

## Theme Issue Article

# A case series of 72 neonates with renal vein thrombosis

## Data from the I-800-NO-CLOTS Registry

Stefan Kuhle<sup>1,2</sup>, Patti Massicotte<sup>3</sup>, Anthony Chan<sup>4</sup>, Lesley Mitchell<sup>1</sup>

<sup>1</sup> Department of Population Health Sciences, The Hospital for Sick Children, Toronto, Canada

<sup>2</sup> Department of Neonatology, University Children's Hospital, Tübingen, Germany

<sup>3</sup> Division of Haematology and Oncology, The Hospital for Sick Children, Toronto, Canada

<sup>4</sup> Department of Paediatrics, McMaster University, Hamilton, Canada

### Summary

Neonatal renal vein thrombosis (RVT) is a well-recognized clinical entity which is associated with serious morbidity. However, current information regarding RVT has been restricted to case reports and small case series. In this study, it was our objective to describe patient demographics, clinical presentation, location and risk factors of RVT. For our study design, we looked at a case series of 72 neonates with RVT referred to the I-800-NO-CLOTS consultation service between 9/1996 and 8/2001. Data on age, gender, associated conditions, prothrombotic disorders, family history, location of the thrombosis, diagnostic techniques, and treatment were prospectively recorded using a standardized form. Our results show that RVT affected males (65%, CI 52-76%) significantly more often than females (35%, CI 24-48%). Median age at presentation was 2 days (0-21 days). RVT was unilateral in 72% (left side: 67%, CI 49-81%; right

side: 33%, CI 19-51%), and bilateral in 28%. The majority (83%) had at least one associated condition: Prematurity (54%), central venous lines (17%), a diabetic mother (13%), asphyxia (6%), infections (6%). Prothrombotic testing was performed in 21 neonates. Activated protein C resistance was found in 8 children (38%), other defects in three. This is the largest case series of neonatal RVT to date. Data from the study show that i) male infants are affected twice as often as females and ii) there appears to be a left-sided predominance of neonatal RVT. Neonatal RVT is only infrequently associated with the presence of a catheter as compared to thrombosis at other sites. The majority of infants have associated conditions with prematurity being most frequent. A small subset of neonates were screened for prothrombotic abnormalities and 50% of the children screened were positive.

### Keywords

Clinical/epidemiological studies, neonates, thrombosis

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## Introduction

Renal vein thrombosis (RVT) is one of the more common forms of neonatal thromboembolism (TE) accounting for 15-20% of systemic TE (1, 2). However, current knowledge about neonatal RVT is derived exclusively from case reports and small case series lacking sufficient power to delineate all aspects of RVT (3).

Neonatal RVT appears to result in significant long-term morbidity (4-8). Little is known about safety and efficacy of treatment of neonatal RVT. The considerable morbidity resulting from neonatal RVT warrants clinical trials investigating appropriate anticoagulant therapy. However, before embarking on clinical trials, more data on the clinical presentation and risk factors of the disease are needed in order to target populations at increased risk for complications.

Correspondence to:

Lesley Mitchell, MSc  
Stollery Children's Hospital  
Department of Pediatrics  
WMC 2C3, 8440 112 St  
Edmonton, AB, T6G 2B7, Canada  
Tel.: +1 780 407-1071, Fax: +1 780 407-1221  
E-mail: LesleyMitchell@cha.ab.ca

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Data in the current manuscript were collected from the 1-800-NO-CLOTS database, which is a part of a free consultation service for pediatric TE. Because of the relatively recent recognition of TE in children, there is a serious lack of available information in relation to appropriate diagnosis, prevention and clinical management. This lack of information in the setting of a quickly growing clinical entity, left many clinicians with insufficient tools for providing the best clinical management. A need existed for distribution of therapeutic guidelines based on best available evidence. Therefore, the 1-800-NO-CLOTS consultation service was initiated in 1994 with the two-fold goal of i) dissemination of the best available information on management of pediatric TE and ii) collection of data on the epidemiology of TE in a large cohort of pediatric patients (9). Free consultations were provided by telephone and the information on children was collected and entered into a centralized database. Between September 1996 and August 2001, 1776 children with systemic TE were reported to the 1-800-NO-CLOTS service (Kuhle et al., submitted for publication). Twenty-six percent (n=464) of all children reported during the study period were neonates with TE.

