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# NEONATAL RENAL VENOUS THROMBOSIS: CLINICAL OUTCOMES AND PREVALENCE OF PROTHROMBOTIC DISORDERS

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**Objective** To determine clinical outcomes and the prevalence of prothrombotic conditions in patients who had neonatal renal venous thrombosis (RVT).

**Study design** A retrospective cohort of neonates with RVT who were admitted to 4 pediatric centers from 1980 to 2001 was identified. Information on clinical presentation, laboratory and radiological investigation, and treatment were abstracted. Survivors were evaluated for renal status and prothrombotic conditions.

**Results** Forty-three patients with neonatal RVT were identified. RVT was unilateral in 24 patients (56%) and associated with 2thrombi at other sites in 32 patienets (74%). Clinical presentations included renal failure in 24 patients (56%), thrombocytopenia, anemia, or both in 22 patients (51%), and renal mass in 21 patients (49%). Neonatal interventions included anti-coagulants in 28 patients (65%), antihypertensive medications in 9 patients (21%), peritoneal dialysis in 2 patients (5%), and nephrectomy in 2 patients (5%). The median age at follow-up was 3.7 years (range, 0.5-20.2 years). Thirteen patients (34%) had hypertension, and 11 patients (29%) had renal failure. End-stage renal disease developed in 3 patients, and they underwent live-related renal transplants. Twelve of the 28 patients (43%) examined had prothrombotic abnormalities.

**Conclusion** Neonatal RVT is associated with significant renal morbidity and a high prevalence of prothrombotic abnormalities. *(J Pediatr 2005;146:811-6)*

Renal venous thrombosis (RVT) is the second most common venous thromboembolic event in neonates.[1-4] RVT has variable clinical features, which can include hematuria, oliguria-anuria, renal mass, hypertension, thrombocytopenia, decreased renal function, and abnormal Doppler ultrasound scanning results. Minimum diagnostic criteria include the presence of microscopic or macroscopic hematuria with ultrasound scanning evidence of an enlarged, echogenic kidney with loss of corticomedullary differentiation.[5] Findings on Doppler ultrasound scanning include a decrease in the amplitude or absence of venous signal, abnormal flow patterns in a number of renal venous branches, or evidence of venous collateral development.[6]

Risk factors for the development of RVT include maternal diabetes mellitus (either type 1 or gestational),[7,8] pathologic states associated with thrombosis (eg, shock, dehydration,[9] perinatal asphyxia,[10] polycythemia, cyanotic heart disease), sepsis,[11] umbilical venous catheterization, and conjoined twins.[12] Inherited prothrombotic abnormalities[13-20] have been described in case reports of RVT. However, the prevalence of these disorders has not been studied in a cohort of patients with neonatal RVT.

Management of RVT is generally supportive, but may also include anticoagulation therapy, fibrinolytic therapy, or both. The sequelae of RVT reported in the literature include glomerular disease (3%-100%), tubular dysfunction (9%-47%), hypertension (9%-100%), and evidence of renal scarring or atrophy (27%-100%).[6,21-35] The reported variation in the degree of morbidity suggests an underlying heterogeneity in the etiology of RVT that may

| | | | |
|---|---|---|---|
| APC | Activated protein C | RVT | Renal venous thrombosis |
| GFR | Glomerular filtration rate | VTE | Venous thromboembolic event |
| PCR | Polymerase chain reaction | | |

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**Table I. Neonatal characteristics**

| Variable* | | |
|---|---|---|
| Gestational age (n = 43) | 38 | 24-42 weeks |
| Birthweight (n = 43) | 3.1 | 0.76-5.7 kg |
| Apgar score at 1 minute (n = 38) | 7 | 0-9 |
| Apgar score at 5 minutes (n = 38) | 9 | 2-10 |
| Male sex (n = 43) | 28 | 65% |
| Mode of delivery (n = 43) | | |
| Vaginal | 23 | 54% |
| Cesarean Section | 16 | 37% |
| Instrumentation | 4 | 9% |

*Values are median (range) or number (%).

lend itself to individualized management strategies to prevent long-term renal complications.

