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REVIEW

Renal Vein Thrombosis

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Objective. *The aim of this article is to review the published English literature on aetiology, pathology, clinical presentation, diagnostic methods and treatment of renal vein thrombosis.*
Materials and methods. *We searched the published literature from Medline & Pubmed using keywords renal vein thrombosis, anti-phospholipid syndrome and nephrotic syndrome. Data was extracted from individual case reports, case series, articles on pathology, diagnostic tests, treatment modalities, and previous reviews. Case reports which did not add any new information were excluded.*
Results. *We selected 60 references based on the above criteria. Renal vein thrombosis is relatively rare. CT angiography is considered the investigation of choice. Alternatives include MR angiography or renal venography in highly selected patients. As the condition is relatively uncommon, consensus on the best form of therapy for this condition has been slow to evolve. The trend in management has shifted to non-surgical therapies particularly systemic anticoagulation except in highly selected group of patients.*

Keywords: Renal vein thrombosis; Antiphospholipid syndrome; Nephrotic syndrome.

Introduction

The term renal vein thrombosis (RVT) is used to describe presence of thrombus in the major renal veins or their tributaries. This condition may either present with acute symptoms or go unnoticed because of lack of symptoms until a complication like pulmonary embolism or worsening renal function, draws attention to it.

As early as the 5th century BC, Hippocrates and ancient Knidian physicians of Asia Minor were familiar with a renal disease resembling RVT.[1] Rayer, a French nephrologist, was the first to describe RVT and its association with proteinuria in 1840.[2] RVT can occur in intrauterine life, mostly due to the presence of Factor V Leiden.[3] RVT is also one of the commonest causes of venous thrombosis in neonates usually following severe dehydration or prolonged hypotension.[4,5] Although trauma, infection and malignancies were considered to be the predominant causes of this vascular complication in the past, RVT in children and adults is most commonly associated with nephrotic syndrome.[6] The exact incidence of RVT due to other causes is not known but the incidence in nephrotic syndrome and membranous nephropathy, the commonest causes of RVT, ranges from 5–62%.[7]

Males are affected more commonly than females. There is no racial predilection. Almost two thirds of patients have bilateral renal vein involvement. In cases of unilateral thrombosis the left renal vein is affected more commonly than the right. RVT may resolve spontaneously without any complication or result in hypertension and renal failure.[8]

We present a review of the English literature pertaining to the aetiological factors, patho-physiological mechanisms underlying the thrombotic process, various diagnostic techniques employed in establishing the diagnosis and therapeutic options for this relatively uncommon vascular complication.

Material and Methods

We searched the literature from the Medline & Pubmed using keywords renal vein thrombosis,

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anti-phospholipid syndrome and nephrotic syndrome. The articles selected included individual case reports, case series, articles on pathology, diagnostic tests and treatment modalities. We also reviewed nephrology text books for any additional information to make this review as comprehensive as possible. However, the case reports which did not add any new information were omitted.

Results

Based on our literature search we selected 60 most appropriate and informative references as listed in bibliography covering various aspects of this condition as presented below.

Pathology

Rudolf Virchow in 1956, was the first to describe the pathophysiology of venous thrombosis involving a combination of three interrelated factors; damage to the vessel wall (endothelial damage), slowing down of the blood flow (stasis), and hyper-coagulability of the blood, popularly known as Virchow's Triad. Although a single abnormality may occasionally be sufficient to precipitate thrombosis, in majority of the cases, a combination of more than one factor promotes venous thrombosis.[9] It is evident from review of the literature that causes and mechanisms of RVT are no different from venous thrombosis elsewhere in the body and are listed in Table 1.

Table 1. Causes of renal vein thrombosis

Endothelial damage[56,34,48,52,10,11]
Blunt trauma
Trauma during venography
Renal transplant
Infiltration by tumour
Acute rejection
Vasculitis
Spontaneous micro-trauma to the endothelium e.g. in homocystinuria
Stasis[5,56,57]
Severe volume losses e.g. GI fluid loss, haemorrhage, dehydration
Post transplant distortion/kink of renal vein
Primary retroperitoneal processes with renal vein compression
Hypercoagulability[2,56,52,58,60,59,19,60,51]
Nephrotic Syndrome
Membranous glomerulonephritis
Membranoproliferative glomerulonephritis
Focal segmental glomerulosclerosis
Minimal change disease
Sepsis: Generalized/Localized (in and around kidney)
Puerperium
Disseminated malignancy
Oral contraceptives
Intrinsic Hypercoagulability
Factor V Leiden (Resistance to activated protein C)
Prothrombin gene mutation (G20210A)
Deficiency of Protein S
Deficiency of Protein C
Deficiency of anti-thrombin
Unknown/Poorly Understood causes
Anti-phospholipid Syndrome
Primary & Secondary e.g., SLE
Behcet's disease
AIDS-associated nephropathy

