ORIGINAL ARTICLE

Perinatal renal venous thrombosis: presenting renal length predicts outcome

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Background: Renal venous thrombosis (RVT) is the most common form of venous thrombosis in neonates, causing both acute and long term kidney dysfunction. Historical predisposing factors include dehydration, maternal diabetes, and umbilical catheters, but recent reports highlight associations with prothrombotic abnormalities.

Study: Twenty three patients with neonatal RVT were analysed over 15 years. Predisposing factors, presentation, and procoagulant status were compared with renal outcome using multilevel modelling.

Results: Median presentation was on day 1: 19/23 (83%) had pre/perinatal problems, including fetal distress (14), intrauterine growth retardation (five), and pre-identified renal abnormalities (two); 8/18 (44%) had procoagulant abnormalities, particularly factor V Leiden mutations (4/18). Long term abnormalities were detected in 28/34 (82%) affected kidneys; mean glomerular filtration rate was 93.6 versus 70.2 ml/min/1.73 m² in unilateral versus bilateral cases (difference 23.4; 95% confidence interval 6.4 to 40.4; $p = 0.01$). No correlation was observed between procoagulant tendencies and outcome, but presenting renal length had a significant negative correlation: mean fall in estimated single kidney glomerular filtration rate was 3 ml/min/1.73 m² (95% confidence interval 3.7 to –2.2; $p = 0.001$) per 1 mm increase, and kidneys larger than 6 cm at presentation never had a normal outcome.

Conclusions: This subgroup of neonatal RVT would be better termed perinatal RVT to reflect antenatal and birth related antecedents. Prothrombotic defects should be considered in all patients with perinatal RVT. Kidney length at presentation correlated negatively with renal outcome. The latter, novel observation raises the question of whether larger organs should be treated more aggressively in future.

Renal venous thrombosis (RVT) is the most common form of venous thrombosis in neonates, and can cause both acute renal failure and long term dysfunction.¹ Classical presentation includes a palpable abdominal mass, gross haematuria, and thrombocytopenia,^{2–5} with predisposing factors such as dehydration, sepsis, birth asphyxia, maternal diabetes, and umbilical catheterisation. Recent surveys have also highlighted the importance of underlying prothrombotic conditions in RVT.^{6–7} These include antithrombin, protein C and S deficiency, and point mutations/substitutions in other coagulation factors.^{8–9} One of the most important appears to be the factor V Leiden (1691G→A) mutation, which impairs activated factor V breakdown, thereby causing activated protein C resistance on coagulation screening.^{10–11} Up to 5% of white people are heterozygotes, which increases their risk of thrombosis 5–7-fold; homozygotes have an 80-fold increase.^{11–12} Other mutations include prothrombin 20210G→A (2% of white people; increased thrombosis risk about threefold¹³) and methylenetetrahydrofolate reductase (MTHFR) 677T genotype (15% of the population are homozygotes and have a slightly increased risk of thrombosis caused by raised homocysteine concentrations^{12–14}).

Little information is currently available on RVT and procoagulant predisposition in the United Kingdom, as the last published report was before many of these mutations were defined.² We report on 23 patients with neonatal RVT managed over 15 years in our tertiary unit, using multilevel modelling to determine which presenting factors correlated significantly with patient and kidney outcomes.

METHODS

Study population

Neonates with RVT were identified from the Nephro-Urology database, which has records of every child admitted to the

Nephrology and Urology wards at the Hospital for Sick Children, Great Ormond Street over the last 25 years. Later presentations of thrombosis after renal transplant were excluded. The study period 1988–2002 was chosen, as earlier cases had significant data loss. Review of retrospective notes was approved by our local research ethics committee. Clinical assessment/follow up was performed as part of routine clinical care.

Presentation

Data collected included antenatal status (fetal abnormalities and growth), perinatal history (gestation, delivery, birth weight, resuscitation), and RVT presentation (age, biochemistry, and haematology). Diagnosis was made by ultrasound. Signs included increased echogenicity around the interlobular vessels, direct visualisation of thrombus in the main renal veins and inferior vena cava, and/or absence of flow on colour or pulsed Doppler scanning, often combined with swelling, increased echogenicity, and patchy loss of corticomedullary differentiation.¹⁵

Prothrombotic analysis

Prothrombotic analysis included concentrations of protein C/S and antithrombin, Exner test and dilute Russell's viper venom time (DRVVT), and anticardiolipin antibodies. From 1998, we routinely assessed factor V Leiden, prothrombin, and MTHFR mutations, and have checked the status of earlier patients at follow up.

