Renal venous thrombosis in neonates: prothrombotic risk factors and long-term follow-up

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The present study was designed to evaluate prothrombotic risk profiles in 59 consecutively recruited white neonates with renal venous thrombosis (RVT). The rates of prothrombotic risk factors (PRs)—for example, the factor V (FV) 1691G>A mutation, the factor II (FII) 20210G>A variant, antithrombin (AT), protein C (PC), protein S (PS), elevated lipoprotein(a) (Lp(a)), total fasting plasma homocysteine (tHcy) levels, and anticardiolipin antibodies (ACAs)—were compared with those of 118 healthy control children. At onset, 32 (54.2%) of the 59 neonates showed underlying clinical conditions; 40 (67.8%) of them and 23 (85.2%) of the 27 infants with idiopathic RVT showed at least one PR. Univariate analysis revealed significantly elevated odds ratios/95% confidence intervals (ORs/95% CIs) for FV and Lp(a). Additionally, PC/AT deficiency and ACAs were found significantly more often in the patient group (P = .04). Multivariate analysis calculated significant ORs/95% CIs only for FV (OR, 9.4; 95% CI, 3.3-26.6) and elevated Lp(a) (OR, 7.6; 95% CI, 2.4-23.8). Of the 59 neonates investigated, 53 revealed renal atrophy, and 13 children additionally suffered from severe arterial hypertension. In conclusion, the present study demonstrates the significance of genetic PR—especially the FV mutation and elevated Lp(a)—for the etiology of neonatal RVT. (Blood. 2004;104:1356-1360)

Introduction

Renal venous thrombosis, although rare in adults, is a well-recognized and potentially fatal entity in children and neonates. Renal venous thrombosis (RVT) is by far the most common manifestation of neonatal thrombosis: The overall incidence of thromboembolic events in the neonatal period is 5 per 100,000 births; more than 40% of all thrombotic manifestations in this age group are symptomatic RVTs. Persisting impairment of kidney function and the need for renal replacement therapy are serious and common complications in patients with RVT.

Renal venous thrombosis occurs predominantly in the neonatal period, and the incidence decreases significantly after the first year of life. It may present with a clinically palpable enlargement of the kidney in association with hematuria, proteinuria, renal failure and oliguria, hypertension, or thrombocytopenia. Long-term functional impairments include hypertension and renal insufficiency. Many imaging modalities have been employed, but ultrasound and color Doppler ultrasound are the techniques most commonly used in the evaluation of neonates with suspected RVT.

Although the etiology of RVT is not fully understood, predisposing factors for neonatal RVT include dehydration, sepsis, birth asphyxia, polycythemia, maternal diabetes, traumatic delivery, congenital renal vein defects, and an indwelling umbilical venous catheter. Little is known of the role of inherited prothrombotic risk factors (PRs) in the development of spontaneous or exogenously triggered RVTs in children. We have previously shown that the factor V 1691G>A (Leiden) mutation and further hereditary prothrombotic risk factors are strong determinants of thromboembolic complications in pediatric patients. However, the role of these risk factors in the pathogenesis of neonatal renal venous thrombosis is not clear so far. Moreover, the published studies on this disease are sparse, and follow-up data on the functional outcome after neonatal RVT in larger numbers of patients are lacking.

Therefore, we performed a multicenter case-control study to assess to what extent single or combined thrombophilic risk factors influence the onset of neonatal renal venous thrombosis in Germany. The follow-up and outcome of these children was additionally studied on an exploratory basis.

Patients, materials, and methods

Ethics

The present study was performed in accordance with the ethical standards laid down in the updated relevant version of the Declaration of Helsinki and was approved by the medical ethics committee at the Westfälische Wilhelms-University, Münster, Germany.

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Patients
White patients with a first symptomatic renal vein thrombosis in the neonatal period were consecutively recruited since January 1989 by the participating centers in the catchment areas of Hamburg, Kiel, Lübeck, Münster, Bielefeld, Düsseldorf, Berlin, Magdeburg, Halle, Frankfurt, and Munich, Germany, and screened for hereditary prothrombotic risk factors between January 1996 and June 2003.

