Review Article

Spontaneous neonatal renal vein thrombosis, a known pathology without clear management guidelines: An overview

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ABSTRACT

Renal vein thrombosis (RVT) was first described in 1837 by Rayer. Although tremendous progress has been achieved in the comprehension of its pathophysiology, its management remains controversial over 20 decades later. Therapeutic modalities vary from supportive measures alone to the utilization of thrombolytic agents whose protocols are derived from adult medicine. This review aims to show how difficult the treatment of RVT still is, especially with regard to the prognosis. The majority of affected neonates end with various renal complications (renal atrophy, dysfunction, hypertension, etc.).

Like others, we suggest that simple unilateral RVT be managed conservatively, while thrombolytic agents may be attempted in unilateral RVT with extension to VCI and in bilateral RVT. Further studies are needed to reach appropriate consensual guidelines.

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1. Introduction

Neonatal renal vein thrombosis (RVT) has been known since the first description by Rayer in 1837 [1]. According to various studies, the incidence has been estimated between 1.3 and 2.2 cases per 100,000 population [2,3], although it is not well established. In spite of being rare, RVT still carries high morbidity and mortality both in the early neonatal period as well as beyond. The long-term RVT morbidity includes systemic hypertension, tubular dysfunction, renal atrophy, and chronic kidney disease in some patients [4].

Over the years, tremendous progress has been achieved in our comprehension of RVT pathogenesis. Hepler in 1934 postulated that thrombosis starts in an arcuate or interlobular vein and may then spread from this point in both directions to involve the renal cortex and occlude the main renal vein [5]. This progression holds, in our opinion, for the spontaneous forms. As RVT may be spontaneous, occurring in infants with certain known predisposing factors, and associated, in these cases, with increased blood viscosity (perinatal asphyxia, hypoxemia, septicemia, dehydration, shock, and polycythemia vera in infants born to diabetic mothers or those with cyanotic heart diseases), or secondary to neonatal emergency procedures such as umbilical catheter placement in apparently healthy infants. In these cases, RVT results as a consequence to induced endothelial injury, with the thrombus progressing centrifugally from the main renal vessel to the periphery. It has also been postulated that low renal perfusion and the double intracapillary network could be the explanation to the neonatal susceptibility to develop renal venous thrombosis [6].

We have also gained knowledge with the discovery of other prothrombotic risk factors, with an estimated incidence, depending on the factor considered, varying from 0.5% to 8.2% [7–10].

The development of hemostasis in the term and preterm newborn infants has also been deciphered in a relatively recent past. It is well established that a large number of hemostatic factors are synthesized by the fetus, as early as the tenth week of gestation predominantly by the liver, and that their blood levels increase with gestational age. Although hemostasis components in neonates are similar to those in older children and adults, their plasma concentrations are, however, much lower, rendering their interpretation difficult before the postnatal age of 6 months [11–15].

2. RVT diagnosis

Renal venous thrombosis can be diagnosed both antenatally and in the early postnatal period using ultrasound + Doppler techniques. Overall, RVT diagnosis has been made in utero (7.3%), within
cases, and often associated with predisposing risk factors [28,29]. In the majority of RVT cases being spontaneous, accounting for up to 80% etc). In term infants, however, the situation is different with the in preterm infants, RVTs included, are often secondary to treatment in preterm infants with those in term-born. It is a well-known fact that most thromboembolic events in preterm infants with those in term-born infants [32].

Guidelines recommended for antithrombotic therapy in neonates and children clearly distinguish clinical situations as follows:

1. In case of confirmed renal venous thrombosis (RVT) in a neonate with umbilical venous catheter, this should be removed 3–5 days after starting anticoagulation treatment.
   - It is, however, unclear whether anticoagulation should immediately be started, or the catheter removal, in association with supportive therapy and radiologic monitoring, would be a better option.
   - If the choice is catheter removal + radiologic monitoring, start anticoagulation with either low molecular weight heparin (LMWH) or unfractionated heparin (UFH) followed by LMWH in case of thrombus extension. Therapy duration: 6 weeks to 3 months.
   - If thrombolysis is required, tissue plasminogen activator (tPA) is the choice. Administer fresh frozen plasma prior to commencing tPA.