Abbreviations: CKD, chronic kidney disease; GFR, glomerular filtration rate; MTHFR, methylenetetrahydrofolate reductase; RVT, renal venous thrombosis

Table 1 Presentation of renal venous thrombosis

Patient	Antenatal and obstetric history	Fetal distress	Age at diagnosis (days)	Haematuria	Palpable mass	Thrombocytopenia
1	Antepartum maternal haemorrhage, emergency LSCS; asystolic at birth	Y	1	Y	N	–
2	Raised α fetoprotein at 18 weeks, subsequent investigations normal; emergency LSCS, meconium stained liquor	Y*	1	N	Y	Y
3	Emergency LSCS at 32/40	Y	2	Y	N	–
4	SVD at 27/40 (twin 1)	–	11	N	N	–
5	Emergency LSCS at 38/40 for maternal pre-eclampsia	N	3	Y	Y	–
6	Abnormal kidneys and IUGR on antenatal ultrasound scans, SVD at term	N	Antenatal	N	N	–
7	Decreased movements from 34/40, Ventouse delivery at 36/40	N	1	N	Y	Y
8	Twin to twin transfusion syndrome	–	1	Anuric	–	–
9	Emergency LSCS at term	Y	1	N	Y	Y
10	IUGR, LSCS at 34/40	–	–	–	–	–
11	SVD at term, meconium stained liquor	Y*	2	Y	N	Y
12	SVD at term, meconium stained liquor	Y*	2	Y	Y	Y
13	Antenatal scan at 36/40 showed polyhydramnios; SVD at term	N	3	N	Y	Y
14	Forceps delivery at term, cord around the neck, meconium stained liquor	Y*	1	Y	Y	Y
15	Normal antenatal scans; emergency LSCS	Y	Antenatal	N	N	Y
16	IUGR, emergency LSCS at term	Y	1	Y	N	N
17	SVD term, but difficult delivery with shoulder dystocia	N	1	Y (at birth)	Bilateral	Y
18	Antenatal scan at 32/40 showed polyhydramnios, emergency LSCS at 38/40; poor feeding, lost 16% birth weight in 1 week	Y	8	N	Y	–
19	IUGR, induced at 36/40	N	21	N	N	N
20	Maternal diabetes, emergency LSCS at 37/40	Y	1	N	Bilateral	Y
21	IUGR. Ventouse delivery at term. Severe asphyxia, cerebral infarction. UAC and UVC	Y	1	Y	Y	Y
22	Emergency LSCS at term. UAC and UVC	Y	1	N	Y	Y
23	Emergency LSCS	Y	1	Y	Y	Y
Totals		14/21	Median: 1	10/21	13/21	13/16

In the fetal distress column, "Y" indicates that distress was recorded; in the obstetric history, "Y*" indicates meconium stained liquor indicating fetal distress. Thrombocytopenia was defined as platelet count of less than 150×10^9 per litre.

IUGR, Intrauterine growth retardation; LSCS, lower segment caesarean section; SVD, spontaneous vertex delivery; UAC, umbilical arterial catheter; UVC, umbilical venous catheter; –, details were unavailable.

Follow up and outcome

Severely affected patients were managed on our chronic renal failure programme; others were reviewed routinely at 6–12 weeks after discharge, then six monthly, and finally yearly. Assessments included growth and blood pressure, urinalysis, plasma biochemistry, and haematology. Radiology comprised renal ultrasound and a dimercaptosuccinic acid isotope scan or intravenous urograms. Glomerular filtration rate (GFR) was measured in most patients using chromium/EDTA clearance, and single-kidney function was estimated by multiplying total GFR by dimercaptosuccinic acid uptake. Chronic kidney disease (CKD) score used the UK Renal Association/NSF definitions (see tables 3 and 4), which are modified from the US K/DOQI guidelines.¹⁶ Results that were repeated over time (such as ultrasound) appeared consistent, hence we analysed the latest results available.

Statistical analysis

Independent samples *t* tests were used to compare means between groups. Multilevel modelling (MLwiN 1.10) was used to investigate associations between outcomes and potential predictors while accounting for within-child correlation of the variables where applicable. Changes in the odds ratios or mean concentrations (as appropriate) associated with the predictors are presented with 95% confidence intervals (CI).

