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RESEARCH ARTICLE

TREATMENT WITH HEPARIN IN CATHETER-UNRELATED EXTENSIVE BILATERAL RENAL VEINS AND INFERIOR CAVA VEIN THROMBOSIS IN A NEWBORN

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ABSTRACT

Renal vein thrombosis (RVT) affects 1.3-2.2/100,000 newborns. The classical presenting triad includes gross haematuria, thrombocytopenia and palpable abdominal mass. RVT can appear due to low-flow intrarenal circulation or umbilical vein catheterization. Perinatal factors like asphyxia, hypovolemia or shock and prothrombotic disorders have also been described as predisposing factors for spontaneous RVT. Although treatment is controversial, thrombolysis has been suggested for extensive cases with bilateral involvement. We present a case of a neonate with extensive bilateral renal vein and inferior cava vein thrombosis who was managed with heparin therapy.

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INTRODUCTION

Renal vein thrombosis (RVT) is the most common form of venous thrombosis in neonates (Bulut *et al., 2018;* Kayemba-Kay's, 2020). Nonetheless, it is a rare condition which is not well known. Some studies estimate an approximate incidence of 1.3-2.2 cases per 100,000 population (Bökenkamp *et al.*, 2000; Heller, 2000). Paediatricians should be aware of the characteristic clinical manifestations of this entity. It usually develops in utero or during the first 72 hours of life (Lau, 1992). Macroscopic haematuria, palpable abdominal mass and thrombopenia have been classically considered as the cardinal symptoms of this condition (Winyard, 2006). The aetiology of RVT remains unknown (Niada, 2018). In cases of spontaneous thrombosis, low renal perfusion, double intrarenal capillary circulation system and lower anticoagulant and fibrinolytic blood levels in neonates could explain intrarenal generation of thrombus (Elsaify, 2009). Diabetes or gestational hyperglycaemia, preeclampsia, chorioamnionitis and autoimmune diseases are some of maternal predisposing factors (Aluloska, 2018). Among neonatal risk factors; prematurity, perinatal asphyxia, infection, hypovolemia, dehydration and polycythaemia, are the most frequent (Heller, 2000; Lau, 2006; Bidadi, 2016). Central venous line catheterization is the most important cause of thrombosis. It is estimated that 75-95% of cases of RVT are secondary to umbilical vein cannulation (Bhat, 2018).

In addition, cases of renal thrombosis related to prothrombotic conditions have been described (Kosch, 2004). Factor V Leiden mutations are the greatest inherited risk factor for venous thromboembolism (Marks, 2005). Treatment is controversial. There are no specific therapeutic guidelines for its management. Some authors defend conservative management, while others support pharmacological or surgical thrombolysis. In cases of bilateral thrombosis authors advocate thrombolysis (Michot, 2011). We present the case of a neonate with extensive bilateral renal vein thrombosis spreading to inferior cava vein and reaching the right atrium, who was managed with anticoagulation alone, suggesting the feasibility of a more conservative management for bilateral RVT with preserved renal function.

CASE REPORT

A boy was delivered at 38 + 2 weeks of gestation by an emergency caesarean section due to non-reassuring foetal monitoring. Pregnancy was complicated with gestational insulin-dependent diabetes mellitus. Prenatal ultrasound evidenced foetal macrosomia. Maternal SARS-COV2 PCR was negative. Delivery room resuscitation with intermittent positive pressure ventilation was required due to absent respiratory effort.

Apgar score was 5/8 at 1 and 5 minutes, respectively. Cord arterial pH was 7.08. He was admitted to neonatal intensive care. Laboratory investigations at birth demonstrated significant metabolic acidosis with severely elevated lactate (15mmol/L), thrombocytopenia, transaminitis (alanine aminotransferase 223 IU/L, aspartate aminotransferase 382 IU/L) and troponin elevation (0.19 ng/mL). Neurologic examination was normal. An initial echocardiogram performed within the first hour of life demonstrated a pediculate and mobile image located at the entrance of right atrium. It was solid and non-vascularized (Figure1). Cardiac function and structure were normal. At 24 hours of life an abdominal mass was found on physical examination. It occupied right iliac fossa and flank. Shortly after, the patient started with gross haematuria.

