

Dialogues in Pediatric Urology



Volume 11, Number 6
June, 1988

This issue's topic:

Renal Vein Thrombosis: Diagnosis and Management

Guest Editor: David T. Mininberg, M.D.

Participants:

Bruce Gilbert, M.D., Ph.D.

Valerie L. Johnson, M.D., Ph.D.

Paula W. Brill, M.D.

James Busset, M.D.

Editor

Richard M. Ehrlich, M.D.
Professor of Surgery/Urology;
Co-Chief of Renal Transplantation,
School of Medicine,
University of California, Los Angeles

Publisher

William J. Miller

Editorial Board

A. Barry Belman, M.D.
Chairman, Department of Pediatric Urology
Children's Hospital National Medical Center,
Washington, D.C.; Professor of Urology
George Washington Medical School

Lester Persky, M.D.
Professor of Urology
Case Western Reserve University
School of Medicine, Cleveland

Donald B. Halverstadt, M.D.
Clinical Professor of Urology & Pediatrics
University of Oklahoma College of Medicine
Chief, Pediatric Urology Service, Children's
Memorial Hospital, Executive Chief of Staff,
State of Oklahoma Teaching Hospitals,
Oklahoma City

Victor A. Politano, M.D.
Professor and Chairman, Dept. of Urology
University of Miami School of Medicine
Miami, Florida

W. Hardy Hendren, III, M.D.
Professor of Surgery
Harvard Medical School;
Chief of Surgery, Children's
Hospital Medical Center, Boston

Edward Tank, M.D.
Associate Professor of Surgery & Pediatrics
University of Oregon School of Medicine
Portland, Oregon

Panayotis Kelalis, M.D.
Professor and Chairman, Department
of Urology, Mayo Clinic, Rochester, Minn.

Robert M. Weiss, M.D.
Professor, Section of Urology
Yale University School of Medicine
New Haven, Conn.

Selwyn Levitt, M.D.
Adjunct Professor of Urology
New York Medical College;
Visiting Clinical Professor of Pediatrics
Albert Einstein College of Medicine;
Co-Director, Section of Pediatric Urology
Westchester Medical Center

Robert H. Whitaker, F.R.C.S.
Consultant Urologist
Addenbrooke's Hospital
Cambridge, England
Associate Lecturer
University of Cambridge

Dialogues in Pediatric Urology (ISSN 0164-9507) is published monthly by William J. Miller Associates, Inc.
45 Villa Road, Pearl River, N.Y. 10965. Second class postage paid at Pearl River, N.Y. 10965.
Subscription rates: \$50 per year within the United States and Canada; \$52 per year elsewhere.
Phone numbers: (914) 735-7853; (212) 921-8837. Postmaster: Send address changes to Dialogues
in Pediatric Urology, 45 Villa Road, Pearl River, N.Y. 10965

EDITOR'S COMMENTS:

In an attempt to remain *au courant*, we continue to update previously published topics and search for new ones. Renal vein thrombosis has never before been a topic of discussion in this publication and it is thoroughly covered in this complete review.

The role of MRI in this condition needs to be better defined, but no doubt MRI will be an important diagnostic tool in the future. We look forward to the prospective data regarding anticoagulation and fibrinolytic therapy in RVT. A recently misdiagnosed case, referred to UCLA, highlights the authors' contention that this condition needs to be high on the list of hematuria in the newborn period.

Our thanks to Dr. Mininberg and his coauthors for a most interesting and informative issue.

Richard M. Ehrlich, M.D.

GUEST EDITOR'S NOTES:

An infant presenting with a palpable renal mass is an alarming prospect for the parent and physician, particularly if the infant is clinically ill as well. In order for the diagnosis of renal vein thrombosis (RVT) to be made, it must be thought of and therein lies the rub. All too often a diagnosis of neoplasm or obstructive uropathy will be pursued without considering RVT. This oversight squanders the opportunity for early therapy of RVT, which many believe would favorably alter the long-term prognosis. The contributors to this issue discuss the pathogenesis, diagnosis, and treatment options for RVT, highlighting the controversies and bringing the issues into focus.

David T. Mininberg, M.D.

Associate Professor of Clinical Urology/Surgery; Director, Pediatric Urology, The New York Hospital—Cornell Medical Center

BRUCE GILBERT, M.D., Ph.D.

Senior Resident in Urology, The New York Hospital—Cornell Medical Center

The triad of gross hematuria, anemia and thrombocytopenia in a neonate suggests a diagnosis of renal vein thrombosis. It has been stated that 20% of gross hematuria occurring during the first month of life is due to renal vein thrombosis. Almost half of all cases of renal vein thrombosis occurs during the first 2 weeks post parturition. The diagnostic maneuvers and options have never been so varied nor so controversial as they are today.

