Classical presentation of a newborn infant with renal vein thrombosis
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Title figure:
Blood clot (source: www.biocurious.com)
Thrombosis in neonates is a rare event, but associated with significant morbidity and even mortality. Renal vein thrombosis (RVT) accounts for approximately 10% of venous thromboses in neonates. Compared to other regions of thrombosis, RVT is less often associated with central venous catheters (1). Various pathomechanisms, which may lead to a RVT, reduce blood flow to the kidneys or provoke hyperosmolality, hypercoagulability or increased blood viscosity (2, 3). Fetal/neonatal as well as maternal risk factors are summarized in Fig. 1. RVT can also occur as an extension of inferior vena cava thrombosis.

Two thirds of neonatal RVTs are diagnosed during the first three days of life. RVTs are associated with male sex and preterm birth. Clinical presentation includes macrohematuria, thrombocytopenia and a palpable abdominal mass in approximately half of the cases (4, 5).
This male infant was born to a 33-year-old G2/P2 at 38 0/7 weeks of gestation after an uncomplicated pregnancy. The mother developed fever during labor and received amoxicillin clavulanate prior to delivery for suspected chorioamnionitis. The infant was delivered by secondary Caesarean section and adapted well with Apgar scores of 8, 9 and 10 at 1, 5 and 10 minutes, respectively. Arterial and venous umbilical cord pH values were 7.28 and 7.42, respectively. Birth weight was 3160 g (P50), length 49 cm (P50) and head circumference 33 cm (P30).

At 34 hours of age, the infant developed macrohematuria. Apart from a palpable mass in the right flank, physical examination was normal. On admission to the NICU, vital signs including blood pressure (80/40 (56) mmHg) were normal. Laboratory investigations showed thrombocytopenia (61 G/l) and renal failure (serum creatinine 124 µmol/l with a maternal serum creatinine prior to delivery of 49 µmol/l). Hemoglobin concentration was 135 g/l, and clotting studies (INR, aPTT, fibrinogen) were within the normal range. Markers of inflammation were not elevated. Urine analysis confirmed macrohematuria, and the urine output was normal (3.1 ml/kg/hour). An abdominal ultrasound examination showed an enlarged right kidney with abolished corticomedullary differentiation and echogenic streaks in the lower pole, compatible with partial renal venous thrombosis (Fig. 2, 3). Apart from a persistent foramen ovale, echocardiography was normal.
Risk factors for neonatal thrombosis (CHD: congenital heart disease; RDS: respiratory distress syndrome) (17).
Renal ultrasound examination on DOL 2: enlarged right kidney (5.35 cm, normal range 3.9 – 5.1 cm).
Renal ultrasound examination on DOL 3: right kidney with echogenic streaks and abolished corticomedullary differentiation.
On follow-up ultrasound examination a few hours later there was extension of the thrombus into the inferior vena cava (IVC) over a length of 2 cm and partial thrombosis of the left renal vein (Fig. 4). After interdisciplinary discussions, anticoagulation with unfractionated heparin (UFH) was started with a heparin bolus, followed by a continuous infusion. Anticoagulation was adjusted using the protocol published by Michelson et al. (6) (Table), aiming at an aPPT of 60 to 85 seconds.

- Loading dose: 75 units/kg i.v. over 10 minutes
- Initial maintenance dose: 28 units/kg/hour for infants < 1 year
- Adjust infusion rate to maintain aPTT between 60–85 seconds or anti-Xa between 0.35–0.70 IU/ml

<table>
<thead>
<tr>
<th>aPTT (seconds)</th>
<th>Bolus (units/kg)</th>
<th>Hold (minutes)</th>
<th>Infusion rate change</th>
<th>Repeat aPTTT</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 50</td>
<td>50</td>
<td>0</td>
<td>+ 10%</td>
<td>4 hours</td>
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<tr>
<td>50-59</td>
<td>0</td>
<td>0</td>
<td>+ 10%</td>
<td>4 hours</td>
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<tr>
<td>60-85</td>
<td>0</td>
<td>0</td>
<td>no change</td>
<td>next day</td>
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<tr>
<td>86-95</td>
<td>0</td>
<td>0</td>
<td>- 10%</td>
<td>4 hours</td>
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<tr>
<td>96-120</td>
<td>0</td>
<td>30</td>
<td>- 10%</td>
<td>4 hours</td>
</tr>
<tr>
<td>&gt; 120</td>
<td>0</td>
<td>60</td>
<td>- 15%</td>
<td>4 hours</td>
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</tbody>
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*Protocol for systemic unfractionated heparin (UFH) administration and dose adjustments for pediatric patients (6).*
Repeated cranial ultrasound examinations (including one obtained prior to starting anticoagulation) showed no signs of intracerebral hemorrhage. After initiation of heparin treatment, no further extension of the thrombosis was documented. Serum creatinine concentrations decreased to 79 µmol/l within 96 hours. Macrohematuria disappeared after one week of life. Blood pressure remained normal.

