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Neonatal renal vein thrombosis

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SUMMARY

Neonatal renal vein thrombosis (RVT) continues to pose significant challenges for pediatric hematologists and nephrologists. The precise mechanism for the onset and propagation of renal thrombosis within the neonatal population is unclear, but there is suggestion that acquired and/or inherited thrombophilia traits may increase the risk for renal thromboembolic disease during the newborn period. This review summarizes the most recent studies of neonatal RVT, examining its most common features, the prevalence of acquired and inherited prothrombotic risk factors among these patients, and evaluates their short and long term renal and thrombotic outcomes as they may relate to these risk factors. Although there is some consensus regarding the management of neonatal RVT, the most recent antithrombotic therapy guidelines for the management of childhood thrombosis do not provide a risk-based algorithm for the acute management of RVT among newborns with hereditary prothrombotic disorders. Whereas neonatal RVT is not a condition associated with a high mortality rate, it is associated with significant morbidity due to renal impairment. Recent evidence to evaluate the effects of heparin-based anticoagulation and thrombolytic therapy on the long term renal function of these patients has yielded conflicting results. Long term cohort studies and randomized trials may be helpful to clarify the impact of acute versus prolonged antithrombotic therapy for reducing the morbidity that is associated with neonatal RVT.

1. Introduction

Renal vein thrombosis (RVT) in neonates is a rare condition of low mortality but high morbidity. Its epidemiology, pathophysiology, risk factors including hereditary prothrombotic disorders, presentations, and diagnosis are presented in this review. Hitherto, our knowledge on the optimal therapeutic approaches is still very deficient and the management of neonatal RVT remains a challenge. Due to the lack of controlled trials on therapies such as anticoagulation in infants, most of the guidelines or recommendations that we are now practising are based on extrapolations from adult studies. As there are basic differences in the hemostatic systems between neonates and adults, and thus the pharmacokinetics and physiological responses to treatments, more robust data on the safety profiles in neonates are need urgently (Figures 1–3).

2. Epidemiology

Neonates have a higher incidence of thrombosis when compared to older children.[1] RVT is the most prevalent non-catheter-related thromboembolism during the neonatal period; and accounts for ~16–20% of all thromboembolic events in newborns.[2–4] Prevalence of RVT in neonates has been difficult to ascertain due to the lack of large scale prospective studies. Nonetheless, the minimum incidence of symptomatic neonatal RVT between 1992 and 1994 was reported to be 2.2 per 100 000 live births in Germany.[5] On the other hand, Zigman et al. reported an incidence of 2.3 cases per year over a 10-year period in Montreal, Canada. Also, a Canadian and International Registry by Schmidt and Andrew estimated the incidence to be 0.5 per 1000 neonatal intensive care unit admissions.[2]

3. Pathophysiology

Most RVTs in neonates are non-catheter-related, and the exact pathophysiology of the thrombosis remains elusive.[2] It has been suggested that neonates are particularly prone to have such thrombotic complications as they have decreased levels of natural

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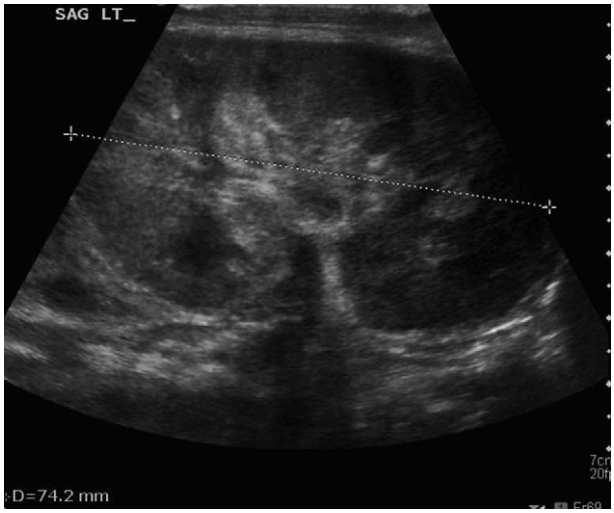

