9. RENAL COMPLICATIONS

Principles

- To institute methods of primary prevention for renal complications.
- To monitor for and identify renal complications in a timely manner.
- To effectively prevent progression of sickle cell nephropathy.
- To appropriately manage patients with end-stage renal disease.

Recommendations

Primary Prevention

- Consideration should be given to starting hydroxyurea in early childhood.

Monitoring and Diagnosis

- Renal function should be monitored at least annually.
- Monitoring should include serum creatinine, urine routine and microscopy (including urine protein), and urine microalbumin (ACR and PCR).
- Any serum creatinine level near the upper limit of the normal range (or upper limit of age-matched controls for children) should be identified and followed closely, with consideration of referral to nephrologist.
- BP should be monitored at least annually.

Secondary Prevention

- Patients with proteinuria should be assessed by a nephrologist.
- ACE inhibitor or ARB therapy should be considered if there is proteinuria, even in the absence of hypertension.
- If ACE inhibitors or ARBs are used, potassium levels should be monitored closely.
- Patients with proteinuria and hypertension should have careful attention to blood pressure control, avoiding diuretics when possible.
- Patients with evidence of sickle cell nephropathy should avoid long-term use of NSAIDs.
- Urinary-tract infections should be identified and treated promptly with appropriate antibiotics.

Management of Chronic Kidney Disease Stage 5

- Patients with CKD should be managed by a nephrologist.
- Hemodialysis and/or renal transplantation may be considered in the treatment of renal failure in SCD patients.
- ESAs may be used.
- In patients receiving ESAs, the baseline hemoglobin preceding renal failure should serve as the target hemoglobin level.
- High doses of erythropoietin may be required.

Pathophysiology

The kidneys of patients with SCD are susceptible to structural and functional abnormalities affecting many parts of the nephron.

Two main mechanisms are responsible for the majority of renal problems in SCD patients. The first is renal medullary sickling. The naturally acidotic, hypertonic, and hypoxic environment in the renal medulla promotes red blood cell (RBC) sickling. Sickling leads to vaso-occlusion in the vasa recta, where severe and recurrent damage can result in loss of medullary blood vessels and nephrons. Clinically, these injuries manifest as: hyposthenuria, tubular dysfunction, and hematuria. Although less common, hemoglobin AS (HbAS) cells can also sickle in the extreme conditions of the renal medulla, leading to similar renal complications in some patients with sickle cell trait.

Secondly, changes occur at the level of the glomerulus. These changes are typically benign in childhood, but can progress with age. Early in life, there are changes in renal physiology characterized by increased renal plasma flow, and increased glomerular filtration rate (GFR). Enhanced creatinine secretion from the proximal tubules in sickle cell anemia (HbSS) patients, in combination with increased GFR, leads to serum creatinine levels that are lower than those seen in control subjects.[1]

Glomerular involvement can progress into sickle glomerulopathy over time. Focal segmental glomerulosclerosis is the most common pathology of the glomerulus, and the most common cause of renal failure in SCD.[2]

Epidemiology

In a prospective, 25-year follow-up study of 934 patients with sickle cell anemia, approximately 4% of patients with HbSS, and 2.4% of patients with hemoglobin SC disease (HbSC) developed renal failure, at median ages of 23 and 50 years, respectively.[3] The Bantu haplotype was also a risk factor for renal failure. Sixty percent of patients over age 40 had proteinuria, and 30% had renal insufficiency. Another large study of 300 adult patients showed increased protein excretion in 68% of SS patients and 32% of patients with other sickling hemoglobinopathies (SC, SD, and S-beta-thalassemia). Prevalence increased with age.[4]

Microalbuminuria is present in approximately 20% to 27% of young people with SCD (ages 2 to 20).[5] At the older end of this age group, the prevalence increases to 46%, approaching the rates seen in adults.[6]