RESULTS

Twenty four patients were identified with neonatal RVT in the Nephro-Urology database in the study period, but one

was excluded because diagnosis was not confirmed radiologically.

Presentation

Median presentation was on day 1 (range antenatal to 21; table 1). Seventeen were boys (74%). Nineteen patients (83%) had antenatal or delivery problems including fetal distress (14), emergency caesarean section (11), and intrauterine growth retardation (five). Two children were diagnosed in utero, one during investigations of intrauterine growth retardation and the other because of a family history of severe thrombophilia with a thrombosis related sibling death. In addition, patient 17 passed blood per urethra as he was delivered, and patient 8 was anuric from birth, suggesting that thrombosis probably occurred before labour/delivery. Patient 19 presented at 21 days with hyperosmolar dehydration, a well recognised complication of Netherton's syndrome (rare autosomal recessive ichthyosiform condition). Other significant pathology included severe birth asphyxia in cases 1 and 21, which resulted in spastic quadriplegia and a left cerebral infarction respectively.

Haematuria was recorded in 10/21 (48%), a palpable mass in 13/21 (62%), and thrombocytopenia in 13/16 (80%); only five (22%) had all three features. Central/umbilical lines were rare before RVT in our series: patients 21 and 22 had both umbilical venous and arterial lines, patient 2 had an umbilical arterial line, and patient 4 had a small bore parenteral feeding line. Six babies (26%) were delivered at or

Table 2 Investigations at presentation of renal venous thrombosis (RVT)

Patient	Length (R/L; mm)	Side	IVC	Prothrombotic risk factors
1	41/47	Bilateral	N	—
2	53/70	Left	N	—
3	41/31	Left	N	—
4	—	Bilateral	Y	—
5	46/52	Left	N	Normal
6	58/52	Bilateral	Y	Factor V Leiden mutation heterozygous, MTHFR C677T mutation heterozygous
7	53/60	Bilateral	Y	—
8	—	Bilateral	—	Normal
9	64/50	Right	Y	Factor V Leiden mutation heterozygous, MTHFR C677T mutation heterozygous
10	—	Bilateral	—	Normal†
11	50/51	Bilateral	N	Normal
12	64/43	Right	Y	Normal
13	43/38	Bilateral	Y	Normal
14	—	Left	N*	Normal
15	45/57	Left	Y*	Heterozygous protein C and protein S deficiency
16	48/59	Left	N*	MTHFR C677T mutation homozygous
17	78/68	Bilateral	Y	Factor V Leiden mutation heterozygous
18	40/50	Left	N*	Normal
19	—	Right	—	MTHFR C677T mutation homozygous
20	61/46	Bilateral	N	Normal
21	46/51	Bilateral (only lower pole affected on right)	N	MTHFR C677T mutation heterozygote
22	69/74	Bilateral	Y*	Normal
23	63/55	Bilateral	Y*	Factor V Leiden mutation heterozygous
Means or frequency	Nrm: 45.8 Uni: 55.8 Bilat: 55.2	Bilat: 13/23 Left: 7/23 Right: 3/23	10/20	8/18

*Left adrenal haemorrhage.

†Patient 10 was initially diagnosed incorrectly as protein C deficient, but it is now recognised that neonates/children have lower concentrations than the adult range (which can also be reduced further during a thrombotic event); he does not have protein C mutations and his concentrations are now within the normal age adjusted range. Nrm, Normal unaffected kidney; Uni, unilateral RVT; Bilat, bilateral RVT; IVC, inferior vena cava involvement; —, information unavailable.

before 36 weeks, one mother had diabetes, and three babies were from twin pregnancies.

Initial investigation and management

RVT was left sided in seven (30%), right in three (13%), and bilateral in 13/23 (57%; table 2). Left adrenal haemorrhage was also detected in six, although frequency is uncertain as this was not documented in earlier patients. The inferior vena cava was involved in 10/20 (50%); seven of these were bilateral RVT. The mean length of kidneys with RVT was 55.4 mm (bilateral 55.2 mm, range 38–78; unilateral 55.8 mm, range 31–70) which was significantly larger than that of unaffected kidneys (45.8 mm, range 31–70; $p < 0.03$).

