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Renal venous thrombosis in neonates:

Prothrombotic risk factors and long-term follow-up

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Abstract

The present study was designed to evaluate prothrombotic risk profiles in 59 consecutively recruited Caucasian neonates with renal venous thrombosis (RVT). The rates of prothrombotic risk factors (PR), e.g. the factor V (FV) G1691A mutation, the factor II (FII) G20210A variant, antithrombin (AT), protein C (PC), protein S (PS), elevated lipoprotein (Lp) (a), total fasting plasma homocysteine levels (tHcy) and anticardiolipin antibodies (ACA), were compared with those of 118 healthy control children.

At onset 32 of the 59 neonates (54.2%) showed underlying clinical conditions, 40 (67.8%) of them and 23 of the 27 (85.2%) infants with idiopathic RVT showed at least one PR. Univariate analysis revealed significantly elevated odds ratios/95% confidence intervals (OR/CI) for FV and Lp(a). Additionally PC-/AT-deficiency and ACA were found significantly more often in the patient group (p=0.04). Multivariate analysis calculated significant OR/CI only for FV (OR/CI:9.4/3.3-26.6) and elevated Lp(a) (OR/CI:7.6/2.4-23.8). 53 of the 59 neonates investigated 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.

Introduction

Although rare in adults, renal venous thrombosis is a well-recognized and potentially fatal entity in children and neonates (1). Renal venous thrombosis (RVT) is by far the most common manifestation of neonatal thrombosis: The incidence of thromboembolic events overall in the neonatal period is 5 per 100,000 births; more than 40% of all thrombotic manifestations in this age group are symptomatic RVTs (2,3). Persisting impairment of kidney function and the need for renal replacement therapy are serious and common complications in patients with RVT (4).

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 (4,5). 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 (6).

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, or an indwelling umbilical venous catheter (7,8). Little is known of the role of inherited prothrombotic risk factors (PR) in the development of spontaneous or exogenously triggered RVTs in children. We have previously shown that the factor V G1691A (Leiden) mutation and further hereditary prothrombotic risk factors are strong determinants of thromboembolic complications in pediatric patients (9-14). However, their role 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 (3,15,16).

Therefore, we performed a multicentre 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 explorative basis.

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 approved by the medical ethics committee at the Westfälische Wilhelms-University, Münster, Germany.

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

Inclusion/exclusion criteria: Inclusion criteria were a symptomatic RVT in the neonatal period confirmed objectively by standard imaging methods. Children > 28 days at RVT onset, and patients with no parental consent were not enrolled in the present study. In addition, due to the lack of adequate pediatric controls children with RVT and incomplete prothrombotic work-up of established PR (n=35) recruited from 1989-1995 (FV G1691A, FII G20210A, Lp(a) not routinely investigated) were not included in the case-control analysis. However, since the two 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 as well as diagnostic and imaging follow-up procedures the entire population of 94 children was studied with respect to recurrent thromboembolism (study endpoint) on an explorative 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 and

without any medication at the time of recruitment, 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 (2,6,17,18,19), venography, CT or 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 (12). Ultrasound criteria for diagnosis of RVT included the lack of flow augmentation, echogenic clot visibility, venous distention by the thrombus, and absence of flow by color or pulsed Doppler scanning. In children with renal venous thrombosis and suspected renal impairment during the follow-up, renal scintigraphy was additionally performed.

Predefined underlying clinical conditions: As described recently (20) 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 multicentre 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 one of the criteria stated here were classified as ”idiopathic”.

Laboratory tests: With parental consent, the factor V G1691A (FV GA) and factor II G20210A (FII GA) mutations, resistance to activated protein C, concentration of lipoprotein (Lp) (a), protein C (PC), protein S (PS), antithrombin (AT), total fasting plasma homocysteine levels (tHcy) and anticardiolipin antibodies (ACA) were routinely investigated in German patients and controls recruited since 1995 using standard laboratory techniques at the time of diagnosis and 3-6 months after acute thrombotic onset (20,21). Beyond the acute event

laboratory analyses were confirmed in Münster as the reference laboratory for the ongoing multicentre study. A type I deficiency (antithrombin, protein C) was diagnosed when functional plasma activity and immunological antigen concentrations of a protein were repeatedly shown to be below 50% of the normal age-related limit (22). A type II deficiency (antithrombin, protein C) was diagnosed in 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, respectively. For ACA (Varelisa cardiolipin antibodies IgG/IgM, Pharmacia Diagnostics, Freiburg, Germany) cut-off values >20 IU/ml (IgG) and >11 IU/ml (IgM) were considered abnormal. Serum levels of Lp(a) >30 mg/dl were considered elevated, and 28 kringle IV repeats were used as the cut-off for the definition of small apo(a) isoforms. Total plasma tHcy levels were measured in EDTA plasma by high-performance liquid chromatography (HPLC) with reverse phase separation and fluorescent detection based on the method of Araki and Sako (23). Plasma tHcy above 10 µmol/l was regarded as elevated (24). Criteria for the hereditary nature of a hemostatic defect were its presence in at least one first degree family member, or the identification of a causative gene mutation, or both.