Inclusion/exclusion criteria
Included patients were a symptomatic RVT in the neonatal period confirmed objectively by standard imaging methods. Children older than 28 days at RVT onset and patients with no parental consent were not enrolled in the present study. In addition, owing to the lack of adequate pediatric controls, children with RVT and incomplete prothrombotic workup of established PRs (n = 35) recruited from 1989-1995 (when factor V [FV] 1691G>A, FII 20210G>A, elevated lipoprotein (a) [Lp(a)] were not routinely investigated) were not included in the case-control analysis. However, since 2 consecutively enrolled cohorts were no different with respect to enrollment criteria, clinical presentation, distribution of term and preterm neonates, associated underlying diseases, anticoagulant/antithrombotic therapy, and diagnostic and imaging follow-up procedures, the entire population of 94 children was studied with respect to recurrent thromboembolism (study end point) on an exploratory basis.

Control group
Patients were compared with 118 healthy neonates from different geographic areas of Germany. Controls were recruited between January 1996 and June 2003. They comprised children with no history of chronic disease or of thromboembolic events, without any medication at the time of recruitment, and who presented as outpatients for evaluation before minor surgery (planned circumcisions and hernias) or bone marrow donation.

Imaging methods used at thrombotic onset, follow-up, and suspected rethrombosis
The methods used were color duplex sonography, venography, computed tomography (CT) or magnetic resonance (MR) imaging for the diagnosis of venous thromboembolism; and cerebral CT scanning, MR imaging, MR angiography, or transcranial Doppler ultrasonography for the diagnosis of thromboembolic ischemic stroke. Ultrasound criteria for diagnosis of RVT included echogenic clot visibility, venous distension by the thrombus, absence of flow by color or pulsed Doppler scanning, and the lack of flow augmentation. In children with renal venous thrombosis and suspected renal impairment during the follow-up, renal scintigraphy was also performed.

Predefined underlying clinical conditions
As described recently, bacterial or viral infections, vascular trauma, surgery, macrosomia, jugular or central lines, solid tumors, autoimmune diseases, renal diseases, metabolic disorders, birth asphyxia, and cardiac malformations were predefined as predisposing clinical conditions in the ongoing multicenter study. In addition, drugs such as steroids and the use of sympathomimetics and coagulation factor concentrates were classified as underlying conditions. Patients suffering from RVT but not showing any of the criteria stated here were classified as idiopathic.

Laboratory tests
With parental consent, the FV GA and FII GA mutations, resistance to activated protein C, concentration of Lp[a], protein C (PC), protein S (PS), antithrombin (AT), total fasting plasma homocysteine (tHcy) levels, and anticardiolipin antibodies (ACAs) were routinely investigated in German patients and controls recruited since 1995 by means of standard laboratory techniques at the time of diagnosis and 3 to 6 months after acute thrombotic onset.

Beyond the acute event, laboratory analyses were confirmed in the pediatric coagulation laboratory and pediatric molecular hemostasis laboratory of the Department of Pediatric Hematology and Oncology of the University of Münster, Germany as the reference laboratory for the ongoing multicenter study. A type I deficiency (antithrombin, protein C) was diagnosed when functional plasma activity and immunologic antigen concentrations of a protein were repeatedly shown to be below 50% of the normal age-related limit. A type II deficiency (antithrombin, protein C) was diagnosed if patients with repeatedly low functional activity along with normal antigen concentrations. The diagnosis of protein S deficiency was based on reduced free protein S antigen levels combined with decreased or normal total protein S antigen concentrations. For ACAs (Varelisa cardiolipin antibodies immunoglobulin G [IgG]/IgM) (Pharmacia Diagnostics, Freiburg, Germany), cutoff values greater than 20 IU/mL (IgG) and greater than 11 IU/mL (IgM) were considered abnormal. Serum levels of Lp(a) greater than 0.3 g/L (30 mg/dL) were considered elevated, and 28 kringle IV repeats were used as the cutoff for the diagnosis of small apolipoprotein(a) [apo(a)] isoforms. The tHcy levels were measured in EDTA (ethylenediaminetetraacetic acid) plasma by high-performance liquid chromatography (HPLC) with reverse phase separation and fluorescent detection based on the method of Araki and Sako. Plasma tHcy above 10 μM was regarded as elevated.