Fig. 1. Ultrasound of the left kidney of a neonate presenting with unilateral renal vein thrombosis at the age of 1 week. The left kidney was enlarged with a measured length of 7.42 cm (normally 4–4.5 cm). There was a marked decrease in corticomedullary differentiation.

anticoagulants such as protein C, protein S, and antithrombin, as well as low levels of fibrinolytic components such as plasminogen.[6–8] Moreover, the susceptibility of the neonatal kidney to develop thrombosis may be secondary to its low renal perfusion pressure and double intracapillary network.[9] Although rarely proven, thrombosis likely initiates in the arcuate or interlobular veins, and then spreads to the larger veins and inferior vena cava (IVC).[3,10]

In the absence of placement of central venous catheter, previous studies have reported that up to 80% of the affected neonates with RVT had coexisting risk factors.[4,11] These risk factors include a history of perinatal asphyxia, maternal diabetes mellitus, prematurity, dehydration and infection.[4,11,12] Under these circumstances, the reduction in perfusion of the kidney leads to vasoconstriction and decline in venous blood flow, leaving the postglomerular circulation particularly vulnerable to thrombosis.[3] In a recent review, approximately one-third of the affected infants were born prematurely and perinatal asphyxia were identified as the cause of RVT in 32%.[13] Congenital heart disease has also been reported in some patients.[11,12,14]

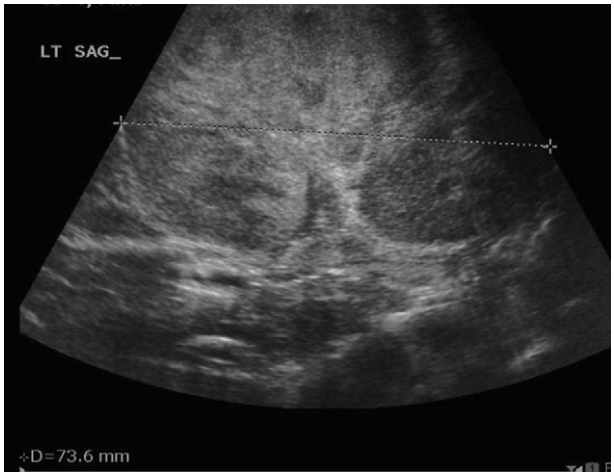

Fig. 2. Repeated ultrasound of the kidney 1 week later. The kidney became more echogenic and less defined in terms of its renal architecture.

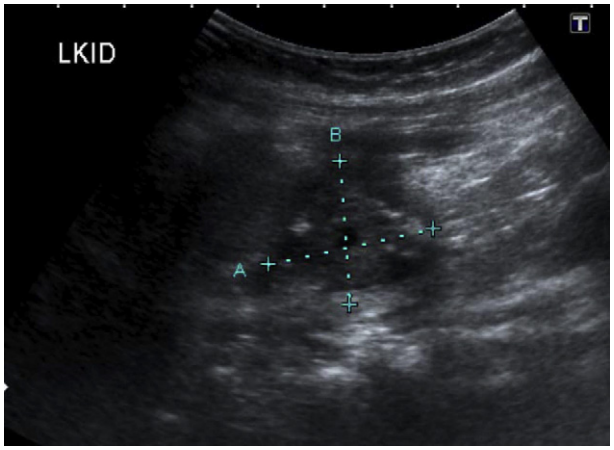

Fig. 3. Ultrasound of the kidney at age 3 months. The kidney has shrunk to 2.5 cm in length and there was lack of renal structure.