Prothrombotic defects were detected in eight of 18 patients assessed (44%; table 2). The most common abnormality was heterozygous factor V Leiden (4/18; 22%). Patient 15 had a strong family history of thrombosis and had combined heterozygous protein C and S deficiency. Patient 21 had both RVT and cerebral infarction; he was heterozygous for MTHFR, although this is not generally considered a thrombotic risk factor now. None were diagnosed with lupus anticoagulant.

All patients were managed by careful attention to fluid balance and nutrition, including intravenous fluids where appropriate. This occasionally proved very difficult—patient 18, for example, required more than 50 mmol/kg/day sodium to compensate for recovery renal losses, which necessitated central access and parenteral supplementation. Four were treated with heparin for one to two weeks: patients 13 and 15 received intravenous unfractionated heparin at a starting dose of 20–25 U/kg/h aiming for an activated partial prothrombin time ratio of 1.5–2.5, and patients 22 and 23 received 150 U/kg subcutaneous low molecular mass heparin

twice a day with the aim of reaching anti-(factor Xa) concentrations of 0.5–0.9 IU/ml. Patient 15 (combined protein C and S deficiency) also received fresh frozen plasma and protein C concentrate acutely, and warfarin long term. No patients received thrombolytic agents. Four patients (1, 8, 22, and 23) required renal replacement therapy during the acute illness (three peritoneal, one haemodialysis).

Outcome

Mean length of follow up was 64 months (range six months to 12 years). One child (case 1) was severely handicapped and died at the age of 5 years from pneumonia; all others survived. Two children (cases 3 and 23) had nephrectomies because of poor function/hypertension. One child (case 22) with CKD stage 5 received a renal transplant.

Impaired renal growth or structure was detected in over 80% of RVT affected organs (tables 3 and 4). All 10 with unilateral involvement were abnormal: kidneys were “small”, below the 10th centile/age¹⁷ or not visualised on ultrasound, and differential contribution was zero in 5/10 patients with maximum uptake of dimercaptosuccinic acid of 31%. In contrast, contralateral kidneys appeared structurally normal; 5/9 (56%) had compensatory hypertrophy (length equal to or greater than 90th centile for age¹⁷); and mean differential function was 90%. In bilateral cases, 18/24 kidneys were small or had structural abnormalities, including reduced cortical mass, scarring, or loss of corticomedullary differentiation. There were distinct differences in function between sides in five patients, suggesting unequal damage despite bilateral diagnosis.

Mean GFR was 93.6 ml/min/1.73 m² in unilateral cases, significantly higher than 70.2 ml/min/1.73 m² in the bilateral group (difference 23.4; 95% CI 6.4 to 40.4; $p = 0.01$). CKD

Table 3 Outcome of patients diagnosed with unilateral renal venous thrombosis

Patient	Creatinine ($\mu\text{mol/l}$)	Kidney size (predicted centile for age ¹⁷)		Functional imaging (DMSA uptake (%))		Other comments	GFR	CKD stage	BP increased
		U	A	U	A				
2	42	–	Small	90	10	–	–	(≥ 1)	N
3	59	>95	Nephrectomy	100	0	–	88*	2	Y
5	60	>95	Not seen	100	0	–	73	2	N
9	57	75	<5	100†	0†	Partly calcified R kidney and IVC thrombus	92	1	N
12	53	95	Not seen	100	0	–	95	1	N
14	47	90	5	77	23	Scarred L kidney with loss of corticomedullary differentiation	102	1	N
15	36	50	<5	92	8	Scarred R kidney	93	1	N
16	43	>95	10	69	31	–	107	1	N
18	29	75	5	95	5	–	102*	1	N
19	28	50	Small	100‡	0‡	–	90	1	N
Means or frequency				90.4	9.6		93.6	1.22	1/10

Kidney size was measured by ultrasound scan. CKD stages are: 1, GFR >90 ml/min/1.73 m², kidney damage with normal or increased GFR; 2, GFR 60–89 ml/min/1.73 m², kidney damage with slight decrease in GFR; 3, GFR 30–59 ml/min/1.73 m², moderate decrease in GFR, with or without other evidence of kidney damage; 4, GFR 15–29 ml/min/1.73 m², large decrease in GFR, with or without other evidence of kidney damage; stage 5, GFR <15 ml/min/1.73 m² or dialysis, established kidney failure.

*GFR calculated using the Schwartz formula²⁸ rather than formal chromium/EDTA clearance.

†Mag 3 (technetium-99m mercaptoacetyl triglycine renogram).

‡Intravenous urogram.