Endothelial damage

Causes of endothelial damage as listed are self explanatory. Homocystinuria is an in-born error of the trans-sulfuration pathway, which predisposes to RVT due to high levels of homocystine causing endothelial damage. [10,11]

Stasis

RVT in severely dehydrated neonates/infants results from volume depletion and consequent reduction in the circulatory blood volume. Blood flow to the kidneys is diverted to other organs resulting in sluggish flow through the renal veins leading to thrombosis. RVT is also known to occur in the absence of clinically obvious shock e.g. following neonatal distress and placement of central venous catheters.[12] Other causes include kinking of the renal vein or compression by pathological processes in the retroperitoneum.

Hypercoagulability

Patients with nephrotic syndrome are at increased risk of developing thromboembolism, the most common of which is RVT.[13] RVT results from a hypercoagulable state caused by the heavy proteinuria. Loss of proteins in nephrotic syndrome results in decreased osmotic pressure. Reduction in the osmotic pressure stimulates the synthesis of proteins in the liver including fibrinogen and beta-thromboglobulin. Additionally increase in platelet count, enhanced platelet aggregation, reduction in coagulation inhibiters especially antithrombin III, and functional protein S promote thrombosis.[14]

Factor V Leiden and mutations of prothrombin gene (G20210A) together constitute the most common hereditary hypercoagulable states. The heterozygous mutation is present in 5% of the general population and 45% to 63% of a thrombophilic population. These two conditions are also known to cause congenital stroke and RVT.[15]

Antiphospholipid Syndrome (APS) first described in the early 80 s, is characterised by the presence of anti-phospholipid antibodies (APA), arterial and venous thrombosis, recurrent abortion and/or thrombocytopenia.[16] This is probably the most common cause of

spontaneous RVT as APA are found in 1–5% of otherwise healthy individuals and 35–40% of patients with SLE. Anti-phospholipid antibodies include anti-cardiolipin (ACA) and lupus anticoagulant (LAC).[17] The arteries and veins of virtually any organ system may be affected in APA, resulting in stroke, myocardial infarction, pulmonary embolism and RVT. APA accounts for 20% of recurrent RVT in young/middle-aged men and women and may be seen with or without renal artery thrombosis.[18] Mechanisms by which anti-phospholipid antibodies induce thrombosis and loss of pregnancy include endothelial activation, interference with placental anticoagulant protein-I (annexin V) and anti-B2- glycoprotein-I antibodies. Additionally there is induction of tissue factor or monocyte chemo-attractant protein I, and inhibition of the anticoagulant function of activated protein C by auto-antibodies. The kidney appears to be a major target organ in both primary and secondary APS.[19] Occasionally APS may progress rapidly with devastating consequences (catastrophic APS) such as multi-organ failure and death. Antiphospholipid antibodies are known to coexist with idiopathic membranous nephropathy in approximately one fourth of patients.[20]

Clinical manifestations

Early reports of RVT emphasized the presence of flank pain, flank tenderness, microscopic haematuria, rapid deterioration of renal function and worsening proteinuria as the cardinal features of RVT.[21] Harrison *et al.* in 1956 reported that patients with RVT may either present with more dramatic classical symptoms or insidious/chronic symptoms manifested as peripheral oedema.[22]

Acute onset RVT usually affects neonates and infants following severe dehydration manifested as dry mouth, scanty urine and loss of skin turgidity. The clinical features suggestive of RVT include nausea, vomiting, fever, flank pain, gross haematuria and palpably enlarged kidneys. Other manifestations include renal failure, thrombocytopenia and anaemia. As loin pain and haematuria predominates the problem may be mistaken for renal colic or pyelonephritis.[23] Male children are affected twice as often as females and the left renal vein is affected twice as often as the right renal vein.[24] Left sided RVT may lead to gonadal vein thrombosis manifested as pelvic congestion syndrom[25] in females and painful swelling of the left testis and varicocele in males.[26]