Pathogenesis and Clinical Presentation. Renal vein thrombosis (RVT) accounts for approximately 20% of gross hematuria seen in the first month of life. Over 40% of RVT occurs during the first 2 postnatal weeks. The incidence of RVT in children varies from 0.26% (4 out of 1,958 autopsies; Ahvenanien et al:

Ann Ped Tenn 1:105, 1954) to 0.70% (45 in 6,200 autopsies in neonates and children; Campbell et al: *J Ped* 20:604, 1942). The incidence in males equals that of females but the left renal vein appears to be more frequently involved in females.

Renal vein thrombosis has been classified by Sandblom (*ACTA P Scand* 35:160, 1948) as either 1) Primary: having no known etiology, or 2) Secondary: with a known precipitating etiologic agent, eg, dehydration, infection.

Etiologic factors in RVT have been grouped as intrinsic, extrinsic and functional. Intrinsic factors include hypovolemia, primary renal disease, trauma, neoplasm and hypercoagulable states. Extrinsic factors include pregnancy and retroperitoneal tumors. Functional factors are primarily related to cardiovascular pathology.

Infants born of diabetic mothers frequently have 25% less extracellular volume than normal. This factor, together with the normal polycythemic state of newborns, results in an increased blood viscosity and hence, a greater predisposition towards thrombosis. Other contributing factors include birth trauma, infection and vascular endothelial damage.

The anatomy of venous drainage is probably key to understanding the pathogenesis of RVT (Baum et al: *J Urol* 119:443, 1978). Blood, returning through tiny subcapsular veins, enters the intrarenal system of veins. Unlike the arterial system which has no collateral pathway, the venous system anastomoses at various levels. They essentially follow the course of the arterial system and converge at the arcuate/interlobar level to form several main trunks which join to form the renal vein. In addition, small veins perforate the renal capsule and connect the subcapsular veins with the veins of the perirenal fat. In turn, these perirenal veins communicate with the adrenal vein above, the gonadal vein below, and the lumbar and ureteral vein medially. The ureteral veins connect the renal vein with the venous drainage of the bladder. The ureteral veins freely anastomose at the lumbar, the gonadal and the capsular veins. The left renal vein receives the gonadal, the inferior phrenic and the adrenal veins. On the right side, these veins drain directly into the inferior vena cava. Occlusion of the renal vein usually induces collateral venous development. Two primary routes have been described: 1) The subcapsular plexus which connects the capsular vein with the perirenal plexus, and 2) Enlargement of the veins received by the left renal vein. Both of these networks communicate with the caval and azygous system.

The clinical presentation of RVT in a neonate usually includes renal enlargement which diminishes as the process resolves, and gross hematuria which usually results from hemorrhagic renal infarction. The common laboratory finds are 1) anemia resulting

from blood flowing past the growing thrombosis with trapping of RBC's in the thrombus in addition to the hematuria; 2) thrombocytopenia; 3) proteinuria, which is a less prominent feature in neonates than in adults, and 4) azotemia if the problem is bilateral □

VALERIE L. JOHNSON, M.D., Ph.D.

Director, Division of Pediatric Nephrology, The New York Hospital—Cornell Medical Center.

In the infant and young child, thrombosis of the renal venous system of one or both kidneys occurs as an acute and life-threatening event. The primary involvement is within the intrarenal venous circulation rather than the main renal vein. For this reason, renal venous thrombosis (RVT) is the preferred term and one which includes the less common lesion. Nearly 90% of patients with RVT are less than one year of age, and approximately 75% are less than one month of age. A 2:1 predominance of males is seen in patients less than one month, but for those over one month of age it is 1:1. There does not seem to be any difference in left-sided, right-sided, and bilateral renal venous thrombosis in males and females. Knowledge of the circumstances in which renal venous thrombosis usually occurs and the clinical signs and symptoms suggestive of the disease, make possible early diagnosis and successful management.

Pathogenesis. Renal venous drainage begins in the subcapsular and stellate veins which converge toward the medulla and renal hilus as cortical radial veins. The arcuate veins drain the cortical radial veins and the ascending vasa recta veins of the medulla. It is in these small veins that the initial thromboses originate, extending distally to involve the cortical radial veins and proximally to involve the interlobar and main renal veins.