The objective of this study was to determine the clinical outcomes and prevalence of prothrombotic conditions in neonates with RVT.

## METHODS

### Study Design and Patient Population

Children who had RVT diagnosed during the neonatal period were identified retrospectively from the Divisions of Neonatology and Nephrology and Health Record Department databases of 4 pediatric centers (Toronto, Hamilton, Ottawa, and London) in the province of Ontario, Canada, using the terms "neonates," "renal venous thrombosis," "hypertension," and "renal failure." Patients were included when a review of clinical data indicated that they satisfied the minimum diagnostic criteria for neonatal RVT, namely the presence of macroscopic or microscopic hematuria with ultrasound scanning evidence of an enlarged, echogenic kidney with loss of corticomedullary differentiation.[5,6,36]

### Data Collection

**Neonatal data.** A retrospective chart review was performed to determine maternal medical and obstetrical history, and the infant's condition at birth including resuscitation, neonatal diagnoses, and outcomes. Collected diagnostic information included urinary abnormalities, results of haematological and biochemical tests, coagulation profile, thrombophilia work-up, and radiology investigations.

**Post-neonatal follow-up information.** Follow-up on the clinical course and outcomes, results of diagnostic tests, and medications were retrieved with a standardized data collection form from the records of the nephrology clinics.

Patients not being observed by a nephrologist at the time this study was initiated were recalled for an evaluation of their renal status. On recall visits, when possible, each patient underwent a physical examination (including anthropometric measurements and blood pressure), Doppler renal ultrasound scanning, urine and blood tests, and work-up for prothrombotic abnormalities. Alternatively, results of previously performed clinical tests were collected. Patients were examined with nuclear renal scanning when clinically indicated. Hypertension was defined as blood pressure higher than the 95th centile for age, sex, and height centiles[37] or the requirement for antihypertensive medication.

### Investigations

The diagnosis of renal atrophy was made when serial measurements (≥2 or more ultrasound scans) of renal length showed declining values less than the third percentile.[38] Glomerular filtration rate (GFR) was estimated with the Schwartz formula.[39] Patients were classified as normal (GFR >80 mL/min/1.73m$^2$), early renal failure (GFR 40-70 mL/min/1.73m$^2$), chronic renal insufficiency (GFR 20-40 mL/min/1.73m$^2$), chronic renal failure (GFR 10-20 mL/min/1.73m$^2$), and end-stage renal disease (GFR <10 mL/min/1.73m$^2$).[40]

### Testing for Prothrombotic Abnormalities

Screening for inherited prothrombotic abnormalities included functional and protein assays of antithrombin, protein C and S levels, and genetic testing for factor V Leiden, prothrombin gene 20210A, and methylenetetrahydrofolate reductase (MTHFR). Other tests included lupus anticoagulant, activated prothrombin time, clotting time, thrombin time, activated protein C (APC) resistance, reptilase time, antiphospholipid antibodies, and factor assays.

Plasma anti-thrombin III activity was measured with a chromogenic assay.[41] Plasma levels of protein C and protein S were determined with commercially available reagents (Protein C, Dade Behring, Newark, Del; Protein S, Diagnostica Stago). PCR of genomic DNA was used to identify factor V Leiden[42] and prothrombin G20210A.[43] The MTHFR C677T polymorphism was identified with polymerase chain reaction (PCR) using the primers sense 5′ TGAAGGAGAAGGTGTCTGCGGGA 3′ and antisense 5′ AGGACGGTGCGGTGAGAGTG 3′ and PCR conditions 94°C—2 minutes, 60°C—2 minutes, 72°C—3 minutes for 30 cycles.

Lupus anticoagulant was identified by measuring clotting in the presence of Russell Viper Venom,[44] activated prothrombin time in the presence of platelet lysate,[45] and clotting time in the presence of tissue thromboplastin. Thrombin time was measured as the clotting time after the addition of thrombin to citrated plasma[46] by using the reptilase-Batroxobin test (Dade Behring, Mississauga, Ontario, Canada). Plasma factors VIII, IX, XI, and XIII and thrombin activity were measured with established methods.[46,47]

### Data Analysis

The data were analyzed with SPSS software (SPSS for Windows, version 9.0, 1999, Chicago, Ill) and presented as median (range) or percentages when appropriate.