4. Presentation

Although most of the affected patients are born at term, RVT has been reported antenatally and up to one month after birth.[2,4,13,15] In a recent review of available information in the literature over a period of 15 years, the compiled data show that 7.3%, 67.1% and 25.6% of neonates presented in utero, within 3 days and more than 3 days postnatally, respectively.[13] Although mostly seen after birth, some of the neonates who present early in life may actually have prenatal onset of RVT, which may explain the occurrence of renal vein or inferior vena cava calcification and may account for their early onset of RVT.[16] On the other hand, a case of in-utero onset RVT has been misdiagnosed as a congenital renal tumour due to an enlarged kidney identified on antenatal ultrasound.[17] These cases highlight the importance of a high index of suspicion in recognizing the presence of *in-utero* RVT, thus avoiding false diagnoses and delaying treatment. Some clinicians prefer the term 'perinatal' over 'neonatal' RVT, in order to appreciate the potential *in-utero* onset of the thrombosis.[2,13,15]

Males are more commonly affected than females, representing 67.2% of cases.[13] It was hypothesized that, as males have a greater risk of congenital renal malformation, the associated structural anomalies may predispose male infants to more risk of developing neonatal RVT.[15] Others have postulated that gender differences in renal perfusion may account for the observed discrepancy.[4] Nonetheless, the exact underlying cause for such gender predilection remains unidentified. The majority of neonatal RVT are unilateral (70.3%), with a left-sided predominance (63.6%).[13] Thrombus extension into the inferior vena was found in approximately 40% of patients and 15% of them may have adrenal haemorrhage.[13]

Affected neonates may present with macroscopic or microscopic hematuria, palpable flank mass and thrombocytopenia. A recent review noted that most of the neonates with RVT had at least one of the three cardinal signs at presentation. Macroscopic hematuria, palpable flank mass and thrombocytopenia were found in 56%, 45% and 48% of the patients, respectively.[13] However, this classic triad is being observed in its entirety only in 13–22% of cases.[15,18]

Although renal function testing is not reported in most of the available studies in the literature, a substantial number of neonates were reported to have renal insufficiencies at presentation.[11] In a multicenter study from Canada, 56% of the neonates had renal insufficiencies at onset[11]; of these, 41% had bilateral involvement.

Thrombus extension beyond the renal vasculature had been seen in ~50–74% of cases[11,12] and distant embolization may be a rare presenting feature of NRVT.[19] Although more commonly seen at a later stage as the disease progresses, neonates with RVT may also present with hypertension at onset in rare situations.[20]

5. Hereditary prothrombotic conditions

The term thrombophilia refers to several prothrombotic conditions that arise from hereditary abnormalities in natural anticoagulant systems (e.g. thrombomodulin–protein C/S system, antithrombin), or in procoagulant elements and/or in fibrinolytic pathways.[21] Several inherited prothrombotic conditions have been reported in association with neonatal renal vein thrombosis (RVT), including factor (F) V Leiden G1691A mutation, FII G20210A prothrombin gene mutation, protein C and protein S deficiencies and the homozygous methylenetetrahydrofolate reductase (MTHFR) C677 T polymorphism.[11,18,22,23]

Factor V Leiden G16191A mutation is a well-described risk factor for venous thromboembolic disease in childhood.[24,25] Several studies have reported a higher prevalence of FV G1691A polymorphisms among neonates with RVT when compared to the general population.[11,18,22,23] In these reports, 14–37% of newborn cases with RVT were heterozygous for the FV Leiden G1691A.[22] In a single centre study of neonatal cases of RVT, both of the patients who were found to have bilateral thromboses were also found to carry heterozygous mutations for FV Leiden G1691A.[23] Similarly, multicentre case series of Canadian newborns with RVT showed an association between *in-utero* RVT and FV G1691A mutations,[18] which had not been shown in previous case series reports. Although both of these studies had small sample sizes, their findings suggest that FV Leiden G1691A polymorphisms may be associated with more severe phenotypes of neonatal RVT.