Renal venous thrombosis is usually bilateral. However, it is generally asymmetric, and only a minor lesion may be present in a contralateral kidney. Massive hemorrhage occurs into the anoxic renal tissues and blood escapes into the tubules and interstitial tissues. Hematuria and oliguria occur as a consequence if large areas are involved. Both the medulla and cortex related to the involved arcuate vein(s) proceed to necrosis and scarring from the contraction of the fibrous tissue. The thrombi initially seem to be comprised of platelets. Varying degrees of recanalization will occur as time passes. Subsequent calcification of the kidney, the adrenal, or of both, may occur.

Acutely the involved kidney(s) is engorged with blood. The magnitude of the swelling of the kidney is dependent upon the extent of the intrarenal thrombosis. In the most serious cases, the swelling secondary to hemorrhagic infarction may be evident on physical examination. On the other hand, if involvement is patchy, the kidney(s) may not be

palpably enlarged.

Renal venous thrombosis occurs in association with hypercoagulability, hyperosmolarity, decreased renal blood flow, and hemoconcentration with or without dehydration. In infants, RVT most commonly occurs following dehydration related to diarrhea and/or vomiting, but sepsis, maternal diabetes, maternal thiazide administration, neonatal asphyxia, and cyanotic congenital heart disease are all felt to be predisposing factors. Angiography has been associated with RVT probably because of the associated osmotic diuresis. Antenatal renal venous thrombosis has also been reported. Extensive burns, involving 60% to 90% of body surface, have also been associated with RVT.

Clinical Signs. The complex of flank mass, hematuria, and thrombocytopenia is highly suggestive of renal venous thrombosis. Examination of the abdomen reveals a unilateral or bilaterally-enlarged kidney(s) approximately 60% of the time. If the inferior vena cava is thrombosed, the lower extremities may be cold, edematous and cyanotic.

Hematuria has been reported in up to 64% of neonates, and 49% of older children. The hematuria is most typically gross.

Oliguria or anuria is also an important clinical sign that presents early in the older child, but may be overlooked in the neonate. Approximately 34% of neonates and 50% of older children demonstrate oliguria.

Diarrhea, usually accompanied by dehydration, often precedes renal venous thrombosis. On the other hand, the clinical features of hypernatremic dehydration are very similar to RVT, making the 2 conditions difficult to differentiate and, furthermore, both conditions may be simultaneously present. Vomiting, pallor, cyanosis, shock, and metabolic acidosis occur in some neonates, infants and children. Of note, these signs are not unique to RVT and may occur in many other conditions.

Systemic blood pressure does not seem to be raised in most patients during the acute stages of the illness, although hypertension may be found several months later.

Laboratory Features. Biochemical findings vary greatly, largely because the renal venous thrombosis may range from a minor, localized site within one kidney to involvement of both kidneys and the vena cava. Decreased renal function may be present as evidenced by an increase in serum creatinine and blood urea nitrogen levels (BUN). BUN's greater than 100 mg/dl have been reported in some series to be present in up to 55% of patients. Associated with renal failure are a metabolic acidosis and hyperkalemia. The serum sodium level tends to be variable. A urine sample obtained close to the time of blood sampling may be helpful in distinguishing between infants with oliguria due to organic lesions (such as renal venous

thrombosis) from those with prerenal azotemia. In organic renal failure, the fractional excretion of sodium tends to be inappropriately high and the urine/plasma BUN ratio is low.

Hematuria, pyuria, and proteinuria are frequently present. Thrombocytopenia (<75,000 platelets) is reported in up to 90% of patients with renal venous thrombosis and is of great diagnostic significance. However, a falling platelet count is also significant. Evidence for a consumptive coagulopathy is often present. The partial thromboplastin time and prothrombin time are prolonged, Factors II, V, VIII, and IX and fibrinogen levels depressed, and fibrin-split products increased. An abnormal peripheral smear with burr and fragmented red cells and progressive anemia also accompany the thrombocytopenia. In one series, anemia was present in 32% of neonates and 62% of older children. All of these findings are similar to those seen in patients with a diffuse intravascular coagulopathy. In fact, in the neonate and small infant these findings make it difficult to differentiate RVT from sepsis. On the other hand, RVT can be precipitated or accompanied by systemic infection, making the differentiation more difficult. For this reason, blood and urine cultures are always of importance in the evaluation of these patients.

Differential Diagnosis. The clinical complex of hematuria, anemia, thrombocytopenia, flank mass(es), and azotemia strongly support a diagnosis of renal venous thrombosis. If one or more of these signs are present, the possibility of a congenital abnormality or acquired condition must be entertained.