2. Unilateral RVT without renal impairment or extension to inferior vena cava (IVC)
   (a) Supportive care with radiologic monitoring. If extension occurs, initiate anticoagulation with LMWH or UFH/LMWH in therapeutic dose; duration 6 weeks to 3 months.
   (b) Unilateral RVT with extension to IVC at diagnosis should immediately benefit from anticoagulation therapy under same modalities as above.

3. Bilateral RVT with evidence of renal impairment should be started on thrombolytic therapy with tPA, followed by anticoagulation with LMWH/UFH.

To these recommendations, we would add close monitoring of central nervous system complications by regular cranial ultrasound as intraventricular hemorrhage is likely.

In our humble opinion, due to lack randomized clinical trials, existing recommendations remain weak, as they are derived from clinical experience reports, both observational and case series. We, therefore, suggest to those interested in anticoagulant drugs dosage, administration modalities, and monitoring to refer to Refs. [30,33–36].

2.1.1. The literature overview (Table 1)

In a trial of heparin anticoagulation in the management of RVT, Nuss et al. concluded that their patients' outcome was marked by renal compromise similar to that reported with supportive care alone; these findings made the authors question the efficacy of heparin treatment [37]. Moreover, two of their six patients presented with bleeding complications. In another report of ten RVT cases by Bidadi et al., including both term and preterm infants managed with anticoagulant alone (4 cases), supportive (4 cases), and anticoagulant in association with thrombolysis (2 cases), the outcome was poor with the development of renal atrophy in 8 cases [38]. Zygman et al. reported, in a review of 23 patients, that renal function impairment occurred in 33% of patients receiving anti-coagulation versus 100% in those who had received supportive...
therapy alone. It is of note that only 16 out of 23 patients (70%) had an ultrasound or nuclear medicine imaging performed. Treatment modalities were: IV heparin or subcutaneous enoxaparin (12 cases), heparin alone (5 cases), enoxaparin (5 cases), heparin followed by enoxaparin (2 cases), and 11 patients were managed supportively [39]. The findings reported by Zygman et al. were contradicted by Nau et al. According to Nau et al., in a larger patient series demonstrating irrespective of the treatment administered, 70.6% of patients with RVT developed renal atrophy [16]. Several other small number case series have reported similar results in the outcome as those previously mentioned above [30,37–39].

In a recent report of three cases (2 in term-born and 1 preterm) by Mikolajczak et al., the long-term outcome can hardly be evaluated in 2 cases as follow-up was limited to 8 weeks only after the acute phase. In one case with bilateral RVT, there was recanalization in one kidney and atrophy in the other [40]. In our opinion, as long as no prospective studies are undertaken and clear consensual recommendations with regard to the appropriate therapeutic