Abdominal ultrasound revealed the presence of bilateral renal thrombosis with extension to the inferior cava vein (already visualized in echocardiography on the first day of life), common iliac vein and bilateral nephromegaly affecting mostly the right kidney (6.3 cm vs. 5.4 cm) (Figure 2). Cortico-medullary differentiation was maintained. Right intrarenal Doppler flow was significantly reduced whereas left intrarenal flow was preserved.

Therapeutic options where considered and anticoagulation with low weight heparin (enoxaparin) was started. Considering the absence of renal impairment and the preservation of left intrarenal Doppler flow, we decided not to start thrombolysis. Close monitorization of renal function and serial ultrasound controls were done. It was latter demonstrated the development of collateral renal vascularization in both kidneys with progressive reduction in right kidney size and a compensatory contralateral hypertrophy (Figure 3). At five days of live, the patient developed arterial hypertension. It required the association of a vasodilator (intravenous hydralazine initially and amlodipine at discharge) with an inhibitor of angiotensin-aldosterone enzyme (enalapril) for an adequate control. Before discharge, prothrombotic risk factors were ruled out in the parents and the newborn, with normal Antithrombin III activity, Protein C and Protein S levels. Thrombophilic genes (Leiden V factor and Prothrombin gene) were also normal. During next three months follow up, renal function remained normal and it was possible to reduce antihypertensive drugs.

DISCUSSION

We present a rare case of catheter-unrelated extensive RVT in which no family or patient congenital prothrombotic disorders were found. Evidence-based guidelines for the management of RVT in neonates are not available. Treatment recommendations are controversial and mostly based on case series. Maternal anticoagulation is not recommended and there are no reports of prenatal interventionin cases of prenatal diagnosis (Moaddab, 2016). Treatment modalities vary among centres from supportive care, anticoagulation to thrombolytic therapy (Kosch, 2014). Supportive management of electrolytes and fluid balance is an available option. Heparin therapy is chosen for unilateral RVT cases without renal impairment or extension to inferior cava vein. The American College of Chest Physicians Evidence-Based Clinical Practice Guidelines 2012 and most of the literature recommend thrombolysis for patients with bilateral RVT and renal impairment (Nold, 2008).

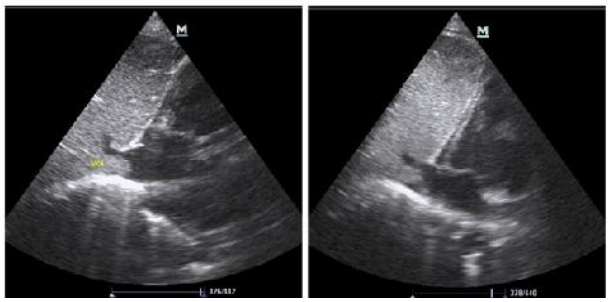

Figure 1. Trastoracic echocardiography. Solid and non-vascularized imagen in the lumen of inferior cava vein.

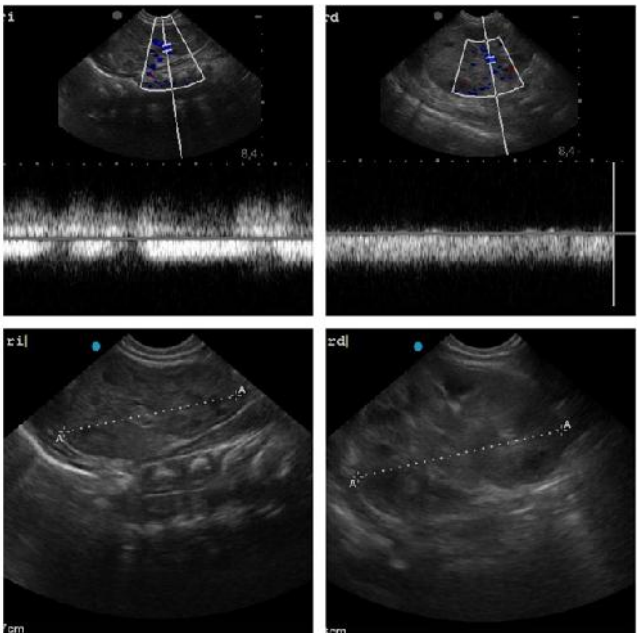

Figure 2: Abdominal ultrasound. Minor asymmetric bilateral intrarenal venous flow is detected in the right kidney. Left kidney 5.37 cm. Right kidney 6.33 cm