In a recent German case–control study of neonatal RVT, 85% of 27 newborns with idiopathic RVT had at least one of the following prothrombotic risk factors: FV Leiden G1691A mutation, FII G20210A gene mutation, increased fasting homocysteine and/or lipoprotein (a) levels or positive anticardiolipin antibodies. However, multivariate analyses showed that only newborns with heterozygous FV Leiden G1691A mutations or increased lipoprotein (a) levels had significantly higher rates of RVT when compared to healthy newborn controls (odds ratio: 9.4; 95% confidence interval: 3.3–26.6; $P < 0.0001$; and 7.6; 2.4–23.8; $P = 0.0005$, respectively).[22] In this study, FII G20210A mutations, fasting elevated homocysteine levels and positive anticardiolipin antibodies were not independent risk factors for neonatal RVT. In line with these results, recent findings from single and multicentre studies have not shown an association between neonatal renal thrombosis and FII G20210A gene mutations.[11,12] In an international case series of 28 newborns with RVT, none of the cases was found to have FII G20210A gene mutations, and a single centre case series reported that only one out of the 28 affected newborns who were screened for prothrombotic disorders was found to have the prothrombin G20210A gene mutation.

Normal age-appropriate natural anticoagulant levels are significantly lower in infants than in adults and it is unclear whether this phenomenon increases the propensity for venous thromboembolic events during interim acute illnesses within the newborn.[21] In an extensive thrombophilia evaluation of 28 newborns with renal vein thromboembolism, 18% of these infants were found to have abnormally low levels of protein C and/or protein S.[11] Similarly, in a Belgian series of five cases with neonatal RVT, one of these patients had isolated protein S deficiency while another patient had deficiencies of both proteins C and S.[23] Depending on the degree of protein C and/or S deficiencies, this may be the first presentation of venous and/or arterial thromboembolic events.[26] Based on these study findings, it is unclear whether low levels of proteins C and/or S are independent risk factors for RVT or whether there are confounding factors that contribute to thromboembolic events in patients with protein C and/or protein S deficiencies.

Several reports have identified elevated FVIII levels as risk factors for venous thromboembolic events in childhood.[27,28] FVIII levels that are >150 IU per deciliter at the time of the diagnosis and persistently elevated 3–6 months after the diagnosis correlate with increased thrombosis risk and poorer prognosis in children with venous thrombotic disease.[27] Further studies are needed to clarify the role of this thrombotic risk factor with the incidence of neonatal RVT. To date, only one report has demonstrated abnormal FVIII levels among patient cases with neonatal RVT. In this study, 7% of neonatal cases with RVT were found to have elevated FVIII levels.[11] However, degree of elevation and the time interval between the thrombotic events and the detection of elevated FVIII levels were not clear in this study, and the authors did not report whether the FVIII levels were persistently elevated during follow-up of the affected patients. FVIII levels may become elevated secondarily as an acute phase reactant or as a result of chronic inflammation and renal disease, which may all be present in an ill neonate with RVT.[29] As a result, further studies with comprehensive multivariate analyses would be important to clarify whether elevated FVIII levels are an independent risk factor for neonatal RVT.

Antithrombin deficiency has also been identified as a risk factor for venous thromboembolism.[30] In three separate case series where antithrombin levels were measured in newborn patients with RVT, there was not a strong association between quantitative or qualitative deficiencies in antithrombin and RVT.[11,22,23] In a multisite German series, three out of 59 patients (5%) had deficient antithrombin levels, but this was not found to be statistically significant after multivariate analysis.[22] A second study of affected Canadian newborns showed that one out of 28 cases (4%) had antithrombin deficiency[11] and it was unclear whether this finding was statistically significant.

The thrombotic risk of heritable prothrombotic conditions is multifactorial and is likely to be modulated by coexisting abnormalities in coagulation and fibrinolysis. Further clarification of the role of prothrombotic conditions in neonatal thromboembolic disease is needed to reduce the incidence of renal vein and other forms of deep venous thrombosis among newborns.