Acute onset RVT may also occur in association with APS, injury to the renal vein during renal venography, trauma, post renal transplantation, surgery around the renal vein and occasionally in nephrotic syndrome. Bilateral RVT or involvement of the solitary kidney may present with features of acute renal failure. Following renal transplants both acute and chronic variants of RVT are recognised.[27]

Investigations

Laboratory

There are no specific laboratory tests to diagnose RVT.

Imaging

In the absence of specific diagnostic laboratory tests and paucity of clinical manifestations, imaging remains the cornerstone of diagnosis. Radiological signs vary according to the speed of onset and degree of occlusion of the renal vein. In cases of rapid onset and complete occlusion the affected kidney becomes enlarged and reaches maximum dimensions within one week. Subsequently however, there is a gradual reduction in the renal size over next few weeks and later renal atrophy. An ultrasound scan shows an enlarged kidney and hyper-echogenic kidney in approximately 90% of the patients in the early phase of acute RVT.[28]

Colour Doppler ultrasound has poor yield in detecting segmental venous thrombosis, but is much superior to ultrasound in detecting flow in the renal artery and the renal vein. It is particularly useful for screening. The Colour Doppler ultrasound is being utilised widely to detect RVT in renal transplant patients with a high degree of sensitivity.[29]

Findings on intravenous urography (IVU) vary according to the clinical situation. With sudden and complete venous occlusion the collecting system may not be visualized due to poor excretion by the affected kidney. However, in most cases due to the development of collateral circulation contrast is excreted by the kidney demonstrating a stretched and distorted renal pelvis and calyces due to the oedematous enlarged kidney in almost 80% patients. Renal venous occlusion leads to the development of varicosities in chronic RVT, which impart a notching appearance to the ureter.[28] During the late vascular phase, collateral venous drainage around the kidney may be seen.[30]

CT scan is currently the imaging of choice for diagnosing RVT as it is non-invasive, relatively less expensive, can be performed quickly, and has a high diagnostic accuracy. Simultaneous intravenous administration of contrast (CT angiography) assists visualization of the renal veins. Indirect radiographic

signs suggesting RVT include increased renal size; RV enlargement; delayed, diminished, or absent opacification of the collecting system; a persistent nephrogram attributable to poor venous washout; prolonged corticomedullary differentiation; thickening of renal fascia; and stranding of perinephric fat. The sensitivity and specificity of CT angiography is almost 100%. It can also demonstrate renal tumour and other renal pathologies simultaneously. The disadvantages of CT include exposure to radiation and use of nephrotoxic iodinated contrast media.[31]

Magnetic Resonance Angiography (MRA) is an alternative imaging modality which has several advantages over CT scan. It is non-invasive, avoids radiation and use of nephrotoxic intravenous contrast agents. It produces high contrast images of flowing blood, vessel walls, kidneys and the surrounding tissues. In one study, MRA could delineate the entire course of the renal vessels in 88% of cases compared to 58% with Colour Doppler ultrasound and 43% on spin-echo MRI. Similarly the anatomic variants, vessel displacement, collateral circulation and neoplastic vessel infiltration were demonstrated more accurately by MRA.[32] Disadvantages include, higher cost, need for anaesthesia in children and claustrophobic adults and marginally inferior sensitivity and specificity compared to CT scan.[33]

Inferior venacavography and selective renal venography is the definitive diagnostic test. A patent IVC without any filling defects in conjunction with clearance of the contrast by the renal vein practically rules out the diagnosis of RVT. Valsalva maneuvour during the study may facilitate the opacification of the renal vein by slowing down the blood flow and hence clearance of the contrast from the IVC. Findings indicative of RVT include lack of washout of contrast or obvious filling defects due to the presence of thrombus. Venography is however, invasive, involves higher radiation exposure and injection of iodinated contrast. Selective renal venography also carries the potential risk of causing de novo RVT due to venous injury. [34]

DTPA Renal scan may show delayed clearance of the tracer. Venographic phase of Tc-99 m MAG3 is particularly useful but is non-specific. Renal Biopsy performed for any other indications may show dilated capillaries and venules.