Congenital lesions presenting as flank masses include hydronephrosis and cystic kidneys. These lesions are readily differentiated from RVT by nephrosoundography. Adrenal masses may also be excluded with this technique. Wilms tumor is rare in the neonatal period, but a number of infants with mesoblastic nephroma have been diagnosed because of the presence of a flank mass. Nephrosoundography again is helpful in differentiating both lesions from renal venous thrombosis.

Other conditions frequently presenting with some of the features of RVT include acute tubular necrosis, acute cortical necrosis, and acute medullary necrosis. The clinical setting predisposing the patient to RVT also frequently results in the development of these conditions. In addition, all 3 of these entities result in reduced renal function and consequent azotemia. However, acute tubular necrosis is infrequently associated with a flank mass, hematuria, anemia or thrombocytopenia. Cortical necrosis and medullary necrosis are associated with hematuria, but do not present with a flank mass. Furthermore, on nephrosoundography asymmetric renal size usually is not seen.

Hemolytic-uremic syndrome (HUS) must also be

differentiated from renal venous thrombosis. Again, the clinical setting in which HUS occurs is also similar to that for RVT. In addition, the patients are anemic, have gross hematuria, and thrombocytopenia. Nephrosoundography is helpful in allowing one to differentiate between these conditions since HUS is not associated with asymmetric renal size. The infrequency of HUS in the neonate makes it easier to eliminate this condition in the differential during this period.

Renal artery thrombosis is a frequent complication of umbilical artery catheterization and must also be differentiated from renal venous thrombosis. The history of umbilical artery catheterization may suggest this possibility. With complete arterial thrombosis, renal function is lost. Therefore, radionuclide studies may not be able to differentiate between them. However, unlike RVT, the affected kidney in renal artery stenosis is more likely to be small. In addition, with partial arterial thrombosis, hypertension is often a presenting clinical sign of this lesion.

Systemic infections, or infections involving only the kidneys, may also present with acute renal failure. Sepsis, as discussed above, is often associated with disseminated intravascular coagulation which may result in RVT and renal failure. In many infants with congenital obstructive uropathy and infection, acute interstitial nephritis and renal failure may complicate the lesion. Enlarged kidneys, anemia and thrombocytopenia may be present. Nephrosoundography will usually differentiate these lesions from renal venous thrombosis. Urinary culture results will also assist in confirming this diagnosis.

General Management. A neonate affected with renal venous thrombosis may be extremely ill with shock, hypotension, and cyanosis. Initial management should be directed towards correction of any of the factors known to initiate the thrombotic process as well as problems of hypovolemia, electrolyte imbalance, hypoxia, sepsis, and azotemia.

As discussed above, intravascular volume depletion may precipitate RVT thrombosis. A sign of significant intravascular volume depletion is a low urine output (<1 ml/kg/hr). On the other hand, with significant involvement of both kidneys, urine volume may range from oliguria to anuria. Therefore, in RVT the problem of overhydration is present with aggressive fluid replacement. If intravascular volume depletion is thought responsible for the diminished urine output, then rehydration should begin with bolus fluid administration in the overall rehydration plan. If urine flow remains inadequate or absent following restoration of intravascular volume, fluid management must be reassessed. Use of a single challenge dose of intravenous furosemide (2 to 3 mg/kg body weight) has occasionally been useful in this setting.

In situations of hyperosmolarity associated with hypernatremia, institution of dialysis may be necessary.

Many times metabolic acidosis, which is an additional complication of the renal failure, may be managed by administration of sodium bicarbonate. However, administration of sodium bicarbonate may aggravate hypernatremia, and dialysis may be a more appropriate treatment modality. Hyperkalemia will also require dialysis.

In the series reported by the European Society for Pediatric Nephrology, more than half of the infants with renal venous thrombosis were azotemic and acidotic. Nearly a third were hyperkalemic. The degree of azotemia, as well as overhydration, hyperkalemia, hyperosmolarity, metabolic acidosis, and hyperphosphatemia are all important in the decision of when to initiate dialysis.

Recent trends have favored early intervention with dialysis. The availability and use of hemodialysis in neonates and infants varies widely among centers. In contrast, peritoneal dialysis can be performed effectively and safely in neonates and infants. In addition to correcting the uremia, electrolyte imbalance and metabolic acidosis are improved and fluid balance is restored. Moreover, significant amounts of carbohydrates are reabsorbed from the peritoneal dialysis fluid improving caloric intake.