6. Diagnosis

Although RVT may present with the cardinal features described above, and may have alterations in various laboratory values, such as thrombocytopenia, elevations of creatinine and proteinuria with hematuria, none of these tests are pathognomonic. Most of the time, accurate and prompt diagnosis requires a high index of suspicion and imaging remains the cornerstone in confirming or ruling out RVT in neonates. Renal venography used to be the main radiographic technique for confirming RVT for many years, but its role has gradually been replaced by ultrasonography.[9,31,32]

Ultrasonography has been gaining popularity in diagnosing RVT in neonates due to its wide availability, high sensitivity and virtually non-invasive nature. It is particularly attractive in cases involving sick neonates as it does not require any sedation and is portable. In brief, ultrasound findings vary with the time of onset, severity and extent of thrombus.[3,9,33–35] Based on the experiences on the sequential grey-scale ultrasonic appearances of involved kidneys in a small number of cases, Cremin et al. proposed a loose staging system for RVT (see Box 1).[35]

Box 1. Sequential ultrasound changes of neonatal renal vein thrombosis[a]

- Early (first week)
  - Globular enlargement of kidney
  - Increase in echogenicity
  - Loss of cortico-medullary boundary
  - Echogenic streaks
  - Loss of normal sinus echoes
- Intermediate (second week)
  - More prominent and diffuse renal enlargement
  - Diffuse 'snow storm' pattern of echogenicity
  - Loss of cortico-medullary differentiation
  - May see co-existing hyperechoeic (hemorrhagic) areas and hypoechoeic (edema/resolving hemorrhagic) areas
  - May see thrombus extension in renal veins and inferior vena cava
- Late (after second week)
  - May be normal in appearance
  - May become atrophic
  - May see calcifications in either or both kidneys and within the vascular system

[a]Modified from Cremin et al.gr3[35]

During the first week, renal enlargement is observed along with diffusely or focally increased echogenicity of the renal parenchyma. Perivascular echogenic streaking correlates to interlobular and interlobar thrombus and the normal cortico-medullary junction may be lost.[35] Though perivascular streaks are highly indicative for neonatal RVT,[36] they disappear within a few days; this renders prompt imaging imperative.[3,34] After the first week, affected kidneys continue to show enlargement in size and decreased in cortico-medullary differentiation. Patchy appearance of hyperechoic and hypoechoic areas that represent haemorrhage and edema are commonly seen at this time. After 2–3 weeks, thrombus within the interlobar venous system becomes calcified and visible under ultrasound in a lacelike or punctuate pattern.[32] Most of the involved kidneys reach the maximum sizes within the first week, and then gradually diminish in size to become atrophic.[37] Colour Doppler ultrasound has been shown to be a very useful clinical tool as it detects high arterial resistance and reversed diastolic flow.[3,10] Prenatal ultrasound can detect *in-utero* onset RVT which is characterized by renal enlargement, and hyperechogenicity with or without calcifications of the renal venous system.[16,17,38] Although ultrasonography may not be sensitive enough to confirm some very minute infarcts and patency in some small vessels, MRV is seldom needed for clarifications.[31,39] One of the obstacles in management of neonates with RVT is the lack of a tool to predict the outcomes of the affected kidneys at onset. Despite the fact that Doppler ultrasound is now very sensitive to confirm or rule out the diagnosis, there is still a lack of reliable features that allow the physicians to predict the long-term prognosis. Winyard et al. reported in their cohort that the lengths of the kidneys at presentation were correlated negatively with the renal outcomes[15] and a mean fall in glomerular filtration rate of 3 mL/min/1.73 m^2 was reported in every 1 mm increase in renal length. In the same study, kidneys longer than 6 cm length at presentation were linked to worse outcomes.[15] However, their findings were not confirmed by others.[32] Instead, in a recent study, the reduction in overall renal perfusion to the kidneys as assessed by color Doppler ultrasound, subcapsular collections secondary to bleeding, patchy cortical hypoechogenicity and irregular pyramids were suggested to be the negative predictors of renal outcomes.[32] These findings, if confirmed, will play pivotal roles in guiding how aggressive the treatment should be in the future.