**Table 1**

| Authors               | Year | N   | Management modalities                                      | Outcomes                                                                 |
|-----------------------|------|-----|-------------------------------------------------------------|---------------------------------------------------------------------------|
| Duncan et al. [41]    | 1977 | 11  | - Supportive (4)                                           | - death (6)                                                              |
|                       |      |     | - Nephrectomy                                              | - Renal atrophy (3)                                                      |
| Belman [42]           | 1976 | 12  | - Supportive (11)                                          | - Nephrectomy (1)                                                        |
|                       |      |     | - Heparin (1)                                              | - Normal (1)                                                             |
| Jobin et al. [27]     | 1982 | 6   | - Supportive (6)                                           | - Death (1)                                                              |
| Mocan et al. [25]     | 1991 | 16  | - Heparin (9)                                              | - Renal atrophy (3)                                                      |
|                       |      |     | - Supportive (7)                                           | - Normal renal function (6)                                              |
| Brun et al. [47]      | 1993 | 39  | - Urokinase + Heparin (25)                                  | - Total recovery (10)                                                    |
|                       |      |     | - Supportive (14)                                          | - Renal atrophy (23)                                                     |
| Nuss [37]             | 1994 | 6   | Heparin                                                    | - 4/5 renal atrophy                                                      |
| Keidan et al. [49]    | 1994 | 6   | - Heparin (2)                                              | - Renal atrophy (4)                                                      |
|                       |      |     | - Supportive (4)                                           | - Reduced GFR (2)                                                        |
| Bokenkamp et al. [2]  | 1994 | 35  | - Low-dose heparin (14)                                    | - Renal atrophy in 26/39 affected kidneys                                 |
|                       |      |     | - Full heparinization (9)                                  |                                                                           |
|                       |      |     | - Thrombolysis (4)                                         |                                                                           |
|                       |      |     | - Supportive (8)                                           |                                                                           |
| Farnoux et al. [48]   | 1998 | 16  | r-tPA + Heparin (7)                                        | - Death (2)                                                              |
|                       |      |     |                                                             | - Renal atrophy (4)                                                      |
| Kosch et al. [46]     | 2004 | 59  | - LMWH (28)                                                | - Complete recovery (1)                                                  |
|                       |      |     | - Heparin (5)                                              | - Unilateral renal atrophy (42)                                          |
|                       |      |     | - Thrombin concentrate (14)                                | - Bilateral renal atrophy (11)                                           |
|                       |      |     | - r-tPA (11)                                               |                                                                           |
|                       |      |     | - Supportive (11)                                          |                                                                           |
| Kuhle et al. [28]     | 2004 | 72  | LMWH                                                       | Outcome available in only 5 cases:                                       |
|                       |      |     |                                                             | - Death (1)                                                              |
|                       |      |     |                                                             | - Thrombus resolution (3)                                                |
|                       |      |     |                                                             | - Renal atrophy (1)                                                      |
|                       |      |     |                                                             | - Death (3)                                                              |
|                       |      |     |                                                             | - Renal failure (11)                                                     |
|                       |      |     |                                                             | - Nephrectomy (2)                                                        |
|                       |      |     |                                                             | - Renal atrophy (26)                                                     |
|                       |      |     |                                                             | - Renal atrophy (19 unilateral cases)                                    |
| Messinger et al. [43] | 2006 | 28  | - 25 Unilateral/3 bilat RVT                               | - 80% Renal growth impairment (18)                                        |
|                       |      |     | - Fibrinolysis (28)                                        |                                                                           |
| Winyard et al. [44]   | 2006 | 23  | - Supportive (19)                                          |                                                                           |
|                       |      |     | - Heparin (4)                                              |                                                                           |
|                       |      |     | - Fibrinolysis (0)                                         |                                                                           |
|                       |      |     | - Morphological renal abnormalities (11)                  |                                                                           |
|                       |      |     | - Nonfunctioning kidney (atrophy) 7/9 seen on follow-up    |                                                                           |
| Hilario et al. [50]   | 2009 | 11  | - Supportive (4)                                           | - Complete recovery (all unilateral) (1)                                  |
|                       |      |     | - LMWH + thrombolysis (6)                                  | - Bilateral RVT (3): death (1), renal atrophy (2)                        |
|                       |      |     | - Heparin (1)                                              | - Death (2)                                                              |
|                       |      |     | - Fibrinolysis (5)                                         |                                                                           |
|                       |      |     | - Heparin (2)                                              |                                                                           |
|                       |      |     | - Vitamin K antagonist (1)                                |                                                                           |
|                       |      |     | - Supportive (3)                                           |                                                                           |
| Michot et al. [45]    | 2011 | 9   | - Anticoagulant alone (4)                                  | - Nephrectomy (1)                                                        |
|                       |      |     | - Supportive (4)                                           | - Renal atrophy (8)                                                      |
|                       |      |     | - Anticoagulation + Thrombolysis (2)                       |                                                                           |
|                       |      |     | - Supportive (2)                                           |                                                                           |
|                       |      |     | - r-tPA (3)                                                |                                                                           |
|                       |      |     | - Partial recanalization in LK + Renal atrophy in RK      |                                                                           |
|                       |      |     | - Flow recovery (2) but no DMSA scintigraphy reported      |                                                                           |
| Bidadi et al. [38]    | 2016 | 10  | - Anticoagulation alone (4)                                | - Renal atrophy (5)                                                      |
|                       |      |     | - Supportive (4)                                           |                                                                           |
|                       |      |     | - Anticoagulation and Thrombolysis (302)                   |                                                                           |
| Niada et al. [30]     | 2017 | 5   | r-tPA (3)                                                  | - Renal atrophy (184) (45.2%)                                            |
|                       |      |     | - Partial recanalization in LK + Renal atrophy in RK      | - Death (13) (3.2%)                                                      |
|                       |      |     | - Anticoagulant (1)                                        | - Nephrectomy (5) (1.23%)                                                |
|                       |      |     |                                                             | - Complete recovery (22) (5.40%) + 2 7                                  |
| Mikołajczak et al. [39]| 2018 | 3   | - Heparin + thrombolysis (1)                               | - Renal function impairment (42) (10.32%)                                 |
|                       |      |     | - LMWH (1)                                                 |                                                                           |
|                       |      |     | - Anticoagulant (1)                                        |                                                                           |
| TOTAL                 |      | 410 | - Supportive treatment (95 cases)                          |                                                                           |
|                       |      |     | - Anticoagulation and thrombolysis (302)                   |                                                                           |
modalities for unilateral and bilateral RVT are put forward, we adhere to the guidelines suggested by the American College of Chest physicians [36]. Future studies will also gain strength and clarity by separating RVT in preterm infants from those in term-born infants. Additionally, treatment recommendations should distinguish spontaneous cases from those secondary to treatment procedures such as central and/or umbilical catheters placement. We still need more work to reach an acceptable level of neonatal RVT management. Amazingly, our present and, yet controversial, discussions, are very much similar to those carried out by our predecessors over 40 years ago [24,41,42].