Complications of peritoneal dialysis include infection, dehydration, hyponatremia, and hyperglycemia. Substantial quantities of serum proteins are also lost during dialysis. For these reasons, careful aseptic technique is required and a strict balance of intake and output maintained. Dextrostix and/or serum glucose must be monitored. In the case of hyperglycemia, insulin may be added to the dialysate. Serum proteins should also be measured, and appropriate albumin replacement given. Peritonitis may be managed with loading doses of intravenous antibiotics and the addition of antibiotics to the dialysate.

Intravascular Coagulopathy. Although correction of the factor(s) precipitating disseminated intravascular coagulopathy (DIC) often will abolish the coagulopathy, this may not occur and other approaches may be necessary. Requirements may vary, but recommendations include fresh-platelet concentrates plus fresh-frozen plasma. Exchange transfusions are an alternate therapeutic approach which are reported to be successful in correcting the coagulopathy.

Heparin Therapy. If there is evidence of continuing intravascular coagulation, such as thrombocytopenia, falling Factor levels, decreasing fibrinogen levels or an increase in fibrin-degradation products, heparin therapy may be indicated in the treatment of renal venous thrombosis. Although heparin treatment should be useful in disrupting the coagulopathy, there are very few controlled studies. Problems in determining appropriate heparin dosage and concerns with bleeding have resulted in the infrequent use of heparin

therapy. Moreover, correction of the factors predisposing to the coagulopathy and administration of fresh-frozen plasma and platelets have been associated with clinical and laboratory improvement of the coagulopathy.

Heparin therapy may be supported in the following instances: 1) In situations in which the factors predisposing to the consumptive coagulopathy cannot be rapidly corrected; 2) In situations in which the factors predisposing to the coagulopathy have been corrected, but administration of fresh-frozen plasma and platelets does not result in improvement of clinical status, improvement of platelet counts or fibrinogen levels, and 3) Thrombosis of the inferior vena cava.

Heparin treatment is continued until the platelet counts return to normal or until there is significant improvement of renal function and other coagulation studies. With discontinuation of therapy, platelet counts and coagulation studies need to be closely monitored. Heparin therapy should be restarted if coagulation abnormalities recur.

Surgery. In the past, unilateral nephrectomy or thrombectomy was undertaken in the acute phase of the illness. Our understanding of the pathophysiology of renal venous thrombosis now makes this procedure unlikely to be helpful. In fact, during the acute phase of the illness when the infant is ill and in fluid and electrolyte imbalance with disturbed acid-base status and in a state of DIC, surgical intervention carries a great risk.

On the other hand, scarring of the kidney may occur within a few months of renal venous thrombosis. Severe hypertension may be a late sequelae of this process. In this instance, elective nephrectomy may be a consideration. Until surgery may be performed, hypertension must be controlled by antihypertensive therapy. If the lesion is bilateral, then indefinite antihypertensive therapy may be required.

Prognosis. Mortality rates as high as 60% have been reported by the European Society for Pediatric Nephrology in children diagnosed as having renal venous thrombosis. Since these data come from an older retrospective study, it is anticipated that with proper management of fluid and electrolyte balance, the use of early peritoneal dialysis, heparin therapy, and elective and selective surgery, the prognosis is significantly improved. In a more recent review of 11 neonates, 10 survived following conservative therapy. A knowledge of the clinical situations predisposing an infant or child to renal venous thrombosis increases the likelihood of considering the diagnosis and therefore initiating therapy early. Techniques of nephrosonography and radionuclide imaging are noninvasive and are readily available to assist in confirming the diagnosis without the risk of exacerbating the renal lesion.

In follow-up, a number of infants with renal venous

thrombosis have been described as having a reticular pattern of calcification on radiographs. These calcifications have been shown to be within the intrarenal veins on pathological examination. These calcifications would be at the presumed site of thrombosis. Varying degrees of renal insufficiency will be encountered depending on the degree of initial renal involvement and healing. The extent of the renal lesion often will appear worse initially because areas close to the initial infarction cease to function well temporarily, but ultimately recover function. Chronic hypertension occurs in some patients with amelioration following nephrectomy of the affected kidney. If both kidneys are involved, nephrectomy is not possible. Nephrotic syndrome following renal venous thrombosis is unlikely and, in most instances, probably reflects an undiagnosed nephrotic syndrome complicated by severe renal venous thrombosis. □