U, Unaffected side; A, affected side; DMSA, dimercaptosuccinic acid; GFR, glomerular filtration rate (expressed in ml/min/1.73 m²); CKD, chronic kidney disease; BP, blood pressure; IVC, inferior vena cava.

scores, which incorporate GFR and imaging data, were also significantly different in the two groups (unilateral 1.22 versus bilateral 2.25; difference 1.03, 95% CI 0.19 to 1.87; $p = 0.02$). Hypertension was rare in our population: one unilateral patient was affected, and became normotensive after nephrectomy, and three bilateral patients. Two of the latter had relatively low GFRs (cases 17 and 23), so CKD may have contributed. All were well controlled by two or fewer drugs.

Multilevel modelling was used to explore the potential influence of birth weight, inferior vena cava involvement, renal length, and coagulation status on outcome. A highly significant correlation was detected with perinatal renal length: for each millimetre increase in renal size the odds of having an abnormal renal ultrasound was multiplied by 1.11 (95% CI 1.01 to 1.22; $p = 0.03$), differential function (%) fell on average by 2.95 (95% CI -4.02 to -1.89 ; $p = 0.001$), and calculated single-kidney GFR decreased by 2.97 ml/min/1.73 m² (95% CI -3.7 to -2.0 ; $p = 0.001$). After size was accounted for, none of the other variables was significantly associated with these outcomes.

DISCUSSION

This is the largest series of patients with RVT in the United Kingdom and the first for over a decade, and it illustrates a number of key features in this condition. These include an increased frequency of perinatal presentation, a high proportion of procoagulant defects, and a novel association linking longer kidney length at presentation with poorer renal outcome.

Perinatal RVT

Based on animal studies and human pathology, RVT starts in small calibre vessels such as the arcuate or interlobular veins before extending to the main renal vein,^{18–20} hence the terminology renal venous thrombosis. Historical associations include dehydration, polycythaemia, maternal diabetes, sepsis, birth asphyxia, and umbilical venous catheters,^{2 18 21} which correlate well with Virchow's thrombotic triad of reduced blood flow, altered blood composition, and/or vessel

wall changes. Hyperosmolar dehydration occurred in 12/16 patients in the last UK RVT report,² but we only observed it in 1/23, and there were far fewer thromboses in children with central lines (4/23) than in older reports. One could argue that these data simply reflect referral bias, but this appears unlikely, as the earlier UK study was also conducted in a tertiary paediatric nephrology centre (Glasgow), the latest Canadian series reports a similar trend towards reduced hypernatraemia related cases (2/43),¹ and only 9/118 patients had umbilical/central lines in the recent German multicentre study.⁷

Mean age at diagnosis in our group was only 2–3 days (reduced from 10 in the Glasgow study³) with a median of the first postnatal day, and only 3/23 (13%) detected after 3 days. Logically, such an early presentation may result from untoward events around birth, and, indeed, 19 of our patients had perinatal problems including fetal distress (14) and intrauterine growth retardation (five). Two also had RVT diagnosed antenatally, which adds to the growing literature in this field,^{22 23} and one passed blood per urethra at delivery, and another never passed urine postnatally. Calcified thrombus was also detected immediately postnatally in the inferior vena cava (patient 6) and adrenal (case 18), lending further support to potential antenatal onset. This raises the question of whether occult antenatal RVT may instigate fetal distress in some patients rather than vice versa. In view of such possibilities and the earlier presentation in contemporary surveys, we suggest that a high proportion of RVT in cohorts such as ours could be more accurately described as “perinatal” rather than “neonatal”.

Only 22% of our patients had all three features of haematuria, palpable mass, and thrombocytopenia, which reinforces the importance of a high level of clinical suspicion with any of these. The majority (13/23; 56%) had bilateral RVT, which is higher than comparable series, but we suspect that this reflects referral bias of more severe cases to our tertiary centre. Other characteristics reiterated the results of others: there was a male predominance, for example, and the left kidney was more often involved. Boys have a higher risk of all congenital renal malformations,²⁴ so there may be