Management

In the past, the treatment of RVT was primarily surgical involving thrombectomy or nephrectomy. Both options are invasive and were associated with significant complications. However, trends have changed over the past decades from surgical to predominantly medical management in the form of initial intravenous and subsequent oral anticoagulation.[35] Anticoagulation therapy may improve renal function particularly in cases of acute RVT, result in re-canalisation or complete resolution of thrombus in the renal veins and reduce the incidence of recurrent thromboembolic complications. Minimally invasive interventions or nephrectomy are employed in highly selected patients.

Asymptomatic patients with unilateral RVT, especially in nephrotic syndrome, may not require any specific treatment. In such patients, active surveillance in conjunction with supportive measures to reduce proteinuria including salt and protein restriction, diuretics and statins may partially reverse the hypercoagulability. Depending on the patient's progress corticosteroids, angiotensin converting enzyme inhibitors (ACEI), angiotensinogen II receptor blockers (ARBs), cyclosporine, cytotoxic agents or mycophenolate and one of the statins may be required.[36,37] However, if the patient's condition deteriorates due either to progression of thrombosis or embolism active intervention should be considered.

Anticoagulation in symptomatic patients should be initiated early to prevent propagation of thrombus and potential serious thromboembolism.[38] Irrespective of whether RVT is acute or chronic, unilateral or bilateral, initial anticoagulation is achieved with parenteral heparin. Patients are subsequently switched over to warfarin, within 3 to 10 days and continued long-term. Warfarin has unique pharmacodynamic properties affecting its absorption, protein binding, metabolism and excretion. It interacts with many other drugs and hence requires careful monitoring and tailoring of the treatment to the individual's needs according to the patient's clinical situation, sensitivity and metabolism.

Duration of anticoagulation therapy varies from a minimum of a year to lifelong, depending upon recurrence of RVT or continued presence of risk factors. The degree of hypo-albuminaemia is considered a good indicator of hypercoagulabity. It is recommended that patients should be treated with anticoagulants as long as serum albumin remains below 2.5 grams/L but recurrent thrombosis can occur on discontinuation of anticoagulation therapy. Therefore it is advisable to maintain anticoagulation until complete resolution of the nephrotic syndrome.[39]

The anticoagulation therapy aims at achieving an INR of 2.5 (range 2.0 to 3.0). Un-fractionated heparin is usually administered as a loading dose of 5000 IU intravenously, followed by 20 000 to 40 000 IU per 24 hours. APTT is monitored twice daily until stable.

Subsequently once daily assay is adequate. Heparin induced thrombocytopenia and serious haemorrhage has been reported in 2% and 3% of patients respectively.[40,41]

Low molecular weight heparins (LMWHep) are becoming increasingly popular because of higher bioavailability, fewer complications, convenience of subcutaneous administration and cost-effectiveness as these can be given in the outpatient setting. The recommended dose of the commonly used agent Enoxaparin Sodium (Clexane) in this setting is 1.5 mg/Kg (150 units) daily.[38]

Specific treatment for the underlying disorders should be instituted simultaneously e.g. steroids/immuno-suppression therapy in APS. Some patients especially neonates with bilateral RVT and renal failure may need urgent and aggressive supportive therapy including renal replacement therapy (dialysis). Likewise patients with catastrophic APS may require immunosuppressant, plasmaphresis and intra-venous immunoglobulin in addition to vigorous supportive measures according to the individual needs.

Selected cases (Table 2) of RVT are suitable for thrombectomy (mechanical thrombectomy) and/or thrombolysis (chemical thrombectomy). The later can be administered systemically or locally. These interventions are performed percutaneously at an early stage, to prevent irreversible damage to the kidney. Administration of thrombolytic agents via a catheter is associated with fewer systemic side effects compared to systemic thrombolytic therapy. Commonly used thrombolytic agents include streptokinase, urokinase[26] and, more recently, recombinant tissue plasminogen activators.[42] Thrombolytic therapy results in rapid improvement in renal function and has low morbidity when used appropriately.[43,44]