References

- Arneil GC, MacDonald AM, Murphy AV, Sweet EM: Renal venous thrombosis. *Clin Nephrol* 1:119-131, 1973.
- Park CH, Gottlieb RP, Yoo HS, Pasto ME: Noninvasive diagnosis and follow-up of childhood renal vein thrombosis by ultrasound, doppler, and renal scintiscan. *Uremia Invest* 9:305-313, 1986.
- Duncan RE, Evans AT, Martin LW: Natural history and treatment of renal vein thrombosis in children. *J Ped Surg* 12:639-645, 1977.
- Keating MA, Althausen AF: The clinical spectrum of renal vein thrombosis. *J Urol* 133:938-945, 1985.
- Sutton TJ, Leblanc A, Gauthier N, Hassan M: Radiological manifestations of neonatal renal vein thrombosis on follow-up examinations. *Radiology* 122:435-438, 1977.
- Belman AB, Susmano DF, Burden JJ, Kaplan GW: Nonoperative treatment of unilateral renal vein thrombosis in the newborn. *JAMA* 211:1165-1168, 1970.
- Belman AB: Renal vein thrombosis in infancy and childhood. *Clin Pediatr* 15:1033-1044, 1976.

PAULA W. BRILL, M.D.

Associate Professor Radiology, The New York Hospital—Cornell Medical Center

Imaging studies in a newborn with suspected renal vein thrombosis (RVT) are directed primarily toward demonstrating renal anatomy and function as well as conditions associated with RVT such as inferior vena cava (IVC) thrombosis and adrenal hemorrhage.

The workup preferably starts with realtime ultrasound. In addition to the well-known advantages of ultrasound being portable, not requiring sedation and using no contrast media or ionizing radiation, modern ultrasound equipment produces images with fine anatomic detail. Once the diagnosis is established, the safety of ultrasound allows close follow-up to be accomplished with ease.

In acute RVT, ultrasound shows renal enlargement and loss of definition of the corticomedullary junction. Diffuse, low-level echoes and irregular areas of echogenicity, probably representing hemorrhage, are seen within the renal parenchyma. As the lesion evolves, areas of the kidney become sonolucent, suggesting necrosis. Renal atrophy and calcification

are frequent late sequelae. Most cases involve only small intraparenchymal renal vein branches which are too small to be seen individually with ultrasound. When the main renal vein is involved, demonstration of the thrombus is possible with excellent quality ultrasound equipment. The thrombus is seen as low to medium level echoes within the renal vein. Thrombosis of the IVC often accompanies RVT and also produces intravascular echoes. The vessels in the newborn are generally too small for the examiner to be able to appreciate diminished or absent pulsations. Doppler studies of blood flow are of interest but are rarely required for diagnosis.

The ultrasound examination rules out other causes of flank mass and/or hematuria such as hydronephrosis, multicystic kidney and tumor. Adrenal hemorrhage, which may occur alone or in combination with RVT, is seen as a suprarenal mass, the echogenicity of which depends on the age of the hemorrhage.

The diagnosis of RVT can usually be made with confidence based on the combination of clinical and sonographic findings. An additional imaging study, which incorporates a measure of renal function, is necessary to assess the degree of functional impairment. Radionuclide scanning is the preferred, functional study in the newborn because of its sensitivity and safety. A bolus injection of an agent such as Tc-99m DTPA (diethylenetriaminepentaacetic acid) is followed by rapid sequence imaging to visualize renal perfusion. The renal parenchyma is imaged during the first one to two minutes after injection before there is interference from radioactivity in the renal pelvis, ureters and bladder. Delayed images up to 24 hours after injection are obtained as needed. The radionuclide scan in RVT shows poor perfusion of an enlarged kidney and poor excretion on early and delayed images. RVT must be distinguished from acute tubular necrosis which is marked by normal or minimally impaired perfusion. With radionuclide scanning, renal function is able to be quantitated even when severely impaired.

Excretory urography is not recommended in the diagnosis of RVT. Usually there is "nonfunction" of the kidney even when function is demonstrable with radionuclide scans. The radiation dose from excretory urography is considerably higher than that from the radionuclide renal scan.

Computer tomography (CT) shows a large, poorly-functioning kidney; the actual thrombus may be visualized in the main renal vein. CT is not required if ultrasound and radionuclide scan findings are typical. Magnetic resonance imaging (MRI) is expected to be of great value in this condition. Imaging may be done in several planes, allowing detailed study of the kidneys, adrenals, renal veins, and IVC. Normal-flowing blood results in the absence of MRI signal, providing a natural contrast between the lumen and vessel wall. The soft-tissue contrast is superior to that of CT. With

new techniques, it has become possible to determine the presence, direction and quantity of blood flow. Deep venous thrombosis results in an intraluminal signal which characteristically decreases between the first and second echoes. Because of the small size of the vessels in the newborn, the evidence of RVT may be indirect. In a recent case report of an infant with left RVT and bilateral adrenal hemorrhage, MRI showed the left kidney to be larger than the right with increased signal from the left renal parenchyma on T2-weighted images. The right renal vein was clearly seen; the left renal vein could not be identified. The need for sedation and the inability to perform MRI on infants on respirators tend to limit the application of this technique in the diagnosis of neonatal RVT at present. □

