Renal venous thrombosis in infancy

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Summary

Renal venous thrombosis (RVT) in infancy occurs in situations associated with reduced renal blood flow and hypercoagulability. The clinical diagnosis is based on finding enlarged kidney(s), haematuria and thrombocytopenia in a setting where the infant is at risk of RVT. Ultrasonography is the imaging modality of choice and should replace the more invasive excretory urography and venography for confirmation of the diagnosis. Impairment of renal function is best documented by radionuclide studies. Treatment is supportive with heparinisation for severe bilateral RVT and inferior vena cava thrombosis. The role of thrombectomy and fibrinolytic therapy is limited in infancy. Survival rates have much improved in recent years. Severe venous infarction leads to atrophy of the affected kidney, which may later be mistaken for congenital renal hypoplasia. RVT may be complicated by hyperreninaemic hypertension, which is curable by nephrectomy.

Renal venous thrombosis (RVT) is an uncommon life-threatening condition in childhood occurring predominantly in the first few months of life. It is associated with perinatal stress, polycythaemia and hyperosmolar states. Survivors are at risk for several long-term complications including atrophy of the affected kidney(s), chronic renal failure and hypertension. The diagnostic and therapeutic approach to this serious condition has changed in recent years. The case histories of 3 infants are reported to illustrate the wide clinical spectrum and current management of RVT in this age group.

Case reports

Case 1

A 3480 g infant was born to an insulin-dependent diabetic mother 5 weeks prematurely and was in a state of asphyxia at birth. On day 2 RVT was diagnosed on the basis of an enlarged left kidney, macroscopic haematuria with renal failure (serum creatinine value 143 \(\mu\)mol/l) and thrombocytopenia (30000/mm\(^3\)). On ultrasonography the right kidney was normal with a bipolar length of 4.2 cm; the left kidney was enlarged (6.4 cm) and showed a distorted, bizarre echopattern with inhomogeneously increased echogenicity and loss of corticomedullary differentiation. Transient hypertension of 110/85 mmHg was recorded. A 10 ml venesection was done for polycythaemia (haematocrit 65%). The infant recovered with supportive therapy and was discharged on day 10, normotensive with the left kidney no longer palpable.

On referral to this hospital at the age of 9 months, clinical examination was negative except for hypertension of 150/90 mmHg. Routine plasma biochemical tests were normal and the glomerular filtration rate (GFR) measured by technetium-99m-Sn-diethylenetriaminepento-acetic acid clearance (\(^{99m}\)Tc DTPA) was 73 ml/min/1.73 m\(^2\). Peripheral vein renin activity was 13.9 ng/ml/h (normal 1 - 4 ng/ml/h).

Left renal ischaemia was suspected but ultrasonography, excretory pyelography, \(^{99m}\)Tc DTPA and dimercaptosuccinic acid (\(^{99m}\)Tc DMSA) scans, computed tomography (CT) and renal arteriography failed to identify the left renal artery and kidney clearly. Plasma renin activity in the right renal vein was 27.7 ng/ml/h and in the inferior vena cava (IVC) at the diaphragm 43.6 ng/ml/h.

Retrograde pyelography was necessary to demarcate the now very small left kidney (1.8 cm), which at subsequent nephrectomy weighed < 2 g. Histopathological examination showed the features of end-stage kidney disease with marked hypertensive changes in the vessels.

After nephrectomy the blood pressure fell to normal within 24 hours. Peripheral plasma renin activity was 2.5 ng/ml/h 1 week postoperatively. Clinical examination was negative and renal function normal 5 years later.

Case 2

A term male infant, delivered by caesarean section for fetal distress, weighed 3170 g at birth. On the 2nd day of life macroscopic haematuria with small clots was noted and bilateral irregular renal masses had become palpable. The blood pressure was 85/40 mmHg.

On referral to this hospital on day 5 the infant was in renal failure (serum creatinine value 398 \(\mu\)mol/l). The haemoglobin value was 14.8 g/dl and the peripheral blood smear, platelet count, partial thromboplastin time (PPT) and prothrombin international normalised ratio (INR) were normal.

On ultrasonography both kidneys were grossly enlarged; the left kidney measured 70 mm and the right 66 mm, and both showed a bizarre 'patchwork' echopattern with areas of decreased and increased echogenicity and perivascular streaks. Thrombus was seen in the IVC (Fig. 1) but the renal veins could not be identified.