Local thrombolytic therapy can be combined with mechanical thrombectomy to achieve complete and rapid clearance of the thrombus. The most appropriate cases for such a combined radiological intervention would be bilateral renal vein involvement, thrombosis of a solitary native kidney or a renal transplant and cases with large thrombus burden where a single modality treatment may not efficiently restore venous circulation. Patients should then be maintained on systemic anticoagulation.[44,45]

A case of RVT associated with sub-hepatic IVC thombosis has been successfully treated with stenting of the IVC. Another case with a similar clinical situation has been managed by renal to inferior mesenteric vein diversion.[46,47] Rarely, nephrectomy may be required as a life-saving measure. This is indicated for renal allograft rupture, complete necrosis of the kidney with impending rupture or as a definitive form of therapy in cases of renal cell carcinoma when the contra-lateral kidney is normal.[48]

IVC filters may be considered in high risk patients in whom the primary aim of treatment is the prevention of pulmonary embolism originating from RVT or from associated thrombosis of the IVC. These have been employed in thrombosis of the IVC in association with germ cell tumours, adrenal tumours, renal injuries and SLE.[49] Use of these filters may also be justified in patients undergoing thrombolytic therapy to prevent pulmonary embolism.[50]

Table 2. Indications of thrombectomy/thrombolysis in RVT[42,44]

Treatment failure while on adequate anticoagulation
Onset of complications e.g. pulmonary embolism
Bilateral RVT
Acute renal failure (Bilateral RVT/RVT in solitary kidney)
Extension into inferior vena cava
Contraindication to systemic anticoagulant therapy.
Renal transplant
Severe, persistent flank pain

Prognosis

The prognosis of RVT depends on multiple factors (Table 3). Review of the early literature highlights alarmingly high mortality (64%) due to the fact that most of the reported data were obtained from autopsies.[51] Common causes of high mortality were renal failure, recurrent thrombo-embolism and sepsis. Prognosis of the condition however, has improved over the last few decades due to availability of dialysis, better diagnostic tests and rational use of anticoagulation.

Laville *et al*. reported 40% mortality in the first six months primarily due either to haemorrhagic complications or sepsis in a study of 27 patients with RVT associated with nephrotic syndrome. Amongst survivors ($n = 16$), nephrotic syndrome resolved in ($n = 12$) 75% of patients and renal function remained stable during follow up. Having analysed various prognostic factors, they concluded that age had no influence on survival or long term renal function but patients older than 55 years were more likely to develop acute renal failure (ARF). Prognosis of patients with membranous glomerulonephritis is more favourable as they are less likely to develop ARF. Similarly

Table 3. Prognostic factors in RVT [3,52,14,44]

The baseline renal function at the onset
Status of contralateral kidney and its vasculature
The speed of onset of the RVT/development of adequate collaterals
Adequacy of management
Severity and progress of the original disease process.

mortality in this group is lower compared to those with RVT associated with other forms of glomerulonephritis or primary renal vein thrombosis. The prognosis is not influenced by unilateral or bilateral renal vein involvement. Normal baseline renal function at presentation appears to be the most important prognostic factor associated with favourable outcome. Recovery of renal function does not necessarily follow renal vein re-canalisation particularly in cases of chronic RVT.[52]

Important efforts have been made to evaluate post thrombotic outcomes in children. Large cohort studies have confirmed low frequency of recurrent thromboembolism, but have shown lack of resolution of thrombus following standard duration anti-coagulation therapy in as many as 50% of the patients. Patients may develop post-thrombotic syndrome characterised by lower limb varices and symptoms of venous hypertension in more than one third of children.[53,54] Heparin therapy has been found to be very beneficial in preserving renal function and reversing any renal dysfunction. Long-term renal function impairment has been reported in 100% of those who did not receive heparin compared to 33% of those who received heparin.[3]

Conclusion

RVT is under reported as some cases go unrecognised due to lack of clinical manifestations. A multinational multi-centre therapeutic trial with long term follow-up is required to determine the optimal diagnostic and therapeutic approach.[54,55] Current trends favour CT scan as the diagnostic modality of choice. Anticoagulation has emerged as the mainstay of treatment in the majority of the cases. Radiological interventions including thrombolysis with or without thrombectomy and ablative surgical measures like nephrectomy are only required in highly selected cases. Advances in the prediction of post thrombotic outcomes are being made to facilitate a risk-stratified approach in anti-thrombotic management to achieve improvements in long-term outcomes.[53]

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