In the current paper, data are presented on patient demographics, clinical presentation, location and risk factors of neonatal RVT from a case series of 72 neonates from the 1-800-NO-CLOTS registry.

## Methods

### Data collection

The 1-800-NO-CLOTS service was managed by two pediatric hematologists (M.A., P.M.) trained in adult thromboembolism, who were available 24-hours-a-day, seven-days-a-week. The service was free to callers. Consultations consisted of personal communication and provision of therapeutic protocols and/or pertinent scientific literature. Data on all calls were collected consecutively using a standardized two-page data sheet which was filled out immediately. The data sheet consisted of closed-ended and partially close-ended questions. The questions on the data sheet were developed based on the clinical experience of Dr. Andrew as well as on the results from the Canadian Pediatric Thrombosis Registry (1, 10).

The partially close-ended questions included identification of the caller including address and subspecialty, patient age, history, underlying diseases, and location of thrombosis and vessels involved.

The close-ended questions (yes/no or multiple choice) included gender, history of thrombosis including family history, conditions associated with an established increased risk for thrombosis (antithrombin / protein C / or protein S deficiency; activated protein C [APC] resistance; antiphospholipid antibodies; hyperhomocysteinemia), presence of a central catheter,

imaging techniques, and previous anticoagulant therapeutic interventions that the patient had received.

The questions asked by the caller as well as the recommendations for diagnosis and therapy and protocols that were given to the caller were also recorded.

Anonymized data were entered into a computer database (SPSS 8.0 for Windows, SPSS Inc., Chicago/IL). All RVT reported were confirmed by at least one objective test.

Testing for prothrombotic markers was performed in the callers' institution and normal ranges generated by their labs were used as basis for diagnosis of a deficiency. In the instance that no local normal ranges were available, coagulation reference values used to assess the neonates in the current study were those published by Andrew et al. (11, 12). For hyperhomocysteinemia, a cut-off level of 8  $\mu\text{M/l}$  was used.

Treatment recommendations were based on the following approach: supportive care alone for unilateral RVT without extension into the inferior vena cava (IVC) and in the absence of renal failure; heparin for unilateral RVT with extension into the IVC or for bilateral RVT because of the risk of pulmonary embolism; fibrinolytic therapy for bilateral RVT and impending renal failure (13). This approach was individualized for every patient at the discretion of 1-800-NO-CLOTS responder.

Fischer's exact test was used to test for differences between the subgroups of neonates with and without a prothrombotic work-up. A p-value < 0.05 was considered significant.

The study was approved by the Ethics Review Board of the Hospital for Sick Children, Toronto, Canada.

## Results

During the study period, callers reported 1776 children presenting with systemic TE. Twenty-six percent (n=464) of all children reported during the study period were neonates. Renal vein thrombosis accounted for 16% of neonatal TE. All patients were exclusively identified by clinical presentation with symptoms of RVT. The RVT were always confirmed by at least one objective imaging test.

### Caller characteristics

Pediatric hematologists placed 63% (n=45) of calls. Thirty-two percent of callers (n=23) identified themselves as neonatologists, 6% (n=5) as other specialists. The majority of calls (88%) came from North America, 76% (n=55) from the USA, 11% (n=8) from Canada. Europe and Australia/New Zealand represented 8% (n=6) of callers.

### Patient characteristics

Renal vein thrombosis affected males (65%; 95% CI 52-76%) significantly more often than females (35%; 95% CI 24-48%). The median age at presentation was 2 days (0-21 days). Two

cases of RVT were diagnosed antenatally, 43% on the first day of life, and 77% within the first week of life. Fifty-four percent (n=38) of the neonates were born preterm (median gestational age 34 weeks, range 25-36 weeks).

### Presentation

All neonates had clinical symptoms of RVT that lead to an ultrasound examination for confirmation of the diagnosis. Details on the presentation of RVT were reported in 34 neonates of the series: 50% had hematuria; a palpable abdominal mass was present in 41%; thrombocytopenia was found in 29%; 18% had increased blood pressure. Of the six infants with increased blood pressure, three had bilateral RVT. Renal insufficiency (anuria/oliguria or high creatinine) was reported in 10 (14%) neonates at the time of the call, seven of which had bilateral RVT. Concomitant adrenal hemorrhage was reported in 2 neonates with left-sided and bilateral RVT, respectively.