Clinical routine procedures performed by the participating centres: Besides the prothrombotic testing mentioned before, the routine diagnostic tests after renal venous thrombosis performed 6 weeks, 3 months, 6 months, 12 months, and two 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, Duplex or color Doppler ultrasound, MRI, and renal scintigraphy, which was only performed in the patients with suspected impaired renal function) (25,26,27). After the initial two-years follow-up patients were additionally examined 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) and the MedCalc software package (MedCalc, Mariakerke, Belgium). To compare the rate of prothrombotic risk factors between 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 ORs together with 95% CIs were estimated from a multivariate analysis using a logistic regression model.

Prevalences of prothrombotic risk factors in patients and control subjects were calculated by χ^2-analysis or, where relevant, by Fisher's exact test. The significance level was set at 0.05.

Results

Final study population (case-control study): From the ongoing multicentre 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 one sister before the age of 18.

For the case-control study 24 female and 35 male patients with confirmed RVT were enrolled. 45 affected patients were term neonates (median/range gestational week: 40/37-42) and 14 premature patients (median/range gestational week: 31/25-36). Interestingly the female/male ratio was shifted towards 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 (27.1%) children anuria had occurred, and 9 (15.3%) subjects presented with a palpable abdominal mass. In 5 (8.5%) neonates adrenal bleeding was observed.

Thrombotic locations: 23 (38.9%) neonates presented with a left renal vein thrombosis, 20 (33.9%) with right-sided and 16 (27.2%) with bilateral RVT. In 15 (25.4%) of these patients 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 Methods section. In the remaining children sepsis (n=10), the use of central venous lines (n=9), birth asphyxia (n=7), maternal administration of betamethason (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 centres, patients were treated with low molecular weight heparin (LMWH, 2-4 hour anti factor Xa-level: 0.4–0.6 IU/ml) or unfractionated heparin (UFH, aPTT increase 1.5 to 2-fold compared to baseline). Intravenous thrombolysis was performed with rt-PA according to doses given in reference 28. 28 of the 59 subjects (47.5%) affected 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% (11/59) received only supportive treatment but no antithrombotic therapy. In accordance with our previously published data (3), however, acute antithrombotic treatment was not associated with the clinical outcome reported by the participating study centres (p=0.3).

Distribution of prothrombotic risk factors: In 40 of the 59 patients (67.8%) at least one established prothrombotic risk factor was found compared with 14 in the 118 control children (11.9%) (OR: 15.6/CI: 7.2-34.2). The distribution of single and combined prothrombotic risk factors in patients is shown in Table 1.

Table 1: Distribution of single (n=28) and combined (n=12) prothrombotic risk factors in neonatal patients at RVT onset (n=59), in recurrent thrombosis (n=4), and healthy controls. Additionally, the interaction between prothrombotic risk factors and underlying clinical condition is shown.

Prothrombotic risk factor	**Onset of renal venous thrombosis**	**Recurrent thrombosis in carriers**	**Control group**
Overall distribution of single and combined prothrombotic risk factors			
Factor V G1691A total	**22/59 (37.3%)**	**3/22 (13.6%)**	**7/118 (5.9%)**
- Homozygous A1691A	1	1	-
- Single heterozygous G1691A	13	-	7
- & Lipoprotein (a) >30 mg/dl	5	1	-
- & Factor II	2	-	-
- & Protein C deficiency	1	-	-
Factor II G20210A total	**5/59 (8.5%)**	**0/5 (-)**	**2/118 (1.7%)**
- Single	-	-	2
- & Factor V G1691A	2*	-	-
- & Lipoprotein (a) >30 mg/dl	3		-
Lipoprotein (a) > 30 mg/dl total	**17/59 (28.8%)**	**1/17 (5.9%)**	**5/118 (4.2%)**
- Single	6	1	5
- & Factor V G1691A	5*	(1)*	-
- & Factor II	3*	-	-
& **Hcy > 10 µmol/l	1	-	-
****Protein C deficiency total**	**3/59 (5.0%)**	**1/3 (33.3%)**	**-**
- Single	2	1	-
- & Factor V G1691A	1*	-	-
****Antithrombin deficiency total**	**3/59 (5.0%)**	-	-
Single	3	-	-
ACA > 2 STD total	**3/59 (5.0%)**	-	-
- Single	3	-	-
Interaction of prothrombotic risk factors (PR) and underlying clinical conditions (UCC)			
PR with UCC	18/59 (30.5%)	2/18 (11.1%)	-
PR without UCC	22/59 (37.3%)	2/22 (9.1%)	-
No PR with UCC	15/59 (25.4%)	-	-
No PR and no UCC	4/59 (6.8%)	-	-

Abbreviations used: ACA: anticardiolipin antibodies; Hcy: homocysteine

* already mentioned before; ** protein C: 5,7 and 12%; antithrombin: 5, 12 and 20%;
hcy: 19 µmol/l (6-12 months after acute onset; confirmed in at least one family member; MTHFR C677T).

