic event occurred during infancy. Urinalysis, blood pressure, renal function tests and the developmental status were normal.

Discussion

Renal vein thrombosis is a rare but potentially serious neonatal disease. Perinatal risk factors such as prematurity, dehydration, and birth asphyxia have lost their direct accountability at the expense of their interaction with constitutional disorders of hemostasis. RVT is the most common non-catheter-related thrombosis in infancy and occurs primarily in the newborn period [1, 2]. We report a newborn case with coexisting RVT and adrenal hemorrhage. Our case was male and he has right-sided RVT and it presented in postnatally fourth days. Adrenal hemorrhage accompanied RVT at the same time. There was no perinatal risk factors such as prematurity, dehydration, birth asphyxia, diabetic mother.

Neonates have a higher incidence of thrombosis when compared to older children. It has been suggested that neonates are particularly prone to have such thrombotic complications as they have decreased levels of natural anticoagulants such as protein C, protein S, and anti-thrombin, as well as low levels of fibrinolytic components such as plasminogen [3].

Several inherited prothrombotic conditions have been reported in association with neonatal RVT, including factor (F) V Leiden G1691A mutation, FII G20210A prothrombin gene mutation, protein C and protein S deficiencies and the

Table 1 Studies in the literature (between 2000 and 2013) that had reported cases of neonatal RVT with prothrombotic risk factors

Author (year)	Unilateral	Bilateral	Heparin or fibrinolytic treated	Supportive only	Prothrombotic risk factors	Renal outcome
Heller (2000)		^a	^a		Factor V Leiden mutation: 9/35 MTHFR genotype: 2/35 Protein C deficiency: 2/35 Antithrombin deficiency: 1/35	^a
Giordano (2001)	+		+		Factor V Leiden, MTHFR and platelet glycoprotein IIIa polymorphisms	Impaired renal function
Kosch (2004)	42/53	11/53	N (43)	N (10)	Factor V 1691G>A, Total: 22/59 Homozygous A1691A: 1 Single heterozygous 1691G>A: 13 With lipoprotein(a) >0.30 g/L: 5 With factor II: 2 With protein C deficiency: 1 Factor II 20210G>A, Total: 5/59 Single: 0 With factor V 1691G>A: 2 With lipoprotein(a) >0.30 g/L: 3 Lipoprotein(a) more than 0.3 g/L, Total: 17/59 Single: 6 With factor V 1691G>A :5 With factor II: 3 With Hcy >10 µM: 1 Protein C deficiency, total: 3/59 Single: 2 With factor V 1691G>A :1 Antithrombin deficiency, total:3/59 Single 3 ACAs greater than 2 SDs, total 3/59 Single 3	Unilateral renal atrophy: 42/53 Bilateral renal atrophy: 11/53 Renal transplantation: 3/53 Severe arterial hypertension, necessitating long-term antihypertensive treatment: 3/53
Marks (2005)	^a	^a	^a	^a	Protein C or S deficiency: 5/28 Abnormal factor VIII levels: 2/28 Factor V Leiden heterozygote: 4/28 Factor V Leiden and MTHFR Heterozygote: 1/28 Lupus anticoagulant: 2/28 Factor V Leiden Homozygote: 1/28 Antithrombin III deficiency: 1/28 Prothrombin gene 20210A Heterozygote: 1/28	^a
Winyard (2006)	+	+		++	Factor V Leiden mutation heterozygous, MTHFR C677T mutation heterozygous: 2/23	Thinned cortex on left, chronic kidney disease, (CKD) stage 1 Partly calcified R kidney, CKD stage 1
	+		+	+	Heterozygous protein C and protein S deficiency: 1/23	Scarred right kidney, CKD stage 1