Criteria for the hereditary nature of a hemostatic defect were its presence in at least one first-degree family member, the identification of a causative gene mutation, or both.

Clinical routine procedures performed by the participating centers
Besides the prothrombotic testing mentioned before, the routine diagnostic tests after renal venous thrombosis performed 6 weeks, 3 months, 6 months, 12 months, and 2 years after initial hospital discharge include physical examination; serial oscillometric blood pressure recordings; urine analysis; a plasma biochemical profile, including plasma creatinine; and imaging methods (ultrasound, Doppler, or Doppler ultrasound, MRI, and renal scintigraphy, which was performed only in the patients with suspected impaired renal function). After the initial 2-year follow-up, patients were examined again after 5 to 10 years depending on the degree of renal function impairment.

Statistical analysis
All statistical analyses were performed with the StatView 5 software package (SAS Institute, Cary, NC) and the MedCalc software package (MedCalc, Mariakerke, Belgium). To compare the rate of prothrombotic risk factors in patients and controls, to evaluate an independent contribution of thrombophilia to the onset of RVT, and to adjust for the possible interaction of combined prothrombotic risk factors, the odds ratios (ORs) together with 95% CIs were estimated from a multivariate analysis by means of a logistic regression model.

Prevalences of prothrombotic risk factors in patients and control subjects were calculated by χ² analysis or, where relevant, by Fisher exact test. The significance level was set at 0.05.

Results
Final study population (case-control study)
From the ongoing multicenter study, the subgroup of 59 out of 94 children with neonatal RVT was analyzed in a case-control design. In this cohort of children suffering neonatal RVT, symptomatic venous thrombosis was present in 7 parents (5.9%) before the age of 35 years, and in 1 sister before the age of 18 years.

For the case-control study 24 female and 35 male patients with confirmed RVT were enrolled. Forty-five affected patients were term neonates (median, 40 gestational weeks; range, 37-42 gestational weeks), and 14 were premature patients (median, 31 gestational weeks; range, 25-36 gestational weeks). Interestingly, the female-male ratio was shifted toward a male predominance (1:1.5).
Leading symptoms at onset of symptomatic renal venous thrombosis

Hematuria and thrombocytopenia were the leading symptoms in 29 of the 59 neonates (49.1%). In 16 children (27.1%), anuria had occurred, and 9 subjects (15.3%) presented with a palpable abdominal mass. In 5 neonates (8.5%), adrenal bleeding was observed.

Thrombotic locations

Twenty-three neonates (38.9%) presented with a left renal vein thrombosis; 20 (33.9%) with right-sided thrombosis; and 16 (27.2%) with bilateral RVT. In 15 of these patients (25.4%), an additional thrombosis of the inferior caval vein was present. Further venous thromboses (deep venous thrombosis, n = 2; hepatic vein, n = 1; and pulmonary embolism, n = 1) or arterial occlusions (ischemic stroke, n = 4; aorta, n = 1; mesenteric artery, n = 1) were diagnosed at symptomatic thrombotic onset.

Additional underlying clinical conditions

RVT occurred spontaneously in 27 children (45.8%) without any underlying clinical conditions predefined in the “Patients, materials, and methods.” In the remaining children, sepsis (n = 10), the use of central venous lines (n = 9), birth asphyxia (n = 7), maternal administration of betamethasone (n = 4), and diabetic fetopathy (n = 2) were associated with the onset of neonatal RVT.