Upon univariate analysis compared to controls, patients showed significantly higher prevalences of FV G1691A (OR: 11.1/CI: 4.2-29.5) and elevated Lp(a) (OR: 9.2/CI: 3.2-26.4). Additionally, protein C deficiency (p=0.04), antithrombin deficiency (p=0.04), and increased ACA (in all cases > 2 STD above the mean: p=0.04) were significantly more common in the patient group, with three cases of each being detected. No significant differences were found for frequencies of FII G20210A (OR: 4.3/CI 0.8-24.2); protein S deficiency was diagnosed neither in the patient nor in the control population investigated. In a multivariate analysis, including all the prothrombotic risk factors significantly associated with RVT in the univariate analysis (FV G1691A, elevated Lp(a), protein C and antithrombin deficiency, presence of increased ACA), only the heterozygous FV mutation (OR/CI: 9.4/3.3-26.6; p<0.0001) and elevated Lp(a) (OR/CI: 7.6/2.4-23.8; p=0.0005) retained their statistically significant association with symptomatic neonatal RVT. Interestingly, 22 of 27 (81.5%) 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=0.6).

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 of the 59 neonates (89.8%: heparin group: 30/33; antithrombin group: 4/4; thrombolysis group: 9/11; supportive therapy: 10/11) with RVT revealed relevant unilateral renal atrophy on ultrasound scan in 42 cases, and bilateral in 11 subjects. In 3 of the 11 children (27.3%) with bilateral RVT and bilateral organ damage a renal transplantation was necessary. 10 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 (explorative description): The median (range) follow-up time was 4.0 years (0.6-15.0 years), and 4 of the 94 children (4.3%) with neonatal RVT suffered a second thromboembolism. Interestingly in 3 of the 4 cases a second symptomatic 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 multicentre case-control study was designed to assess the extent to which single and combined clotting factor abnormalities influence the onset of neonatal renal venous thrombosis in Germany, and furthermore, to evaluate on an explorative 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 thrombophilic risk factors, e.g. the FV G1691A mutation, the FII G20210A variant, elevated concentrations of Lp(a), protein C deficiency, and antithrombin deficiency, acquired increased ACA were also involved in the first thrombotic onset in the neonatal period. Our data support case reports by Leret et al. and Giordano et al. demonstrating that RVT in neonates are associated with the heterozygous FV G1691A alone or in combination with further PR, such as the heterozygous FII G20210A variant (15,16).

On the one hand, taking into account the number of single and combined prothrombotic risk factors, logistic regression as a multivariate statistical model clearly demonstrates that the FV G1691A 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 PR not reaching statistical significance: thus, to clarify the role of the FII G20210A variant, protein C-, protein S-, antithrombin deficiency, increased homocysteine and ACA, further

international studies based on the same ethnical background 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 combination of underlying disorders, e.g. asphyxia, sepsis, diabetic fetopathy, central lines or the administration of prepartal betamethason in combination with prothrombotic risk factors appear also 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 (3, 29).

Although the present study was focused mainly on the role of thrombophilia at the onset of neonatal RVT, preliminary follow-up data are available suggesting a poor long-term outcome. 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 RVT (25,30,31): Keidan and co-workers observed complete atrophy of the affected kidneys in 4 out of 6 affected neonates after RVT, and Mocan et al. reported in a follow-up study a normal ultrasound of the kidney in only 2 of 14 studied RVT patients (25,30). Renal impairment was not associated with the presence of prothrombotic risk factors or the acute anticoagulant/antithrombotic 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 centres. The latter issues 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 anticoagulant/antithrombotic therapy during the follow-up, this issue needs to be addressed in further prospective intervention studies.

In 4 of 94 patients (entire cohort) a recurrent thromboembolic 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 only represents the ”top 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 has passed puberty. In accordance with our previously published data (11), 2 of the 12 (16.7%) children with neonatal RVT with combined PR suffered a recurrent thrombotic event, suggesting that the presence of combined hereditary risk factors significantly increases the risk for recurrence of venous thrombosis in patients also with RVT (11, 33).

In conclusion, the present study demonstrates the significance of genetic prothrombotic risk factors - especially the FV G1691A mutation and the elevation of Lp (a) - for the etiology of renal venous thrombosis in Caucasian neonates. Based on 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, e.g. the FV G1691A mutation, the FII G20210A variant, Lp(a), protein C, protein S, antithrombin and ACA, is recommended in Caucasian neonates with RVT. To our knowledge no controlled data are available with respect to the interaction between PR and neonatal RVT in children of non-Caucasian ethnicity. Therefore this screening recommendation is restricted to Caucasian patients only. Since secondary antithrombotic treatment is available in situations at risk, 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, multicentre studies to clarify the role of prothrombotic risk factors not reaching 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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