Clinical Presentation, Investigation and Management

Hyposthenuria

Hyposthenuria is the inability to concentrate urine maximally, and is the most frequent clinically recognized renal abnormality in SCD patients. It is due primarily to the loss of deep juxtamedullary nephrons, which are necessary for maximal urine concentration.[7] Hyposthenuria may occur in childhood in patients with HbSS, often presenting as enuresis.[8,9] It is more likely to occur later in life in patients with Hb S-beta-thalassemia, other SCDs, and sickle trait. Hyposthenuria may be suspected based on a history of urinary frequency, nocturia or enuresis, and polyuria. The maximum urine osmolality is around 400 to 450 mosm/kg at age 10 years as compared with normal children where the maximum osmolality is up to 12 mosm/kg.[10] A low urine osmolality in the presence of normal or increased serum osmolality can confirm the diagnosis. Although data are very limited, intranasal DDAVP may help to decrease symptoms.[9] Patients should be educated on the importance of liberal oral hydration to prevent RBC dehydration.

Tubular Dysfunction

Due to an incomplete distal renal tubular acidosis, SCD patients can have impaired urinary acidification. The degree of this effect is related to the extent of hyposthenuria. Patients rarely become acidotic unless other causes of acidosis are also present.

Impaired potassium excretion as a result of impaired distal nephron function has also been described in SS patients.[11] Even when present, serum potassium concentration is usually normal unless the patient develops renal insufficiency. Patients with impaired potassium excretion are at additional risk of hyperkalemia with the use of drugs such as ACE inhibitors or aldosterone antagonists, or when other factors are present such as volume depletion or rhabdomyolysis.

Hematuria

Hematuria is one of the most common renal complications in patients with SCD and other sickle hemoglobinopathies. Ischemia due to medullary sickling can lead to hematuria, which is typically mild and self-limiting.[10] Interestingly, in 80% of cases the bleeding comes from the left kidney.[12,13] This is thought to be due to compression of the left renal vein between the aorta and superior mesenteric artery, which may slow flow to the renal medulla and promote sickling.[33]

More severe ischemia can result in renal medullary infarction or papillary necrosis, which often presents with gross hematuria. Although renal infarction is typically painless, it can be complicated by obstruction or pyelonephritis. In addition to hematuria, patients with acute, large renal infarcts are likely to present with pain in the flank, abdomen or lower back.[14] This may be accompanied by nausea and vomiting, fever,[14] and hypertension.[15] The diagnosis is confirmed with contrast-enhanced CT or angiography.

Renal medullary carcinoma is a rare malignancy of the kidney that can present with hematuria, flank pain, urinary-tract infection, or abdominal mass. It occurs almost exclusively in sickle hemoglobin (HbS) carriers but has also been diagnosed rarely in patients with sickle cell anemia (SCA).[16] It has a significant male preponderance in childhood. Renal medullary carcinoma can be suspected based on imaging studies, but definitive diagnosis is based on pathology.[17] This is a highly aggressive malignancy, which is typically resistant to conventional chemotherapy, and average survival is less than 12 months.

Sickle Glomerulopathy: Proteinuria and Chronic Kidney Disease

Clinically, proteinuria is the most common manifestation of glomerulopathy. Furthermore, as many as 40% of patients with HbSS and nephrotic syndrome may go on to develop progressive chronic kidney disease (CKD), leading to CKD stage 5. Increased urinary albumin and immunoglobulin G (IgG) excretion are the earliest detectable abnormalities.[4,18] Routine urinalysis may be used to screen for proteinuria; urinary protein to creatinine ratio and albumin to creatinine ratio (ACR) can be measured on a spot urine sample. In patients with positive protein on urinalysis or elevated protein-to-creatinine ratio (PCR) or ACR, 24-hour urine collection can quanitify protein excretion.

Serum creatinine and urea should also be measured. Because of the increased physiologic tubular secretion of creatinine, it has been proposed that the upper limit of "normal" serum creatinine for patients with HbSS be decreased to 80 µmol/L for men and 68 µmol/L for women.[1] There are no data on upper limit of "normal" serum creatinine for pediatric patients with HbSS. If significant abnormalities are detected, consultation with a nephrologist, and consideration of renal biopsy, may be indicated.