### Location

The RVT was unilateral in 72% (left side: 67%, CI 49-81%; right side: 33%, CI 19-51%), and bilateral in 28%. Other vessels were affected in 72% (n=52) of neonates with the inferior vena cava being most frequently involved (60%; n=43). Concurrent systemic arterial TE was found in four cases, arterial ischemic stroke in five cases, and sinovenous thrombosis in one case. One patient suffered from pulmonary embolism.

### Associated conditions

The majority (83%) had at least one associated condition: prematurity (54%), central venous lines (17%), a diabetic mother (13%), asphyxia (6%), infections (6%). A positive family history for thrombosis was present in 12% of patients.

Prothrombotic testing was performed in 21 neonates. APC resistance and/or heterozygous Factor V Leiden mutation was found in 8 children (38%), homozygous prothrombin G20210A mutation in one, combined defects in two. The 21 neonates who were tested for prothrombotic disorders did not differ significantly from those who were not tested in terms of family history, disease severity, or presence of exogenous factors. In neonates with exogenous triggers, 7/16 (44%) infants tested had at least one prothrombotic risk factor. In those with spontaneous RVT, 3/4 (75%) had at least one prothrombotic risk factor.

### Diagnosis and treatment

The majority of RVT (99%) were diagnosed by ultrasound. At the time of call, 59% of the neonates had not received any form of treatment. In the remaining children, unfractionated heparin was begun in 14%, low molecular weight heparin (LMWH) in 25%, and lytic therapy in 10%.

Of the seven neonates that had received lytic therapy, three had involvement of the IVC, three had bilateral RVT, and one had unilateral RVT.

The treatment initiated before the call and the treatment suggested by 1-800-NO-CLOTS are summarized in Table 1.

**Table 1: Treatment data of 72 neonates with renal vein thrombosis reported to the 1-800-NO-CLOTS service.**

	Treatment	Begun	Suggested
<b>Unilateral RVT</b> (n=23)	No treatment	70% (n=16)	48% (n=11)
	UFH	9% (n=2)	4% (n=1)
	LMWH	26% (n=6)	48% (n=11)
	Warfarin	0	0
	Fibrinolytics	4% (n=1)	0
<b>Unilateral RVT + IVC</b> (n=26)	No treatment	46% (n=12)	12% (n=3)
	UFH	19% (n=5)	27% (n=7)
	LMWH	27% (n=7)	65% (n=17)
	Warfarin	4% (n=1)	0
	Fibrinolytics	12% (n=3)	4% (n=1)
<b>Unilateral RVT + renal insufficiency ± IVC</b> (n=3)	No treatment	100% (n=3)	0
	UFH	0	67% (n=2)
	LMWH	0	100% (n=3)
	Warfarin	0	0
	Fibrinolytics	0	100% (n=3)
<b>Bilateral RVT</b> (n=13)	No treatment	69% (n=9)	0
	UFH	15% (n=2)	46% (n=6)
	LMWH	8% (n=1)	77% (n=10)
	Warfarin	0	8% (n=1)
	Fibrinolytics	15% (n=2)	31% (n=4)
<b>Bilateral RVT + renal insufficiency ± IVC</b> (n=7)	No treatment	29% (n=2)	0
	UFH	14% (n=1)	57% (n=4)
	LMWH	57% (n=4)	71% (n=5)
	Warfarin	0	14% (n=1)
	Fibrinolytics	14% (n=1)	57% (n=4)

Abbreviations: RVT, renal vein thrombosis; IVC, inferior vena cava; UFH, unfractionated heparin; LMWH, low molecular weight heparin.

### Questions asked by the callers

Forty-two percent (n=30) of the callers asked if the RVT in question required treatment at all. How to treat the RVT was asked in 39% (n=28) of cases. Seven (n=5) and six percent (n=4) of the callers asked specific questions about how to use anticoagulants and fibrinolytics, respectively. The duration of treatment was asked for in 15% (n=11) of cases. Four (n=3) and six percent (n=4) of the callers had questions about the further radiographic and/or prothrombotic work-up of the patient.