Table 1 continued

Author (year)	Unilateral	Bilateral	Heparin or fibrinolytic treated	Supportive only	Prothrombotic risk factors	Renal outcome
	+		+	+	MTHFR C677T mutation homozygous: 1/23	Normal
		++			Factor V Leiden mutation heterozygous: 2/23	Cortical thinning, CKD stage 3 Small kidney, GFR: normal
		+		+	MTHFR C677T mutation homozygous: 1/23	Scar right lower pole, CKD stage 2 Nephrectomy, CKD stage 3
		+		+	MTHFR C677T mutation heterozygote: 1/23	
Messinger (2006)	+		+		Factor V 1691G3A (factor V Leiden) heterozygote mutation: 1/11	Unilateral small kidney
Harris (2010)	+		+		Heterozygous for Factor V Leiden prothrombin and antithrombin gene mutation	Atrophic right kidney
Muwakkit (2009)	+		+		Homozygosity for both factor V Leiden (G1691A) and MTHFR C677T mutations	
Wannes (2012)	+		+		Heterozygous carrier of both factor V Leiden and MTHFR gene mutation	

^a Distribution of patients according to the prothrombotic risk factors unspecified in the article

+ One patient

++ Two patients

homozygous methylenetetrahydrofolate reductase (MTHFR) C677 T polymorphism [4–10]. Table 1 describes studies in the literature (between 2000 and 2013) that had reported cases of neonatal RVT with prothrombotic risk factors

The presence of factor V Leiden mutation markedly increases the risk for renal vein thrombosis, particularly in neonates. Homozygosity is much rarer and is clinically associated with more severe thrombotic disease [11].

Heller et al. [11] showed that non catheter-related abdominal thrombosis on neonates has a higher incidence of genetic prothrombotic risk factors. Some of these factors are genetic mutations of methylenetetrahydrofolate reductase (MTHFR-677 and MTHFR-1298), plasminogen activator inhibitor-1 4G/5G polymorphism and factor V Leiden mutation. Winyard et al. [12] have shown an association between MTHFR 677T mutation and RVT at 3 of 23 newborn renal vein thromboses. Our case had homozygous for factor V Leiden and heterozygous for MTHFR-677T, MTHFR-1298C mutations.

Renal vein thrombosis and adrenal hemorrhage can both be encountered in the neonatal period and they may occur at the same time [13]. Although this condition is seen more frequently in the left kidney because the thrombus spreads directly from the involved left renal vein into the left adrenal vein that joins it, this case have a right-sided RVT and contralateral adrenal hemorrhage.

Affected neonates may present with macroscopic or microscopic hematuria, palpable flank mass and thrombocytopenia. A recent review noted that most of the neonates with RVT had at least one of the three cardinal signs at presentation [2]. This case presented with macroscopic hematuria and thrombocytopenia.

Ultrasound is a useful and convenient clinical tool for the diagnosis of RVT. Sonographic features of RVT include enlarged and echogenic kidneys with attenuation or loss of corticomedullary differentiation. Calcification and thrombus may be seen extending outside the kidneys to the inferior vena cava. Doppler studies are particularly useful for detecting the resistance or absence of flow in renal venous branches and collateral vessels. Renal scarring and atrophy are well-recognized features after RVT in affected kidneys, which can also be assessed by a radionuclide scan. Ultrasound used for the diagnosis of adrenal hemorrhage in this case. RVT has been diagnosed with Doppler ultrasonography [1, 2].

The decision to start anticoagulation therapy may be influenced by the extent of RVT, whether there is unilateral or bilateral renal involvement, the presence or absence of renal impairment and the detection of a thrombophilic predisposition. Recently, the trend has been toward the use of LMWH rather than unfractionated heparin. However, almost 40 % of the affected neonates were managed by

supportive care alone. In this case, RVT was unilateral and was not to spread vena cava inferior. There was no renal impairment. Because of prothrombotic risk factors, we started anticoagulation therapy with LMWH and treatment was continued for six months.

The management should involve a multidisciplinary team that includes neonatologists, radiologists, hematologists, and nephrologists. Search for inborn blood coagulation disorders should be systematic in the newborn infant with venous thrombosis because of the risk of recurrence, even in the presence of a known acquired risk factor [2].

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