### Ethics Approval

The study was approved by the research ethics boards at all 4 institutions. Informed consent was obtained from the

**Table II. Presentation, extent, treatment, and clinical outcomes**

| Characteristic | Subtype | Number of patients (n = 43) | Percentage (%) |
|---|---|---|---|
| ***Clinical presentation*** | | | |
| | Renal failure | 24 | 56% |
| | Thrombocytopenia/anemia | 22 | 5% |
| | Abdominal mass | 21 | 9% |
| | Dehydration | 3 | 7% |
| | Antenatal | 2 | 5% |
| ***Extent of thromboses*** | | | |
| | Unilateral | 24 | 56% |
| | Bilateral | 19 | 44% |
| | Associated with other thrombi | 32 | 74% |
| ***Specific neonatal treatments*** | | | |
| | Subcutaneous low-molecular weight heparin | 17 | 40% |
| | Systemic heparin | 7 | 16% |
| | Systemic tissue plasminogen activator | 3 | 7% |
| | Warfarin | 1 | 2% |
| ***Other neonatal treatments*** | | | |
| | Anti-hypertensives | 9 | 21% |
| | Peritoneal dialysis | 2 | 5% |
| | Unilateral nephrectomy | 2 | 5% |

parents or guardians of the patients in the study and from the subjects themselves when appropriate.

## RESULTS

### Neonatal Presentation of RVT and Renal Morbidity

Forty-eight neonates with a possible diagnosis of renal venous thrombosis were identified from the databases. Of these, 43 met the eligibility criteria; all patients exhibited Doppler ultrasound scanning evidence of RVT. Five neonates were excluded because they did not fulfill the inclusion criteria.

Information on the neonatal demographic characteristics and risk factors for RVT is presented in Table I. Predisposing factors were identified in 21 neonates (49%) and included the presence of an umbilical venous catheter (n = 7), perinatal asphyxia (n = 5), congenital heart disease (n = 3), maternal diabetes mellitus (n = 3), hypernatremic dehydration (n = 2), and twin pregnancy (n = 1).

Data on the mode of presentation, extent of the thrombus, and neonatal management are presented in Table II. The most common presenting features were renal failure, thrombocytopenia, and/or anemia and palpable renal mass. Ten of the 24 neonates (42%) who had renal failure had bilateral RVT. RVT was associated with thrombi at other sites in three quarters of our cases, with thrombi noted in the inferior vena cava (n = 25), inferior vena cava and adrenal vein (n = 5), inferior vena cava and portal vein (n = 1), and the adrenal vein (n = 1). Six of the 7 neonates who had an umbilical venous catheter had associated thrombi in the inferior vena cava. In the 23 of the 28 neonates with RVT who received anticoagulation/anti-thrombolytic therapy, there was presence of thrombi at other sites.

### Post-neonatal Clinical Outcomes Follow-up Data

Of the 43 neonates with RVT, 3 infants died between the ages of 1 and 3 months. Mortality was attributed to causes unrelated to RVT and included respiratory failure caused by chronic lung disease and sepsis in 1 infant, postoperative bilateral chylothorax and hydrocephalus in another infant with transposition of the great arteries, and an endocardial cushion defect and congenital diffuse lymphangiomatosis in a third infant with trisomy 21.

Forty children in the initial cohort (n = 43) were recalled prospectively for follow-up. One subject refused to attend the clinic for assessment, and 1 subject was lost to follow-up. Thus data are available for 38 patients. The median age at follow-up was 3.7 years (range, 0.5-20.2 years). Clinical assessment revealed hypertension in 13 subjects (34%) and renal failure in 11 subjects (29%). Of these subjects, on the basis of the calculated GFR, 3 had end stage renal failure, 2 had chronic renal failure, 4 had chronic renal insufficiency, and 2 had early renal failure. All 3 children who had end-stage renal disease underwent live-related renal transplant. Nephrectomy was performed in 2 children for management of hypertension at the age of 1 year in one and 11 years in the other. Renal atrophy was detected in 25 children (66%).