Acute antithrombotic treatment

At the discretion of the participating study centers, patients were treated with low-molecular-weight heparin (LMWH) (2- to 4-hour anti-factor Xa level, 0.4 to 0.6 IU/mL) or unfractionated heparin (UFH) (activated partial thromboplastin time [aPTT] increase, 1.5- to 2-fold compared with baseline). Intravenous thrombolysis was performed with rt-PA according to doses given in Nowak-Goettel et al.28

Of the 59 subjects affected, 28 (47.5%) were treated with low-molecular-weight heparin, 5 (8.5%) with unfractionated heparin, and 4 (6.8%) with antithrombin concentrates, while another 11 (18.6%) underwent intravenous thrombolytic therapy. In addition, 18.6% (11 of 59) received only supportive treatment but no antithrombotic therapy. In accordance with our previously published data,2 however, acute antithrombotic treatment was not associated with the clinical outcome reported by the participating study centers (P = .3).
than 2 standard deviations [SDs] above the mean; \( P = .04 \) were
significantly more common in the patient group, with 3 cases of
each detected. No significant differences were found for frequen-
ties of FII 20210G>A (OR, 4.3; 95% CI, 0.8-24.2); protein S
deficiency was not diagnosed in either the patient or the control
colation investigated. In a multivariate analysis that included all
the prothrombotic risk factors significantly associated with RVT in
the univariate analysis (FV 1691G>A, elevated Lp(a), protein C
and antithrombin deficiency, presence of increased ACAs), only
the heterozygous FII mutation (OR, 9.4; 95% CI, 3.3-26.6; \( P < .0001 \))
and elevated Lp(a) (OR, 7.6; 95% CI, 2.4-23.8; \( P = .0005 \)) retained
their statistically significant association with symptomatic
neonatal RVT. Interestingly, 22 (81.5%) of 27 neonates with
idiopathic RVT showed at least one PR. The distribution of single
and combined prothrombotic risk factors was not associated with
long-term renal impairment \( (P = .6) \).

**Outcome**

The primary aim of this study was to evaluate the rate of
prothrombotic risk factors as an underlying condition in neonatal
RVT patients. However, information is also available on the
long-term clinical outcome. During the follow-up period, 53
(89.8%) of the 59 neonates with RVT (heparin group, 30 of 33;
antithrombin group, 4 of 4; thrombolysis group, 9 of 11; supportive
therapy, 10 of 11) revealed relevant unilateral renal atrophy on
ultrasound scan in 42 cases, and bilateral renal atrophy in 11
subjects. In 3 (27.3%) of the 11 children with bilateral RVT and
bilateral organ damage, a renal transplantation was necessary.
Ten children with unilateral atrophy and the 3 children with bilateral
atrophy before transplantation suffered from severe arterial
hypertension, necessitating long-term antihypertensive treatment.
in one girl, a nephrectomy had to be performed at the age of 2 because of
extensive arterial hypertension.

**Recurrent thromboembolism (exploratory study)**

The median follow-up time was 4.0 years (range, 0.6-15.0 years), and 4
(4.3%) of the 94 children with neonatal RVT suffered a second
thromboembolism. Interestingly, in 3 of the 4 cases, a second sympto-
atimic thrombosis occurred during puberty. No patient received secondary
prophylactic antithrombotic treatment at the time of recurrence.
All patients with recurrent events had at least one prothrombotic defect
(single PR, \( n = 2 \); combined PR, \( n = 2 \)).

**Discussion**

The present multicenter case-control study was designed to assess
the extent to which single and combined clotting factor abnormali-
ties influence the onset of neonatal renal venous thrombosis in
Germany and, furthermore, to evaluate on an exploratory basis
renal impairment and recurrent symptomatic venous thrombosis.

Data presented here clearly demonstrate that prothrombotic risk
factors were observed significantly more frequently in patients with
RVT than in healthy control children. Besides the genetic thrombo-
ophilic risk factors—for example, the FV 1691G>A mutation, the
FII 20210G>A variant, elevated concentrations of Lp(a), protein C
deficiency, and antithrombin deficiency—increased ACAs were
also involved in the first thrombotic onset in the neonatal
period. Our data support case reports by Leret et al16 and Giordano
et al15 demonstrating that RVT in neonates is associated with the
heterozygous FV 1691G>A alone or in combination with further
PR, such as the heterozygous FII 20210G>A variant.