### Outcome

Five callers reported the long-term outcome to the service: One neonate with unilateral RVT, IVC involvement, and renal insufficiency died of a cerebral hemorrhage following treatment with tPA. In three infants, RVT resolved and kidney function normalized after treatment with tPA (n=2) and LMWH (n=1). One neonate with bilateral RVT and IVC involvement remained with an atrophic left kidney despite treatment with LMWH.

## Discussion

The current paper represents the largest prospective case series of neonatal RVT to date. Data from the study show that i) male infants are affected twice as often as females and ii) there appears to be a left-sided predominance of neonatal RVT. The majority of cases are diagnosed on the first day of life. Renal vein thrombosis in the newborn is only infrequently associated with the presence of a catheter as compared to thrombosis at other sites. In the majority of cases, affected infants have associated conditions, with prematurity being the most frequent. A small subset of neonates were screened for prothrombotic abnormalities, and 50% of the children screened were positive.

Neonatal RVT is a well-recognized clinical entity. Data from the Canadian neonatal thrombosis registry demonstrated that RVT accounts for about 20% of TE in neonates (1). In keeping with this finding, 16% of neonatal TE in the 1-800-NO-CLOTS registry were located in the renal veins. Data in the literature regarding gender distribution in neonatal RVT are controversial. While the current study as well as the German neonatal thrombosis registry found that male infants are significantly more often affected than female infants, other case series did not find any gender difference (8, 14). However, sample sizes of previous studies were probably too small to detect a difference. The reasons for the male predominance remain yet to be clarified. However, it may be speculated that there are gender-related differences in renal perfusion that might increase the risk for RVT in male fetuses.

The majority of neonates in the study had associated conditions, with more than 50% of cases being premature. In addition, most cases of neonatal RVT were diagnosed on the first day of life. Early presentation of neonatal RVT has also been reported by other authors (3, 5, 8). A plausible interpreta-

tion for these observations is that a significant number of RVT occur antenatally. The in utero occurrence of RVT may cause fetal distress and potentially lead to premature birth. Because of the association of neonatal RVT with prematurity and fetal distress, the latter are often considered risk factors for RVT. In fact, both prematurity and fetal distress may actually be caused by, rather than consequences of, RVT.

The left-sided predominance of neonatal RVT has not been reported previously (3). The observation may be explained by the anatomical course of the left renal vein underneath the aorta. Left-sided RVT is occasionally associated with ipsilateral adrenal hemorrhage (15), as seen in two of the patients in the present study. In these cases, adrenal hemorrhage probably occurred as a result of extension of the thrombus into the left adrenal vein which drains into the renal vein on the left side.

In the current study, neonatal RVT was associated with the presence of a catheter in almost 20% of the cases. Previously, RVT has primarily been considered a non-CVL-related form of TE (1). In "classic", non-CVL-related RVT, thrombus formation occurs in the small vessels of the kidney and may extend into the renal vein and IVC. In the neonates with CVL-related RVT in the current study, the thrombus most likely formed first in the vessel adjacent to the CVL and then extended into the kidney. This observation may have implications for the management of neonatal RVT as treatment and prognosis may differ. The risk for pulmonary embolism may be higher with CVL-related RVT because of the affection of the IVC. On average, neonates with CVL-related RVT in this study were older than the neonates with non-CVL related RVT (data not shown).

Hereditary prothrombotic risk factors may also have a role in the pathogenesis of neonatal RVT. In the current study, only a small subset of neonates (29%) were screened for prothrombotic abnormalities and 50% of the children screened were positive. Testing for prothrombotic disorders was performed at the discretion of the attending physician before consultation of 1-800-NO-CLOTS. The subgroup of patients tested for prothrombotic disorders appeared not to represent a more severely affected subgroup. However, patients without exogenous triggers were more likely to have a positive prothrombotic test result than those with an underlying disorder albeit the numbers were too small to reach statistical significance. Also, it cannot be excluded that patients were reported to the service because of their prothrombotic disorder and thus are overrepresented. This is reflected by the finding that in neonates with a positive prothrombotic test, about half of the callers asked about the duration of anticoagulant therapy given the prothrombotic risk factor found (data not shown). Hence, the role of prothrombotic factors in the management of RVT remains to be clarified and the incidence found in the present study should not be generalized.