Focal segmental glomerulosclerosis is the most common cause of CKD in SCD. A kidney biopsy may be indicated to exclude other renal pathology, such as membranoproliferative glomerulonephritis, and to confirm FSGS.

Primary prevention may be possible if hydroxyurea is started in early childhood.[19]

Secondary Prevention of Sickle Cell Nephropathy

Angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARBs) may be initiated to prevent progressive renal disease in patients with glomerulopathy, even in the absence of hypertension.[20,21] A small, randomized, controlled trial demonstrated a significant improvement in albuminuria with ACE inhibitor treatment.[21,22] During an average of 2 years of follow-up in a large longitudinal cohort of children, treatement with hydroxyurea or ACE inhibitors led to complete reversal of microalbuminuria in 44% and 56% of subjects, respectively.[5] Close monitoring of serum potassium level is required when using ACE inhibitors and ARBs in these patients.

Patients should avoid long-term use of NSAIDs because of the physiologic effect of reduced glomerular filtration rate (GFR) and renal blood flow in patients with SCD.[23,24] If non-steroidal anti-inflammatory drugs (NSAIDs) are used, careful patient education is required.

Blood pressure control – ACE inhibitors (or ARBs) should be first-line therapy, followed by standard approaches, but diuretics should be avoided due to the likelihood of concomitant hyposthenuria, causing volume depletion and risk of RBC dehydration. To our knowledge, there have been no studies examining specific target blood pressure in this population.

Early and complete treatment of urinary-tract infection.

Erythropoietin

Because of the combination of decreased endogenous erythropoietin production and chronic hemolysis, the required dose of erythropoietin may be higher than what is typically used in CKD – even more so in patients receiving hydroxyurea. The baseline hemoglobin preceding renal failure should serve as the target hemoglobin level.[25] Risks and benefits of erythropoiesis-stimulating agents (ESAs) need to be carefully balanced, particularly in patients with previous thrombotic or cardiovascular complications.

Management of CKD Stage 5

Diagnosis of CKD stage 5 is associated with an increased relative risk of mortality in patients with SCD.[3] In a study of 77 patients with SCD and CKD stage 5, most were treated with hemodialysis, and survival was similar to that seen in other non-diabetics with CKD stage 5 (actuarial survival of 59% at 30 months vs 48% in diabetics and 66% in non-diabetics).[26] Although hemodialysis has been the traditional treatment of choice, multisystem disease – including cardiovascular disease, susceptibility to infections, anemia and decreased ability to excrete potassium – can pose additional risks. This has led some to suggest early consideration of renal transplant.[27,28]

There is increasing experience with renal transplantation in SCA.[28,29] A case-control study of 82 patients post-renal transplant for sickle cell nephropathy (SCN) showed short-term outcomes that were similar to age-matched kidney-transplant recipients with other causes of end-stage renal disease, including delayed graft function, pre-discharge acute rejection, and 1-year graft survival. There was a trend, however, to lower 3-year, deceased donor graft survival, and a significant 3-year risk of graft loss. Furthermore, the adjusted mortality risk was higher compared with non-SCN controls at 1 year (relative risk [RR]=2.95, *P*=0.001) and at 3 years (RR=2.82, *P*=0.0001). More recently, the graft survival at 6 years was found to be around 70% for patients transplanted between 2000 and 2011.[30,31] Renal transplantation appears to be relatively safe and effective in adolescents, with 60% graft survival and 89% patient survival following 10 renal transplants in 9 patients, but results were poorer than those observed in adolescents with other causes of renal disease.[32] Acute sickling episodes may increase in frequency in some patients following transplantation.[28]

There is an overall trend toward improved survival in patients with renal transplant for SCN when compared to those treated on hemodialysis.[34] This must be weighed against the risks associated with renal transplantation and, ultimately, the decision regarding the most appropriate therapy should be made on an individual basis.

Acute Kidney Injury

A broad differential diagnosis should be considered when a patient with SCA develops acute kidney injury. Multi-organ dysfunction syndrome can be related to infection or a vaso-occlusive episode in patients with SCD.[35] Treatment with simple or exchange transfusion should be considered in these cases.

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