Table 4 Outcome of patients diagnosed with bilateral renal venous thrombosis

Patient	Creatinine ($\mu\text{mol/l}$)	Kidney size (predicted centile for age ¹⁷)		Functional imaging (DMSA uptake/%)		Other comments	GFR	CKD stage	BP increased
		Right	Left	Right	Left				
4	49	50	Not seen	96	4	–	82	2	N
6	68	50	<5	62	38	Thinned cortex on left	74	2	N
7	51	Small	Small	–	–	–	91	1	N
8	99	<5	<5	–	–	Loss of corticomedullary differentiation	43	3	N
10	44	>95	<5	94	6	Scarred right kidney	93	1	N
11	52	<5	<5	50	50	Bilateral focal defects	68	2	Y
13	45	Small	Small	Trace excretion (IVU)	Normal pattern (IVU)	Cortical thinning, loss of corticomedullary differentiation	70	2	N
17	119	<5	75	1	99	Cortical thinning	32	3	Y
20	39	Not seen	50	2	98	–	95	1	N
21	45	50	50	56	44	Scar right lower pole	84	2	N
22	502	<5	<5	Poor function; treated with chronic peritoneal dialysis, then a renal transplant	–	Bilateral loss of corticomedullary differentiation	*	5	N
23	59	<5	50	Nephrectomy	–	–	40	3	Y
Means or frequency							70.2	2.25	3/12

Kidney size was measured by ultrasound scan. CKD stages are: 1, GFR >90 ml/min/1.73 m², kidney damage with normal or increased GFR; 2, GFR 60–89 ml/min/1.73 m², kidney damage with slight decrease in GFR; 3, GFR 30–59 ml/min/1.73 m², moderate decrease in GFR, with or without other evidence of kidney damage; 4, GFR 15–29 ml/min/1.73 m², large decrease in GFR, with or without other evidence of kidney damage; stage 5, GFR <15 ml/min/1.73 m² or dialysis, established kidney failure. Patient 1 is not included in the chart because follow up scans were not performed (died at the age of 5 years).

*GFR less than 15 ml/min/1.73 m² by definition as patient required renal replacement therapy.¹⁶

DMSA, Dimercaptosuccinic acid; GFR, glomerular filtration rate (expressed in ml/min/1.73 m²); CKD, chronic kidney disease; BP, blood pressure; –, result unavailable.

subtle structural differences that predispose to RVT. Similarly, the left sided predominance may result from anatomical differences in the connections/relations of the left renal vein.

Prothrombotic tendencies

Prothrombotic abnormalities were detected in just under half (44%) of our patients. Higher proportions, over 50%, were reported in questionnaire based studies, but these were compiled by specialists in prothrombotic conditions.^{6–7} Interestingly, they also suggested that prothrombotic defects predisposed to RVT in the absence of other risk factors: at least one prothrombotic risk factor was detected in 23/27 (85%) or 3/4 (75%) of idiopathic RVT compared with 17/32 (53%) or 7/16 (44%) with other potential causes. We did not find this association, but detected a much higher rate of perinatal pathology; this may be because we had detailed clinical information and correctly reclassified some cases that might otherwise have been termed idiopathic. Factor V Leiden mutations were the most common defects detected here and in most other RVT and infant thrombosis series.^{1–6–8} There is also emerging evidence that high lipoprotein concentrations may contribute to RVT,⁷ but we did not assess this factor.

Identifying a procoagulant tendency may help to predict/prevent future thrombotic episodes, as 4/94 in one study had recurrent thromboembolism.⁷ Our cohort have not had further events, but one of our children with the Leiden mutation required a major orthopaedic operation that involved immobilisation for several weeks; we used prolonged heparinisation to minimise thrombosis risk and there were no problems. Moreover, after screening parents of affected children, we identified one mother who had three early miscarriages, which is a well established association with underlying prothrombotic tendencies,²⁵ and another who was taking the oral contraceptive pill, whom we warned about thrombosis risk with her Leiden mutation.²⁶ These cases illustrate the potential medicolegal implications of

screening (or not) for underlying prothrombotic tendencies in patients with RVT and the families of affected children.

Larger kidneys have worse outcome: size matters!

Renal atrophy and diminished function is well recognised after RVT,^{1–7–18–27} but this has usually been only assessed by ultrasound and a creatinine based GFR using the Schwartz formula.²⁸ In contrast, and in common with the earlier UK study, we investigated outcome using ultrasound, a functional radionuclide scan (predominantly dimercaptosuccinic acid), and a formal chromium/EDTA GFR. Using multilevel modelling, we reported for the first time that absolute renal length at presentation had a highly significant negative correlation with outcome—that is, larger perinatal kidneys had reduced long term function. A similar negative correlation was observed on adjustment for gestation and birth weight to generate presentation length centiles^{29–30} (data not shown), but such data manipulation appears unnecessary with such a clear cut result using simple length. No other presentation factors, including the presence or absence of a prothrombotic tendency, correlated significantly with outcome.