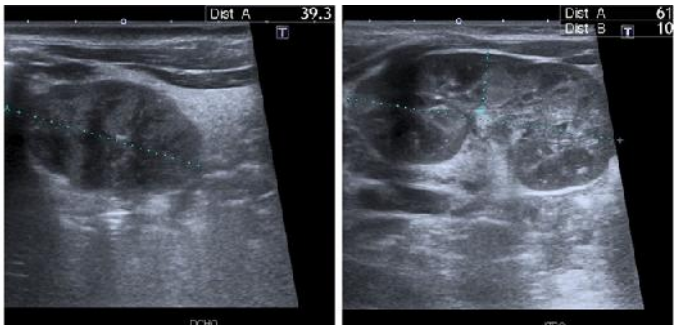

Figure 3. Abdominal ultrasound. Right renal atrophy with increased left longitudinal diameter in relation to compensatory hypertrophy

Infusion of recombinant tissue plasminogen activator (rt-PA) acts producing plasmin which leads to clot dissolution, but many complications have been described due to its use (Niada, 2018). Intracranial haemorrhage and peritoneal bleeding are the most frequent ones (Jaako Dardashti, 2009). An overview of the literature recently published shows that different modalities of treatment have similar outcomes and kidney atrophy does not relate with the treatment selected (Kayemba-Kay's, 2020). In our case, renal function was normal and due to the high risk of thrombolysis, we decide not to start this therapy. Given the good evolution of the patient, conservative

heparin management with clinical and ultrasound follow-up could be an alternative in bilateral RVT cases with preserved renal function.

Most cases of RVT are diagnosed after birth (Moaddab, 2016). It has been described that 7.3% of cases occurs intrauterine, 67.1% in the first 72 hours of life and the remaining 25.6% from the third day on (Bulut, 2018). In our case presence of inferior cava vein thrombus in the first hour of life suggests that thrombosis took place in utero, but diagnosis was done shortly after delivery. As predisposing factors gestational diabetes and perinatal asphyxia were present in our patient. Fetal vascular malperfusion, which may be secondary to gestational diabetes, has not been described as a factor related to RVT. However, several authors have published cases of extensive bilateral renal thrombosis in neonates with this background; and therefore, it should be considered (Giacchetti, 2017; Brown, 2019). An exceptional aspect of our case is that cava vein involvement was present from birth without a history of umbilical venous catheterization. The Danish group in their series of 99 patients did not report any case of extensive thrombosis with inferior cava vein involvement not related to the central catheter. All neonates with RVT should be screened for prothrombotic risks, including maternal lupus inhibitor. Caution should be exercised because 3 out of 4 patients with RVT had a second prothrombotic event at puberty in patients with prothrombotic disorders (Kosch, 2014).

It should also be noted from this case that our patient presented with the pathognomonic clinical triad: abdominal mass, gross haematuria and thrombocytopenia. However, it is important to maintain a high index of suspicion because only 22% of patients present with these three symptoms (Winyard, 2006). The presence of oliguria, proteinuria and hypertension are other frequent clinical signs (Bidadi, 2016). Indirect ultrasound signs that suggest RVT are renal enlargement, hyperechoic streaks and loss of corticomedullary differentiation. Colour and spectral Doppler can also help in the diagnosis (Elsaify, 2009). However, diagnostic confirmation would require other imaging tests such as computed tomography or nuclear magnetic resonance. In our patient ultrasound allowed diagnostic confirmation without requiring additional tests. Although mortality is low (5%), morbidity of this condition remains high regardless of treatment modality. Kidney damage is the main complication, which appears in 70.6% of the cases. Hypertension, tubular dysfunction, renal atrophy and chronic kidney disease are the most frequent functional abnormalities (Lau, 2007). In the case of our patient renal function was preserved, however, he presented arterial hypertension refractory to treatment with a single antihypertensive drug. This complication, described in other series, is estimated to affect 19-22% neonates with RVT.

Key points: Bilateral renal venous thrombosis in neonates is a rare condition. However, it is the most common form of venous thrombosis in this population. Central venous line catheterization is the most important cause of thrombosis. Without a history of catheterization, RVT can occur secondary to fetal vascular malperfusion, mostly in presence of gestational diabetes. It should be suspected in the presence of clinical findings like haematuria, abdominal mass and thrombopenia. More studies are needed to define specific treatment guidelines. Heparin conservative management could be a safer therapeutic option for bilateral RVT with preserved renal function, as in the case we present. Long-term follow-up, especially in those cases of bilateral thrombosis, is very important in order to detect late complications of kidney function.

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