References

- Fishman MC, Naidich JB, Stein HL: Vascular magnetic resonance imaging. *Radiologic Clinics of North America* 24:485-501, 1986.
- Koch KJ, Cory DA: Simultaneous renal vein thrombosis and bilateral adrenal hemorrhage: MRI demonstration. *Journal of CAT* 10:681-683, 1986.
- Neddleman L, Rifkin MD: Vascular ultrasonography: abdominal applications. *Radiologic Clinics of North America* 24:461-484, 1986.
- Wolfson BJ, Gainey MA, Faerber EN, Capitanio MA: Renal masses in children: an integrated approach to diagnosis. *Urologic Clinics of North America* 12:755-869, 1985.

JAMES BUSSEL, M.D.

Assistant Professor Pediatrics, The New York Hospital—Cornell Medical Center

Since significant loss of renal function is common with RVT, any therapy that can improve long-term outcome is worthy of consideration. The role of heparinization in renal vein thrombosis is not well defined at this time.

The clinical information available is not very useful for evaluating whether or not heparin should be used in all, some, or any patients. Unequivocal benefit of heparin therapy is certainly not evident in reported cases. Patients who did not receive heparin were reported to have complete recovery of renal function in some cases. It is impossible at this time to assess whether or not the cases were comparable and therefore, whether heparin really is useful based on the clinical evidence.

Before commenting on the mechanisms of heparin effect and how they might relate to treatment of RVT, it is important to discuss several aspects of coagulation and fibrinolysis in the newborn since there are important differences from the adult. In the newborn, the overall levels of clotting factors are lower, particularly the vitamin K-dependent clotting factors. This is especially true of a premature infant as compared with a term infant. Secondly, the naturally-occurring inhibitors of coagulation also occur at lower levels, ie, the level of antithrombin III is normally 40 to 60% of adult normal and in the

range that in an adult might contribute to hypercoagulability and the development of thrombosis. This is particularly important because heparin's anticoagulant effect appears to be largely, if not entirely, due to the conversion of antithrombin III into an effective inhibitor of serine proteases such as factor Xa, thrombin, etc. Recent studies on heparinization have suggested that the apparent volume of distribution for heparin in neonates is larger than it is in adults. The latter two facts indicate that not only must a greater dose of heparin be given to achieve the same levels of heparin in the blood or in the plasma, but in addition many clinicians use daily infusion of fresh-frozen plasma to provide additional antithrombin III so that the infused heparin would be effective.

The major problem with heparin usage, which is unique to sick newborns, is the possible enhancement of overt or subclinical intracranial hemorrhage. It is mandatory therefore that before beginning anticoagulant (or fibrinolytic) therapy, infants be evaluated at least by ultrasound to make sure they do not have even a small asymptomatic intracranial hemorrhage which might be precipitated into a catastrophic event by these therapies. Another problem with heparin therapy in the newborn (not unique to the newborn but essentially unexplored) is heparin-associated thrombocytopenia. The exact mechanisms causing this phenomenon are debated, although heparin-dependent antiplatelet antibodies may play an important role in many cases. Since it appears that this problem in adults may occur more frequently than had hitherto been appreciated, it is important to monitor the platelet count carefully in patients on heparin treatment because some of the failures may be due to potentiated thrombosis via this mechanism.

The fibrinolytic or clot-breakdown system in infants is also somewhat decreased in capacity as compared with adults. Fetal fibrinogen is more glycosylated than fibrinogen in adults. Plasminogen levels are lower and, in addition, activation of plasminogen appears to proceed at a slower rate. These findings may represent a rationale to employ some form of fibrinolytic therapy since the infant's natural ability to resorb clots may be diminished in comparison to that of the adult. On the one hand, the usage of fibrinolytic therapy in infants has generally been ineffective; systemic fibrinolytic therapy appears to be of dubious value. Fibrinolytic therapy delivered directly into the middle of a clot by a well-placed catheter is potentially of interest but largely unevaluated particularly, in newborns. However, the renal vein thrombosis fibrinolytic therapy should probably be used only in dire situations since venous, as opposed to arterial, thrombosis does not inevitably result in immediate tissue infarction, and therefore makes these clots less requiring of immediate urgent action.