7. Risk of mortality and long-term morbidity

Among all types of thromboembolic complications in neonates, RVT holds the lowest mortality rate at 5%[2] and death is attributed to other concurrent medical conditions rather than to the RVT.[2,11–13] Though mortality rates are low, the morbidities are considerable and significant. A variety of complications have been reported in neonates with RVT. Acute complications observed include adrenal haemorrhage,[3,13,16,40] arterial ischemic stroke, thromboembolism, central sinovenous thrombosis and pulmonary embolism.[4,12] Depending on the severity and laterality of kidneys affected, long term clinical outcomes may vary from maintenance of normal renal function to the development of chronic renal injuries and end stage renal diseases.[13] Hypertension develops in about 19% and 22% of those with unilateral and bilateral neonatal RVT, respectively.[13] Nephrectomy has also been reported in patients with neonatal RVT, secondary to uncontrollable hypertension.[11,15] Tubular dysfunction, partial to total fibrosis and dysfunctional kidneys, or chronic kidney infections have all been described in patients suffering from neonatal RVT.[5,11,14,41] Long-term morbidities, which are more worrisome, such as chronic renal insufficiency have been reported in up to 71% of patients.[13] The renal outcomes of the affected kidneys have not been altered by the modalities of therapy received, as approximately three-quarters of affected kidneys become atrophic regardless of the treatment.[13] Chronic renal insufficiency resulting from acute and chronic renal injuries was reported in 29% of patients.[11] However, chronic kidney injury that progresses to end stage renal failure, requiring renal replacement therapy or renal transplant, occurs in only 3% of patients and is more commonly seen in patients with bilateral RVT.[13]

8. Acute management

During acute phase, a collaborative approach by a team of neonatologists, haematologists, nephrologists and radiologists is essential. Although most of the neonates with RVT in acute phases are symptomatic, imaging studies are frequently needed for prompt confirmation of the diagnosis and accurate assessment of the extent of the thrombosis. While the haematologists should be consulted for initiation of anticoagulation and/or fibrinolytic therapy (see below), nephrologists are useful in management of the fluid and electrolytes, especially in sick neonates with acute renal injury that requires renal replacement therapy.

The decision to start anticoagulation therapy may be influenced by the extent of RVT, whether there is unilateral or bilateral renal involvement, the presence or absence of renal impairment and the detection of a thrombophilic predisposition. A recent survey of Canadian paediatric haematologists demonstrated that there is no clear consensus for the management of neonatal RVT among the surveyed physicians.[42] In 2008, the American College of Chest Physicians (ACCP) updated their evidence-based guidelines for antithrombotic therapy in newborns and children.[43] According to these guidelines, unfractionated or low molecular weight heparin therapies are recommended for the treatment of unilateral RVT with extension into the inferior vena cava. For bilateral RVT with or

without renal impairment, the ACCP guidelines suggest initial thrombolysis with tissue plasminogen activator and anticoagulation therapy with unfractionated heparin followed by continued anticoagulation with unfractionated or low molecular weight heparin. In the absence of renal insufficiency, either supportive care or heparin therapy are acceptable approaches for the management of unilateral RVT. However, these guidelines do not provide clear recommendations for the initiation of anticoagulation or thrombolytic therapies in settings of unilateral RVT with renal impairment or for patients with identified prothrombotic risk factors. Long term follow-up data are needed to determine whether antithrombotic therapy after the diagnosis of neonatal RVT has significant implications on short-term bleeding risk, long term renal outcomes, thrombotic recurrence risk and/or mortality.

It is unknown whether patients with deficient levels of natural anticoagulant factors such as antithrombin, protein C and protein S, would benefit from replacement of these factors during the acute phase of antithrombotic therapy.[30,44,45] Patients with severe forms of these inherited conditions may require lifelong anticoagulation to prevent recurrent thrombotic events.