Thirteen of the 38 children (34%) underwent a technetium-99m diethylenetriamine penta-acetic acid renal scan. Six patients (16 %) had non-functioning unilateral kidneys (<10% differential function or indistinguishable from background activity), 7 patients (35%) had unilateral function

**Table III. Results of prothrombotic work-up**

| Prothrombotic condition | Number of patients (total number of patients tested = 28) | Percentage (%) |
|---|---|---|
| Protein C or S deficiency | 5 | 18% |
| Abnormal factor VIII levels | 2 | 7% |
| Factor V Leiden heterozygote | 4 | 14% |
| Factor V Leiden and MTHFR heterozygote | 1 | 4% |
| Lupus anticoagulant | 2 | 7% |
| Factor V Leiden homozygote | 1 | 4% |
| Antithrombin III deficiency | 1 | 4% |
| Prothrombin gene 20210A heterozygote | 1 | 4% |

between 10% and 35%, and no patient had a differential function of the affected kidney >35%.

### Prothrombotic Abnormalities

Consent was obtained for 28 of the 43 (65%) patients for evaluation of prothrombotic abnormalities. At the time of follow-up, none of these infants had had a recurrence of a venous thromboembolic event (VTE). One infant without a prothrombotic abnormality died at the age of 2.5 months. In 3 of 28 infants (10%), the family history was positive for thrombotic conditions. Twelve of 28 children tested (43%) had abnormal prothrombotic results, which are listed in Table III. Four children had >1 type of prothrombotic abnormality. One patient with lupus anticoagulant was heterozygous for factor V Leiden and MTHFR.

## DISCUSSION

Since the 1970s, 16 studies have reported on the long-term outcome of neonatal RVT.[6,21-35] The duration of follow-up ranged from 1 to 192 months. A large variation in the rates of glomerular and tubular defects, systemic hypertension, and abnormalities on renal imaging among studies has been noted, which could possibly be explained by the differences in the number of cases reported in each study and the duration of follow-up. In the largest series to date of 59 neonates with RVT,[35] significant renal morbidity was reported despite the use of anticoagulant/antithrombotic treatment.

Significant renal morbidity was also noted in our cohort during the neonatal period and on follow-up. Our study is the second largest series that describes the outcome of patients with neonatal RVT and has the longest duration of follow-up. The cases described were identified from 4 pediatric centers within the province of Ontario. Because these centers have the support of neonatal and nephrology services, they were likely to represent the moderate-to-severe cases. Because they were identified from various databases, neonates with mild disease may have not been referred to these centers, and silent clinical disease may remain undiagnosed. Thus, this should not be viewed as an epidemiological study.

The neonatal clinical presentation and associated risk factors were in accord with the previous published data.[1-20] Management of neonatal RVT is mainly supportive, with careful attention to fluids and electrolytes, treatment of infection, dialysis when necessary, and the use of thrombolytic agents. Several studies[30,32,33] have attempted to evaluate the role of thrombolytic agents in this population. The results are inconclusive, and the benefit of such therapies in preventing long-term morbidity remains unclear.

All patients with neonatal RVT should be followed up to document the normalizing of renal function. Patients with bilateral RVT require lifelong follow-up because of the high likelihood of chronic renal failure. It should be recognized that some neonates who are labeled as having unilateral RVT may have bilateral disease or damage to the contralateral kidney (for example, from acute renal failure caused by acute tubular necrosis developing into cortical necrosis) and may need a longer follow-up period. Patients require a clinical examination for the sequelae of chronic renal failure, including hypertension and proteinuria, both of which may cause progression of renal failure and could be amenable to treatment. Renal function should be monitored by using serial plasma creatinine levels and calculation of GFR. Formal measurement of GFR is recommended at 12 months of age to ascertain cases of chronic renal failure; however, it should be kept in mind that the estimated GFR may be overestimated from plasma creatinine (because of muscle bulk). Serial Doppler ultrasound scanning examination should be performed to delineate the extent of the thrombus that may help in outlining the length of anticoagulant treatment. It will also demonstrate the change from the acute finding of enlarged, echogenic kidney(s) to the chronic changes with renal atrophy. Nuclear medicine imaging with technetium-99m dimercaptosuccinic acid is indicated to assess the functional status of the kidney.