After eight days of intravenous UFH, anticoagulation was changed to enoxaparin, a low-molecular-weight heparin (LMWH), administered subcutaneously via an Insufilon® catheter. On day 13, improved blood flow in the IVC could be demonstrated on ultrasound. The infant was discharged home on day of life 14.

At one month of age, the thrombi in the IVC and the left kidney had completely resolved, and only discreet signs of the thrombosis in the lower pole of the right kidney were still detectable. Renal function had normalized (serum creatinine of 33 µmol/l). Treatment with subcutaneous LMWH was continued for a total of 3 months. Most recently, one year after discharge, renal function, blood pressure, and renal ultrasound examinations have been normal.

Family history was positive for sickle cell anemia in two paternal uncles and for pulmonary embolism in a grandmother at the age of 60 years. The patient’s parents already had one healthy child. Investigations
Abdominal ultrasound examination on DOL 3: absent flow in the inferior vena cava.
for hereditary thrombophilias were negative. Sickle cell trait was excluded by hemoglobin electrophoresis at the age of six months. The etiology of RVT remained unexplained in our patient. Chorionamnionitis was the only maternal risk factor (Fig. 1), however, the baby had no signs of a neonatal infection.
This case report describes an infant with the so-called classical clinical presentation of RVT (macrohematuria, palpable renal mass, and thrombocytopenia). However, the full triad has been reported to be only present in 13 % of RVT cases (7). If RVT is suspected, the diagnosis must be confirmed by imaging. In neonates, the initial method of choice is Doppler ultrasonography (8).

In addition, laboratory markers such as full blood count and renal function tests should be analyzed. Coagulation tests, including activated partial thromboplastin time (aPTT), fibrinogen and INR, are crucial to exclude an acute hemostatic problem such as DIC and to acquire base-line values before starting treatment.

If bilateral RVT is diagnosed, renal function tests, electrolytes and diuresis must be monitored because of the risk of acute renal failure. In unilateral disease, creatinine and urea concentrations usually remain normal. Arterial hypertension can develop after RVT and blood pressure must therefore be monitored regularly.

The role of anticoagulation in RVT is controversially discussed in the literature. Strategies regarding initiation of treatment, route of application, choice of anticoagulants and treatment duration differ widely due to a lack of randomized controlled trials (9, 10).
In cases of isolated unilateral RVT, supportive care with close monitoring is suggested since no benefit has been demonstrated while bleeding complications can occur. In contrast, for patients with unilateral RVT and extension into the IVC, anticoagulation for six weeks to three months should be considered. If both kidneys are affected with renal impairment, either thrombolytic treatment with systemic tissue plasminogen activator (tPA) followed by anticoagulation or anticoagulation only for six weeks to three months is generally recommended.

Suggested strategies include treatment either with LMWH alone or to start with UFH followed by LMWH. We chose to start with UFH because of its rapid onset of action, its short half life and its reversibility by protamine sulfate should side effects (bleeding, heparin induced thrombocytopenia) occur. Disadvantages of anticoagulation with UFH include the need for intravenous administration, frequent blood tests and dose adjustments. Once adequate anticoagulation has been established and the patient is stable, treatment can be changed to subcutaneous LMWH.

Major bleeding episodes in children receiving UFH treatment have been described in 1.5% to 24% of patients (11). Heparin-induced thrombocytopenia by UFH is relatively rare, occurring in less than 2.5% of pediatric patients (12).
Therapeutic dosing of LMWH is based on anti-FXa levels. The suggested dose for subcutaneously administered enoxaparin in infants < 2 months of age is 1.5 mg/kg 12 hourly. Anti-FXa levels 4–6 hours after subcutaneous injection should be between 0.5–1 U/ml. Enoxaparin is easy to administer, even in an outpatient setting (12). Although adverse events are considered to be rare, several major complications including major bleeding episodes, hematoma formation at the administration site, gastrointestinal bleeding, and intracranial hemorrhage have been described with an overall incidence of approximately 5 % (13–14).

Inherited prothrombotic conditions like protein C or S deficiency, antithrombin deficiency, factor V Leiden, and mutation of prothrombin 20210A are more common in newborns with RVT as compared to the general population and should be tested in patients with an unclear origin of RVT. Babies born to mothers with antiphospholipid syndrome or lupus should be screened for lupus anticoagulant.

Survival rates of infants with RVT are excellent. However, long-term sequelae, including irreversible renal damage (71%) and arterial hypertension (19%) can occur (4). Therefore, nephrology follow-up is required. Importantly, there is a 6.8 % risk for a second episode of venous thrombosis during puberty.
RVT should be suspected in newborns with hematuria, palpable abdominal mass and/or thrombocytopenia, especially if neonatal or maternal risk factors for hemostasis imbalance are present. The aim of heparin treatment is to prevent life-threatening events, thrombus extension, and long-term complications. However, there is limited evidence to guide decision-making and anticoagulation significantly increases the risk of bleeding.
REFERENCES