The effect of heparin-based anticoagulation in long-term renal size and function remains uncertain. Recent data from a retrospective chart review of 23 newborns with RVT from 1980 to 2001 showed that 33% of patients who received heparin therapy had evidence of renal atrophy compared to 100% of those who did not receive anticoagulation treatment.[11] In the same study, out of the four patients who developed secondary hypertension, only one had been treated with low molecular weight heparin whereas three had not been anticoagulated. However, these findings were not supported by a larger case series where 30 out of 33 newborns with RVT that were treated with unfractionated or low molecular weight heparin developed renal atrophy while 10 out of the 11 patients who did not receive heparin also developed renal atrophy.[22] These results are in line with those from a more recent review of antithrombotic therapy for neonatal RVT where there was no significant difference between the renal outcomes for patients who were treated with antifibrinolytics, heparin or supportive therapy ($P = 0.52$).[12]

9. Long term follow-up

After apparent recovery from acute phase, renal complications such as hypertension, renal atrophy and chronic renal insufficiency may persist.[46] Hence, affected neonates warrant long-term close follow-up. If the neonate is on chronic anticoagulation therapy, follow-up with the haematologist is also essential. Patients who suffer from bilateral RVT are particularly prone to have renal insufficiency, and persistent hypertension has been reported in one-fifth of the neonates.[13] During follow-up, the authors recommend that in addition to routine anthropometric measurements to follow the physical growth, blood pressure should be monitored at every visit. Elevated blood pressure should be managed accordingly. Baseline and serial renal function tests are recommended especially in patients with deterioration in renal functions. It is also recommended to check the urine for any presence of microalbumin or protein and their concentration capability. As proteinuria is associated with poor cardiovascular outcomes, presence of protein in urine should prompt the treatment with either angiotensin converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARB).[47] Renal ultrasound with Doppler should be performed at regular intervals to monitor the sizes of, and blood flow to, the affected kidney(s). Renal ultrasound can also corroborate whether there is any compensated growth of the normal kidney in patients with unilateral involvement. The frequency and intensity of follow-up should be tailored to each individual patient, with more frequent follow-up in patients with documented renal dysfunction or deterioration.

Infants with inherited prothrombotic disorders may have an increased risk of recurrent RVT when compared to neonates without inherited thrombophilia.[22] Interestingly, it appears that the highest risk of recurrence may be after the onset of puberty. Based on these findings, it would be reasonable to screen all newborns with RVT for thrombophilic risk factors, which may facilitate clinical decisions related to duration of antithrombotic therapy and thromboprophylaxis in the future. Because of their increased propensity for thromboembolic disease, individuals with inherited thrombophilia may benefit from a risk-stratified approach for antithrombotic therapy in the acute phase of RVT. In addition to surveillance renal ultrasonography, individuals with more severe inherited prothrombotic tendencies may require prolonged anticoagulation treatment to achieve maximal therapeutic benefit and to reduce the risk of long term morbidity. Children with elevated procoagulant factor levels, such as FVIII, may also benefit from serial monitoring of plasma circulating levels of these proteins to monitor their thrombosis risk and the need for ongoing antithrombotic prophylaxis.[27] Further data are needed to evaluate these hypotheses within the context of neonatal renal thrombotic disease.

10. Conclusion

Despite advances in our understanding of the pathogenesis and risk factors for neonatal RVT, this condition continues to pose significant challenges for paediatric haematologists and nephrologists. Recent data suggest that infants with heritable thrombophilia have an increased incidence of severe phenotypes of renal venous thrombosis, including *in-utero* and/or bilateral involvement and recurrent thromboembolic disease. At present, there is a paucity of consensus guidelines for the management of RVT among newborn infants. It is likely that a risk-stratified approach would be appropriate to direct the medical management of RVT among infants with and without inherited thrombotic predispositions. However, further studies are necessary to clarify the short and long term effects of anticoagulation and thrombolytic therapies on renal outcomes and thrombosis recurrence among these patients.

Practice points

- Renal vein thrombosis in neonates is a rare condition that carries a low mortality risk, but a high rate of morbidity
- The pathophysiology of neonatal RVT involves the reduction of renal vascular perfusion in infants with coexisting risk factors
- Prompt diagnosis requires a high index of suspicion, as its presentation may occur *in utero* and only less than 25% of patients have the classic triad including hematuria, flank palpable mass and thrombocytopenia
- Prothrombotic conditions may related to a more severe clinical presentation
- Currently, there is a paucity of consensus in regards to the management among newborn infants with RV

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