Technetium-99m DMSA scan showed no uptake in the right kidney and poor uptake with a large cold area in the left kidney. Four months later the right kidney showed only a small area of \(^{99m}\)Tc DMSA but uptake in the left kidney had returned to normal. At the age of 3 weeks calcification of the IVC thrombus was shown by CT.

Renal function was supported with peritoneal dialysis via an acute Tenckhoff catheter for 4 days. Intravenous heparin 25 U/kg/h was given for 11 days.

On reassessment at the age of 15 months the blood pressure was 90/60 mmHg and the infant was growing normally. Ultrasonography showed partial recanalisation of the IVC (Fig. 2). The right kidney had atrophied and measured 31 mm. The left kidney showed compensatory hypertrophy (70 mm), but irregularly increased echogenicity with indistinct corticomedullary differentiation was still present. Technetium-99m DTPA clearance was 103 ml/min/1.73 m\(^2\), with the right kidney contributing < 5%; \(^{99m}\)Tc DMSA uptake in the left kidney was normal but the right kidney was small with poor uptake. Peripheral plasma renin activity was 0.28 ng/ml/h.
Case 3

A 7-day-old baby boy was admitted to hospital > 10% dehydrated, hypernatraemic, acidic and shocked. On clinical examination both kidneys were markedly enlarged and appeared tender. Delivery at a rural hospital had been uneventful, his birth weight was 3500 g and he had been breast-fed. For 24 hours he had refused feeds and macroscopic haematuria had been noted.

Initial investigations showed the following: haemoglobin value 19.4 g/dl, platelet count 61000/mm³, serum sodium value 185 mmol/l, urea 75 mmol/l, creatinine 1143 μmol/l, prothrombin INR 1.5, PTT normal, fibrinogen 78 mg/dl and fibrin degradation products > 10 < 40 μg/ml.

The infant was resuscitated and treated with intravenous cefotaxime, intermittent peritoneal dialysis and a continuous intravenous heparin infusion for 7 days. At no stage was hypertension recorded.

Ultrasonography confirmed the enlargement of the kidneys (right 52 mm, left 60 mm) with poor corticomedullary differentiation bilaterally. The main stem renal veins and IVC were patent. Follow-up scan 3 days later showed further enlargement of the left kidney (68 mm), which now showed inhomogeneously increased echogenicity with perivascular streaks.

At the age of 3 months the infant was thriving, with normal urinalysis and renal function. Blood pressure levels up to 115/60 mmHg have been recorded and he remains under observation. Peripheral vein plasma activity was 0.96 ng/ml/h.

On repeat ultrasonography the left kidney measured 56 mm (normal) and the right kidney 54 mm. The echopattern in both kidneys was now distorted with echogenic perivascular streaks. The IVC and renal veins were patent.

Technetium-99m DTPA clearance was 123 ml/min/173 ml², the left kidney contributing about 40% to total function. The ⁹⁹ᵐTc DMSA uptake in the left kidney was decreased overall and segmentally, the right kidney was normal.

Discussion

RVT in childhood occurs mostly in the 1st month of life (74%), and may occur in utero. It is 2-3 times more common in boys than girls. It may occur spontaneously, but situations can usually be identified that predispose to RVT, i.e. reduced renal blood flow, haemoconcentration, increased blood viscosity, hyperosmolarity and hypercoagulability. Perinatal hypoxia, shock, polyhydramnios, cyanotic congenital heart disease, hypernatraemic dehydration, septicemia and indwelling umbilical venous catheters are the major associated factors in the newborn period. Infants of diabetic mothers are at risk because of polyhydramnios, increased platelet stickiness due to intra-uterine hyperglycaemia and their relatively low extracellular fluid volume.

Clinical diagnosis

The initial event is catastrophic rather than slowly progressive, but may be so mild as to go unnoticed. Clinical diagnosis is based on finding macroscopic haematuria (> 60%) and proteinuria, enlargement of one or both kidneys, which may appear tender, and thrombocytopenia (> 80%) in a setting where the infant is at risk of RVT. Anaemia and evidence of intravascular coagulation with fragmented red blood cells on smear, decreased clotting factors and increased fibrin split products may be present.
The signs and symptoms of the underlying illness may dominate the clinical picture. Non-specific refusal of feeds, vomiting, diarrhoea, respiratory distress, pallor, shock and metabolic acidosis, fever and convulsions may be present. Hypertension in the acute phase is rare. Peripheral and scrotal oedema and cyanosis of the legs may be present if the IVC is thrombosed.