None of our RVT kidneys with a size of 60 mm or over had a normal follow up ultrasound and all kidneys of CKD stage 3 or greater were in this group. Should we therefore be treating larger kidneys more aggressively? Two of these patients (cases 22 and 23) were treated with heparin because their clinical presentation was severe, with major renal impairment, but this did not result in a good outcome. Some small series suggest that heparinisation is beneficial,²⁷ but this is not corroborated by bigger cohorts; moreover, haemorrhage can occur.³¹ Thrombolytic agents including streptokinase, urokinase, and recombinant tissue plasminogen activators have been used,³² and there are case reports of successful thrombus dissolution.^{33–34} These treatments are also potentially dangerous, however, as both haemorrhagic rupture of the affected kidney and cerebral haemorrhage have been recorded.^{35–36} Treatment recommendations are uncertain

What is already known on this topic

- RVT is the most common form of venous thrombosis in neonates
- Associated conditions in older series include dehydration, sepsis, maternal diabetes, birth asphyxia, and umbilical venous catheters.
- Procoagulant defects are found in a substantial proportion of patients with RVT

What this study adds

- Antenatal and birth related antecedents were found to be very common; hence perinatal RVT may be a more appropriate description for this group
- Procoagulant screening should be considered, as about half of the children are likely to have underlying defects. These may not influence immediate management but may have long term implications for both the children and affected family members.
- Outcome was related to renal size in this group: larger kidneys had a worse prognosis and may warrant more aggressive treatment

therefore until there are randomised controlled trials of thrombolytic treatment for RVT, as recently advocated for all forms of thrombosis in infancy.³⁷

CONCLUSION

Antenatal and birth related antecedents were very common in our cohort; hence perinatal rather than neonatal RVT may be a more appropriate description for this group. Thrombosis was often associated with underlying prothrombotic tendencies, and we recommend that formal screening for such defects should be considered in all patients, irrespective of other potential predisposing conditions. We also report for the first time that renal prognosis is worse in kidneys that are larger at presentation, perhaps identifying patients that may benefit from more aggressive treatment.