There are no evidence-based guidelines for treatment of neonatal RVT (13). The lack of information on appropriate

clinical management is indicated by the fact that almost 2/3 of children were not treated at the time of the call. In fact, the reason for the calls where requests for a consultation from the 1-800-NO-CLOTS service on whether and how to treat these children. In the remaining children, 1/4 were treated with low molecular weight heparin, and 1/10 were treated with either unfractionated heparin or lytic therapy. Remarkably, the use of lytic therapy was not correlated to disease severity. The uncertainty and heterogeneity in approach to treatment highlights the absence of proper clinical studies in this area.

There are some potential limitations to the data presented here that need to be acknowledged. Given the nature of the 1-800-NO-CLOTS service, a referral bias towards more severe and complicated cases cannot be excluded. However, the presentation and extension of RVT in the present study does not differ greatly from previous reports (4, 7, 8). The neonates reported represent a mostly North American population, and results may differ from those of other populations. Finally, a problem inherent to the study design is the lack of outcome data for the patients presented. The outcome reported in five neonates in the current study is likely biased, and does not allow

any conclusion about safety and efficacy of treatment. Future studies are necessary to assess outcomes of neonatal RVT.

In conclusion, neonatal RVT affect males more often, are unilateral showing a left-sided predominance, present on the first day of life, are associated with an underlying disorder such as prematurity, and are not commonly associated with an indwelling catheter. Treatment modalities are heterogeneous in these patients. Carefully designed clinical trials are needed to determine the best treatment for neonatal RVT.

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### References

- Schmidt B, Andrew M. Neonatal thrombosis: Report of a prospective Canadian and international registry. *Pediatrics* 1995; 96: 939-43.
- Nowak-Gottl U, von Kries R, Gobel U. Neonatal symptomatic thromboembolism in Germany: Two year survey. *Arch Dis Child Fetal Neonatal Ed* 1997; 76: F163-7.
- Andrew M, Brooker LA. Hemostatic complications in renal disorders of the young. *Pediatr Nephrol* 1996; 10: 88-99.
- Mocan H, Beattie TJ, Murphy AV. Renal venous thrombosis in infancy: Long-term follow-up. *Pediatr Nephrol* 1991; 5: 45-9.
- Keidan I, Lotan D, Gazit G, et al. Early neonatal renal venous thrombosis: Long-term outcome. *Acta Paediatr* 1994; 83: 1225-7.
- Nuss R, Hays T, Manco-Johnson M. Efficacy and safety of heparin anticoagulation for neonatal renal vein thrombosis. *Am J Pediatr Hematol Oncol* 1994; 16: 127-31.
- Bokenkamp A, von Kries R, Nowak-Gottl U, et al. Neonatal renal venous thrombosis in Germany between 1992 and 1994: Epidemiology, treatment and outcome. *Eur J Pediatr* 2000; 159: 44-8.
- Zigman A, Yazbeck S, Emil S, et al. Renal vein thrombosis: A 10-year review. *J Pediatr Surg* 2000; 35: 1540-2.
- Andrew M. Society for pediatric research presidential address 1998: The SPR and 1-800-No-Clots: A common vision. *Pediatr Res* 1998; 44: 964-73.
- Andrew M, David M, Adams M, et al. Venous thromboembolic complications (VTE) in children: First analyses of the Canadian registry of VTE. *Blood* 1994; 83: 1251-7.
- Andrew M, Paes B, Milner R, et al. Development of the human coagulation system in the full-term infant. *Blood* 1987; 70: 165-72.
- Andrew M, Paes B, Milner R, et al. Development of the human coagulation system in the healthy premature infant. *Blood* 1988; 72: 1651-7.
- Andrew M, Monagle P, Brooker L. Thromboembolic complications during infancy and childhood. Hamilton, BC Decker; 2000.
- Ricci MA, Lloyd DA. Renal venous thrombosis in infants and children. *Arch Surg* 1990; 125: 1195-9.
- Orazi C, Fariello G, Malena S, et al. Renal vein thrombosis and adrenal hemorrhage in the newborn: Ultrasound evaluation of 4 cases. *J Clin Ultrasound* 1993; 21: 163-9.