The kidney in the normal newborn is usually palpable and about the size of the distal phalanx of an adult thumb. In early infancy the differential diagnosis of flank masses includes severe acute pyelonephritis and perinephric abscess, obstructive uropathy, cystic disease of the kidneys, nephroblastoma, mesoblastic nephroma and neuroblastoma, suprapenal haemorrhage with or without renal venous thrombosis, acute cortical and tubular necrosis, Beckwith-Wiedemann syndrome and infiltrative conditions such as leukaemia.

The presence of small clots in the urine is not unusual and differentiates RVT from acute tubular necrosis caused by perinatal hypoxia. 

The newborn has limited reserve renal function and in infancy the severity of renal failure is inversely related to age at onset. Hypovolaemic prerenal failure and acute tubular necrosis may contribute to the azotaemia. It is not possible to make a prognosis on the basis of the initial level of serum creatinine, although raised levels suggest bilateral involvement.

Pathogenesis

In the young infant RVT originates in the smaller venous tributaries from where it spreads asymmetrically to involve the cortex and medulla, and at times the main stem renal vein, the suprarenal haemorrhage, and the azygous, hemi-azygous and vertebral systems.

Renal venous obstruction results in oedema and congestion leading to enlargement of the kidney. Haemorrhage occurs into the anoxic renal parenchyma, with fibrosis and contraction occurring later. Localised haemorrhagic infarction leads to focal scarring detectable on 99mTc DMSA scan. More extensive damage results in atrophy with loss of function; this resembles congenital renal hypoplasia or post-obstructive atrophy.

Investigation

Ultrasonography is the method of choice for imaging flank masses. An overall increase in size of the kidneys in RVT is invariable, but is often asymmetrical. Gross distortion of the normal intrarenal architecture with obliteration of the central echo occurs. A 'patchwork' echopattern is seen with foci of increased echogenicity due to haemorrhagic infarction and perivascular haemorrhage, and areas of normal or decreased echogenicity due to oedema. Normal corticomedullary differentiation is lost.

The ultrasonographic appearances vary with the interval after the thrombotic event. If the scan is done early, before haemorrhage into the kidney parenchyma has occurred, the oedematous renal cortex appears globally hypo-echoic; conversely in late massive haemorrhagic infarction the entire kidney is markedly hyper-echoic. Renal venous flow may be detected by Doppler ultrasonography.

The distorted intrarenal echopattern is not pathognomonic of RVT, but the diagnosis is confirmed if thrombus is seen in the renal vein or IVC. Most other causes of enlargement of the kidneys are readily excluded on ultrasonography.

Ultrasonographic appearances improve over a period of several weeks, but a rapid return to normal size within 1 - 2 weeks may indicate early atrophy rather than recovery. Compensatory hypertrophy of the contralateral kidney is indicative of irreversible damage to one kidney. A severely affected kidney atrophies over a period of 3-4 months.

Excretory urography in the newborn is unsatisfactory owing to the low GFR, poor concentration of contrast and gas patterns in the bowel, and the hyperosmolar contrast adds to the risk of extension of the thrombosis. It is difficult or impossible to see the kidney in over 90% of cases of RVT.

Less invasive ultrasonography should replace excretory urography, and IVC and selective renal venography.

CT adds little more information than is available from ultrasonography and scintigraphy. No reports of magnetic resonance imaging in RVT have been published.

Radionuclide studies will demonstrate decreased 99mTc DTPA excretion or reduced 99mTc DMSA uptake, which is non-specific but a reliable measure of differential and follow-up renal function. A 2-4 mm peripheral rim 99mTc DTPA nephrogram may be seen in a non-functioning kidney and is indicative of perirenal capsular collateral drainage.

Sequential radionuclide studies (99mTc DTPA) have demonstrated a maximal rate of recovery of function of the affected kidney within 3 weeks, but further improvement continued over 6 months, by which time almost normal function was regained despite initial non-function.

Full recovery of function does not occur in areas where uptake of 99mTc DMSA is absent in the acute phase, and later scarring and atrophy are likely. Occlusion of the IVC may be demonstrated by bolus injection of radionuclide into a foot vein.