2.2. RVT outcome: have we achieved major progress?

To answer to this provocative question is not easy. We have obviously learned a lot more about the RVT pathophysiology, and knowledge has emerged on the possible contribution of thrombophilia to the etiologies of renal venous thrombosis. Antenatal and early postnatal recognition of RVT with precise ultrasound and Doppler confirmation are part of achieved progress.

Our management practice, however, seems to be hampered by several factors, of which mixture of secondary and spontaneous cases and unilateral versus bilateral cases and premature infants RVT make the analysis of therapeutic approaches difficult.

In our opinion, prior to making a choice of therapy to apply when managing RVTs, it is important to consider the parameters, which are as follows:

1. Whether RVT is unilateral or bilateral; 70.3% of cases are unilateral [16].
2. Whether there is an extension to inferior vena cava (IVC); present in 40% cases [16].
3. Anticoagulants and/or thrombolysis can possibly induce hemorrhage in the newborn [16].
4. Bilateral RVT and those with extension to IVC deserve, in our opinion, special attention as the risk for short and long-term complications is much higher.

Taking into account various outcome results published for nearly 50 years (Table 1), we state that very less has been achieved in terms of renal function improvement/regain. We, therefore, have to overcome the challenges and attain higher goals with less renal atrophies and less impaired kidney function.

The high index of clinical suspicion in newborn infants with predisposing factors remains mandatory as it could aid in both early diagnosis and management.

Conflicts of interest

No conflict of interest to declare.

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