On the one hand, when the number of single and combined
prothrombotic risk factors are taken into account, logistic regres-
sion as a multivariate statistical model clearly demonstrates that the
FV 1691G>A mutation and elevated Lp(a) concentrations are
significant and independent risk factors for the development of
RVT in neonates. On the other hand, as a limitation of the present
study, no conclusion can be drawn from the data presented here
with respect to PRs’ not reaching statistical significance: thus, to
clarify the role of the FII 20210G>A variant; of deficiencies in
protein C, protein S, and antithrombin; and increased homocysteine
and ACAs; further international studies performed in white chil-
dren are recommended to increase the statistical power.

Besides the role of inherited or acquired thrombophilia as an
underlying pathomechanism of RVT in the neonate, data of the
present study also suggest that renal venous thrombosis in children
is a multifactorial disease: The existence of underlying disorders—
for example, asphyxia, sepsis, diabetic fetopathy, central lines, or
the administration of prenatal betamethasone—in combination
with prothrombotic risk factors also appear to play a major role in
the pathogenesis of the event. In addition, in accordance with
previously published data, we observed more affected male than
female newborns.2,29

Although the present study focused mainly on the role of
thrombophilia at the onset of neonatal RVT, preliminary follow-up
data suggesting a poor long-term outcome are available. Only 6 of
59 neonates with RVT in our study showed no organ damage in the
follow-up investigation. These data are in accordance with smaller
series with a poor outcome after RVT25,30,31: Keidan and cowor-
kers8 observed complete atrophy of the affected kidneys in 4 of 6
affected neonates after RVT, and in a follow-up study Mocan et al25
reported a normal ultrasound of the kidney in only 2 of 14 RVT
patients studied. Renal impairment was not associated with the
presence of prothrombotic risk factors or the acute anticoagulant/
anthithrombotic treatment performed. Since no evidence-based
guidelines are available so far with respect to acute antithrombotic
treatment of neonates suffering RVT, treatment modalities varied
among the participating study centers. The variations in treatment
and the fact that in the present study no randomization of
antithrombotic drugs was performed have to be discussed as further
limitations of the study presented here. Although no statistical
correlation was found between renal impairment and acute antico-
gulant/antithrombotic therapy during the follow-up, this issue
needs to be addressed in further prospective intervention studies.

In 4 of 94 patients (the entire cohort) a recurrent thromboem-
bolic event occurred during the follow-up period. Interestingly, 3 of
4 events occurred during puberty, a time point also known as the
second peak for childhood thrombosis.32 In addition, none of the 4
patients received secondary prophylactic antithrombotic treatment
at the time of recurrence. The recurrence rate of 4.3% in the cohort
presented here with a median patient follow-up of 4 years
represents only the tip of the iceberg, and the appropriate incidence
of recurrence will be manifest within the next 10 to 15 years when
the majority of children enrolled in the present study have passed
puberty. In accordance with our previously published data,31 2
(16.7%) of the 12 children with neonatal RVT with combined PRs
suffered a recurrent thrombotic event, suggesting that the presence
of combined hereditary risk factors also significantly increases the
risk for recurrence of venous thrombosis in patients with RVT.11,33

In conclusion, the present study demonstrates the significance
of genetic prothrombotic risk factors—especially the FV 1691G>A mu-
tation and the elevation of Lp(a)—for the etiology of renal venous
thrombosis in white neonates. On the basis of the data presented here
and the fact that the family history was positive for venous thrombosis in 11.9% of cases, screening for thrombophilic risk factors—for example, the FV 1691G>A mutation, the FII 20210G>A variant, Lp(a), protein C, protein S, antithrombin, and ACAs—is recommended in white neonates with RVT. To our knowledge, no controlled data are available with respect to the interaction between PR and neonatal RVT in nonwhite children. Therefore, this screening recommendation is restricted to white patients only. Since secondary antithrombotic treatment is available in at-risk situations, such as immobilization or surgery, a screening for prothrombotic risk factors after neonatal RVT may help to stratify the risk of recurrence.11 Besides controlled, randomized, multicenter studies to clarify the role of prothrombotic risk factors that did not reach significance in the cohort investigated here, further international trials are needed to prospectively examine the benefit of different acute and secondary anticoagulant/antithrombotic treatment strategies.

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References

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