### Thrombophilic Disorders as Etiology of Neonatal RVT

A high prevalence of inherited prothrombotic conditions was documented in 43% of our tested population. In our series, the main abnormality identified was protein C or S deficiency in 5 subjects, followed by factor V Leiden heterozygosity in 4 subjects.

The literature on the association of prothrombotic abnormalities and neonatal RVT is limited to several case reports and 2 case control studies.[13-20,35] Heller et al[17] evaluated 65 neonates and infants as old as 1 year who had abdominal venous thrombosis and 100 age- and sex-matched healthy control subjects for prothrombotic conditions. Of these 65 subjects, 31 neonates and infants had RVT. Among patients with RVT, factor V Leiden mutation was found in 9, MTHFR genotype was found in 2, protein C deficiency was found in 2, and antithrombin deficiency was found in 1.

In the most recent study by Kosch et al,[35] the presence of at least 1 established prothrombotic risk factor was noted in 67.8% of the patients with neonatal RVT, compared with 11.9% in the control children. Abnormalities identified were the presence of factor V mutation and elevated lipoprotein a levels, protein C and antithrombin deficiencies, and increased anti-cardiolipin antibodies. With our findings, these results strongly suggest that genetic prothrombotic risk factors play an important role in RVT. Our study systematically estimated the prevalence of prothombotic abnormalities in patients with neonatal RVT.

Despite the presence of prothrombotic abnormalities, none of our patients have yet experienced a recurrence of VTE after the neonatal period. In the study by Kosch et al,[35] the risk of recurrent thrombosis was reported to be 4.3% (with 3 of 4 cases of recurrent symptomatic thrombosis occurring during puberty from the original cohort of 94 neonates), although little information was provided about the location of the thrombi and whether they were spontaneous or provoked by other environmental risk factors. In the series by Kosch et al,[35] 1 patient had homozygous factor V Leiden and another had protein C deficiency. Long-term anticoagulation therapy may be appropriate for abnormalities such as these. However, at this time, there are no data to support this; each case has to be considered with an individual risk-benefit ratio.

It is well known that thrombosis is multifactorial. The interaction of existing or acquired risk factors with the presence of inherited prothrombotic abnormalities predispose individuals to VTE. In such individuals, the risk of occurrence of thrombosis in the presence of acquired risk factors such as surgery, immobilization caused by plaster casts and prolonged travel, and the use of oral contraceptives and pregnancy in women is unknown.[48] Therefore testing patients with thrombosis for prothrombotic abnormalities may be advantageous. If an abnormality is identified, these patients should be referred to specialists who can advise the patient/family about symptoms and signs of deep vein thrombosis/pulmonary embolism, provide guidelines on the intermittent use of preventive treatment with anticoagulation in high-risk situations such as surgery or prolonged immobilization for a fractured bone, and advise women about potential pregnancy and the use of birth control measures. However, no consensus exists in the literature on the provision of thromboprophylaxis during the aforementioned situations because the clinical decision is clouded by lack of knowledge of the risk/benefit ratio about the use of anticoagulation and the risk of recurrences on VTEs in these patients.

Neonates with RVT should be tested with a full thrombophilia screen to identify antithrombin, protein C and S deficiencies, and factor V Leiden and prothrombin 20210A gene defects. If protein C and S deficiencies are noted in the neonatal period, these values need to be rechecked after the acute event and while the patient is not receiving anticoagulation therapy. The full thrombophilia screen should include anti-cardiolipin antibodies and lupus anticoagulant, although it is more sensible to check the mother for these because there are reports of transplacental anticardiolipin immunoglobulin G causing thrombosis in neonates. There is emerging data on the association of elevated lipoprotein (a) levels[35] and neonatal RVT, although it is unclear how relevant these levels are and whether special diets or other treatments can normalize them, affect outcome, or both.

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