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REFERENCES

- 1 Marks SD, Massicotte MP, Steele BT, et al. Neonatal renal venous thrombosis: clinical outcomes and prevalence of prothrombotic disorders. *J Pediatr* 2005;**146**:811–16.
- 2 Mocan H, Beattie TJ, Murphy AV. Renal venous thrombosis in infancy: long-term follow-up. *Pediatr Nephrol* 1991;**5**:45–9.
- 3 Keidan I, Lotan D, Gazit G, et al. Early neonatal renal venous thrombosis: long-term outcome. *Acta Paediatr* 1994;**83**:1225–7.
- 4 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.
- 5 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.
- 6 Kuhle S, Massicotte P, Chan A, et al. A case series of 72 neonates with renal vein thrombosis. Data from the 1-800-NO-CLOTS Registry. *Thromb Haemost* 2004;**92**:729–33.
- 7 Kosch A, Kuwertz-Broking E, Heller C, et al. Renal venous thrombosis in neonates: prothrombotic risk factors and long-term follow-up. *Blood* 2004;**104**:1356–60.
- 8 Heller C, Schobess R, Kurnik K, et al. Abdominal venous thrombosis in neonates and infants: role of prothrombotic risk factors: a multicentre case-control study. For the Childhood Thrombophilia Study Group. *Br J Haematol* 2000;**111**:534–9.
- 9 Lawson SE, Butler D, Enayat MS, et al. Congenital thrombophilia and thrombosis: a study in a single centre. *Arch Dis Child* 1999;**81**:176–8.
- 10 Bertina RM, Koeleman BP, Koster T, et al. Mutation in blood coagulation factor V associated with resistance to activated protein C. *Nature* 1994;**369**:64–7.
- 11 Rosendaal FR. Venous thrombosis: a multicausal disease. *Lancet* 1999;**353**:1167–73.
- 12 Seligsohn U, Lubetsky A. Genetic susceptibility to venous thrombosis. *N Engl J Med* 2001;**344**:1222–31.
- 13 Poort SR, Rosendaal FR, Reitsma PH, et al. A common genetic variation in the 3'-untranslated region of the prothrombin gene is associated with elevated plasma prothrombin levels and an increase in venous thrombosis. *Blood* 1996;**88**:3698–703.
- 14 Frosst P, Blom HJ, Milos R, et al. A candidate genetic risk factor for vascular disease: a common mutation in methylenetetrahydrofolate reductase. *Nat Genet* 1995;**10**:111–13.
- 15 Hibbert J, Howlett DC, Greenwood KL, et al. The ultrasound appearances of neonatal renal vein thrombosis. *Br J Radiol* 1997;**70**:1191–4.
- 16 K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Am J Kidney Dis* 2002;**39**:S1–266.
- 17 Han BK, Babcock DS. Sonographic measurements and appearance of normal kidneys in children. *AJR Am J Roentgenol* 1985;**145**:611–16.
- 18 Arneil GC. Renal venous thrombosis. *Contrib Nephrol* 1979;**15**:21–9.
- 19 Ulich F. Renal venous thrombosis. *Renal vein thrombosis*. New York: Futura Publishing Company, 1983:69–91.
- 20 Arneil GC, MacDonald AM, Sweet EM. Renal venous thrombosis. *Clin Nephrol* 1973;**1**:119–31.
- 21 Belman AB. Renal vein thrombosis in infancy and childhood: a contemporary survey. *Clin Pediatr (Phila)* 1976;**15**:1033–44.
- 22 Wilkinson AG, Murphy AV, Stewart G. Renal venous thrombosis with calcification and preservation of renal function. *Pediatr Radiol* 2001;**31**:140–3.
- 23 Diallo AB, Boag GJ, Moussally F, et al. Renal venous thrombosis: an unusual cause of fetal distress. *Eur J Obstet Gynecol Reprod Biol* 1998;**79**:109–13.
- 24 Lewis M. Report of the Paediatric Renal Registry 1999. UK Renal Registry Report 2004. Edited by Ansell D and Feest T. Bristol, UK, UK Renal Registry, 2004:187–211.
- 25 Reznikoff-Etievant MF, Cayol V, Carbonne B, et al. Factor V Leiden and G20210A prothrombin mutations are risk factors for very early recurrent miscarriage. *Br J Obstet Gynaecol* 2001;**108**:1251–4.
- 26 Tanis BC, Rosendaal FR. Venous and arterial thrombosis during oral contraceptive use: risks and risk factors. *Semin Vasc Med* 2003;**3**:69–84.
- 27 Zigman A, Yazbeck S, Emil S, et al. Renal vein thrombosis: a 10-year review. *J Pediatr Surg* 2000;**35**:1540–2.
- 28 Schwartz GJ, Haycock GB, Edelmann CM Jr, et al. A simple estimate of glomerular filtration rate in children derived from body length and plasma creatinine. *Pediatrics* 1976;**58**:259–63.
- 29 Scott JE, Hunter EW, Lee RE, et al. Ultrasound measurement of renal size in newborn infants. *Arch Dis Child* 1990;**65**:361–4.
- 30 Chitty LS, Altman DG. Charts of fetal size: kidney and renal pelvis measurements. *Prenat Diagn* 2003;**23**:891–7.
- 31 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.
- 32 Brun P, Beaufils F, Pillion G, et al. [Thrombosis of the renal veins in the newborn: treatment and long term prognosis]. *Ann Pediatr (Paris)* 1993;**40**:75–80.
- 33 Klinge J, Scharf J, Rupprecht T, et al. Selective thrombolysis in a newborn with bilateral renal venous and cerebral thrombosis and heterozygous APC resistance. *Nephrol Dial Transplant* 1998;**13**:3205–7.
- 34 Dillon PW, Fox PS, Berg CJ, et al. Recombinant tissue plasminogen activator for neonatal and pediatric vascular thrombolytic therapy. *J Pediatr Surg* 1993;**28**:1264–8.
- 35 Haffner D, Wuhl E, Zieger B, et al. Bilateral renal venous thrombosis in a neonate associated with resistance to activated protein C. *Pediatr Nephrol* 1996;**10**:737–9.
- 36 Weinschenk N, Pelidis M, Fiascone J. Combination thrombolytic and anticoagulant therapy for bilateral renal vein thrombosis in a premature infant. *Am J Perinatol* 2001;**18**:293–7.
- 37 John CM, Harkensee C. Thrombolytic agents for arterial and venous thromboses in neonates. *Cochrane Database Syst Rev* 2005;**CD004342**.