Bullet-shaped calcification to the right of vertebral bodies T11-L1 is a pathognomonic sequel of IVC thrombosis. Lattice-like calcium deposition within the kidney and calcification in the renal vein may be recognised on radiography or CT.

Course

Haemorrhagic venous infarction results in fibrosis and scar-ring, leading to renal ischaemia and hyperreninaemic hyperten-sion. Hypertension may develop despite renal function being normal, and may follow subclinical and even intrauterine RVT. Hypertension is more likely if renal atrophy results, but has been reported in patients with normal-sized kidneys following RVT.

An atrophic non-functioning kidney may be difficult to identify by the usual means, yet when the ischaemic remnant is surgically removed the hypertension is cured.

The incidence of hypertension following venous infarction is unknown. Olson reported 6/40 survivors who developed hypertension following RVT, 2 of whom were cured by nephrectomy. Jobin et al. found mild asymptomatic hypertension and normal renal function in 5 out of 6 patients reassessed 21 months to 12 years after RVT, but none required treatment and plasma renin activity was normal in all but 1 patient.

Partial or complete recovery occurs by recanalisation or the development of adequate collateral venous drainage. If RVT occurs unilaterally, compensatory hypertrophy of the contra-lateral kidney will maintain normal overall function. Bilateral RVT is more likely to result in chronic renal failure but this is not inevitable.

Slowly progressive chronic renal failure with small 'hypo-plastic' kidneys may develop later, since growth of the damaged kidneys may not keep pace with the child's growth.

Rarely nephrotic syndrome and renal tubular dysfunction follow RVT.
**Treatment**

Management is aimed at treatment of the underlying disease and precipitating factors, correction of acid-base and electrolyte imbalance, support of kidney function and antibiotics if infection is suspected. Dialysis is indicated if, despite corrective measures, oligo-anuria with serum creatinine levels > 300–400 μmol/l and major electrolyte or acid-base imbalance persist. An acute Tenckhoff catheter, which may be implanted at the bedside, facilitates prolonged peritoneal dialysis.

In the absence of controlled data the value of anticoagulant therapy remains uncertain. Thrombosis is often extensive by the time the initial diagnosis is made, and it is not known whether heparinisation limits the severity of the long-term damage. It is indicated for severe bilateral RVT with or without IVC thrombosis and if consumptive coagulopathy persists. Systemic anticoagulation should halt progression of the thrombotic process, prevent occurrence of extrarenal thrombo-embolic complications and facilitate recanalisation. After a priming dose of 100 U/kg intravenously, a continuous infusion of heparin 25 U/kg/h is given for 5 days or longer until the clotting profile is normal. In practice, heparin dosage is difficult to control, but the capillary clotting time should be kept at 2–3 times normal. Heparin is most effective if given early.

Streptokinase and urokinase facilitate conversion of plasminogen to the proteolytic enzyme plasmin, which is capable of lysing clots. Successful systemic fibrinolytic therapy has been reported in adults, but carries the risk of major haemorrhage. Selective locally infused low-dose streptokinase 50 U/kg/h for 2–4 days via an indwelling catheter is more effective with less risk of haemorrhage.

Thrombectomy is only feasible if thrombus has been demonstrated in the IVC or main stem renal veins. Successfully treated cases have been reported, but it is unknown whether the results of surgical intervention in the newborn are any better than less hazardous conservative measures.

Acute nephrectomy is contraindicated, since the potential for recovery is considerable and surgery carries a greater risk than conservative measures.

Elective nephrectomy for hypertension may become necessary later. Whether a non-functioning kidney should be removed is the absence of hypertension is debatable. However, long-term follow-up for the detection of the development of hypertension will be necessary for several years if nephrectomy is not done.

**Prognosis**

The likelihood of recovery does not correlate with the severity of the renal failure at onset. Atrophy of the kidneys or development of hypertension are similarly unpredictable. Atrophy after undiagnosed RVT may be mistaken for congenital renal hypoplasia later in life.

The prognosis is related to the clinical setting in which it occurs. As recently as 1985, Clark et al. stated that most newborns with bilateral RVT die, particularly if there is vena caval extension. Arneil reported a mortality rate of 66% in the <1-month age group.

Immediate survival is now much improved but more data on the long-term outcome are required.

Prevention should focus on avoiding situations that put the infant at risk of RVT.

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**REFERENCES**