In considering the potential usefulness of heparin, 2 possible effects need to be differentiated: 1) An acute effect of high-dose heparin which would cause any possible further formation of a new clot to immediately cease so that there would be no extension of the existing thrombus. This would help to minimize the extent of the damage to the kidney. 2) An unproven effect of heparin to speed the resolution of the existing thrombus. This latter effect, if it occurs, also might aid in the salvage of renal function.

Studies of venous thrombosis and its immediate treatment in adults have shown that immediate high-dose heparinization, followed by a continuous infusion of heparin to maintain a state of anticoagulation, can indeed effectively stop the process of ongoing thrombosis acutely in the overwhelming majority of cases. A critical element in this schema is to use initially a substantial bolus of heparin; studies have shown that without the initial large heparin bolus, 50% of patients will demonstrate an increased size of their clot 2 days after beginning heparin. The second element is that continuous IV infusion of heparin is required to maintain the effect, usually keeping the PTT at approximately twice the upper limit of normal. Use of heparin in newborns suggests that it will be effective if used in such a fashion, although most practitioners would only prolong the PTT to 1½ times the upper limit of normal. The general recommendation is that the initial bolus should be less than that used in adults (50 to 75 units/kg bodyweight as compared with 100 units/kg in adults) because of the more precarious coagulation system in the newborn; but the continuous infusion rate must be greater (25 to 40 units/kg/hour instead of 10 to 25 units/kg/hour in adults) because of the larger volume of distribution. The use of FFP, or eventually antithrombin III concentrate in conjunction with heparin, has already been mentioned. The second use of heparin to speed resolution of a clot is theoretical and has never been well documented. However, the surface of a clot is an area where active thrombosis and fibrinolysis will be occurring so that giving continuous heparinization, even at relatively low doses, should be adequate to prevent further clotting on the surface and therefore aid in its resorption.

In the absence of controlled studies, it is difficult to specify when, or if, to use heparin or even when fibrinolytic therapy might be required. Factors that might be important in considering the use of heparin, aside from the mandatory evaluation for the possibility of CNS hemorrhage, would include the degree of renal impairment, as assessed by renal scan to discover the degree of perfusion of the affected kidney, and the extent of the clot. Any help in preventing extension of the thrombus, and/or hastening its absorption, may contribute to the extent

of function recovered by the affected kidney; if the kidney has little flow, there would seem to be more need to heparinize than if renal flow is good. If the clot extends out of the renal vein significantly into the inferior vena cava, there is probably more reason to heparinize to avoid or mitigate pulmonary emboli. Finally, if serial studies demonstrate growth of the thrombus, then heparinization should be considered. Hematuria *per se* should not contraindicate anticoagulation unless there is unequivocal evidence of a drop in the hematocrit. If heparinization is undertaken, it is probably worthwhile to anticoagulate at "full dose" for 3 to 7 days (prolong the PTT to at least 60 by adjusting the initial recommendations for the continuous infusion until this is achieved) and then to back off to lower doses or 2 or 3 times daily boluses since there probably is an important effect of heparinization even if the PTT is minimally prolonged. In conclusion, it is likely, though by no means proven, that heparin may hasten the resorption of renal vein thrombosis and also is very likely to be of value in the long-term preservation of renal function. However, no controlled studies exist and it is clear that in certain series there has been a high rate of improvement and regaining of function even without the use of any anticoagulation. Heparinization creates some serious risks in newborns, especially in regard to intracranial hemorrhage, and therefore cannot be undertaken lightly. The neonatal subcommittee of the International Committee of Thrombosis and Hemostasis is creating criteria and, eventually, a registry as well as trials of anticoagulation and fibrinolysis in the neonate. Hopefully, controlled data will be forthcoming in the next few years. □

WHAT'S AHEAD

Here are some of the topics which will be discussed in the upcoming issues of *Dialogues in Pediatric Urology* and the Guest Editors of these issues:

Laparoscopy

(Guest Editor: Robert M. Weiss, M.D.)

Continent Cutaneous Diversions

(Guest Editor: Boyd Winslow, M.D.)

Oligohydramnios

(Guest Editor: Michael Packer, M.D.)

Opinions expressed in this publication are the sole responsibility of the individuals named and do not necessarily reflect the opinions of the editorial board or the publisher and members of his organization.

All rights reserved. No part of this publication may be reproduced or utilized in any form or by any means, electronic or mechanical including photocopying, recording or by any information retrieval system without written permission from the publisher.

Copyright © 1988 by William J. Miller Associates, Inc.