Comments on renal abnormalities of sickle cell disease

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Renal abnormalities are common complications of sickle cell disease (SCD). Improved care of patients with SCD has resulted in longer survival and as a consequence, the long-term complications observed in patients with sickle cell anemia (SCA) have become more evident including urinary concentrating defects, impaired urinary acidification, cortical scarring and proteinuria (20-30%).

SCD and sickle cell trait (SCT) account for 1% of all new cases of end stage renal disease (ESRD). After developing ESRD the mean survival is four years with 40% of SCA patients dying within 20 months of starting dialysis. A cohort study involving 1056 patients with a median age of 20 years showed that after 40 years of follow up 12% developed renal failure at a median age of 37 years[1-3].

After the initial report by Etteldorf et al. in 1952 describing an increase in the glomerular filtration rate (GFR) of children with SCD, the majority of the published data supports the presence of glomerular hyperfiltration[4].

Beginning with the mannitol clearance as used by Etteldorf, several other methods have been used to measure GFR in children with conflicting results. These methods include the Schwartz equation (using serum creatinine, height and a constant to calculate creatinine clearance), sodium thiosulfate, ^{99m}Tc-DTPA clearance, 24h creatinine clearance, cystatin C (a low-molecular-weight protein) and the Cockroft-Gault equation. Depending upon the method used to estimate kidney function, the GFR in children may be elevated, normal, or depressed and as a consequence, the importance of using an accurate method of GFR measurement has generated many debates among authors. All of these studies confirm the presence of hyperfiltration in children but a major limitation to compare those results is that GFR values were not compared to normal control data collected concomitantly[5].

Furthermore, there are also many reports on the GFR in adults with SCA that used different evaluation methods including inulin clearance and ^{51}Cr-EDTA clearance in addition to those reported in children; the results are confounding[5].

Interestingly, when the kidneys of 15 children with SCA were evaluated by histology in one study, enlargement of the juxtamedullary glomeruli was observed, while in another study with other types of chronic anemia patients, only slight glomerular enlargement was found. Similarly, renal histology of six adult SCA patients with proteinuria showed higher mean glomerular diameters compared to normal controls[6,7]. These morphological findings lend support to the hypothesis of arteriolar dilatation which leads to increased blood flow and hyperfiltration. Prolonged hyperfiltration results in renal damage and the development of proteinuria; the combination of hyperfiltration and proteinuria cause glomerulosclerosis and renal failure[1,5].

Renal biopsy in SC nephropathy (SCD and SCT) shows focal segmental glomerulosclerosis (FSGS) and less frequently membranoproliferative glomerulonephritis (MPGN), probably due to continuous glomerular ischemia, hypoxia, intraglomerular hypertension and hypertrophy leading to glomerulosclerosis and ESRD[8,9].

Progressive declines in GFR are often associated with increasing proteinuria but the course is different to that observed in nephrotic syndrome of idiopathic FSGS and minimal change disease[2,9].

Other renal abnormalities are seen in SCA patients such as, for example, the development of urinary tract infections, especially by encapsulated organisms, due to impaired immunity secondary to autosplenectomy and papillary necrosis[10].

Hypertension occurs in around 6% of SCD patients as a consequence of reduced vascular reactivity and an increased production of prostaglandins[11].

It seems that renal manifestations are generally less common or less severe in SCT patients but include painless microscopic or gross hematuria with bleeding predominantly from left kidney. This phenomenon probably happens due to the greater length of the left renal vein that is compressed between the aorta and superior mesenteric artery causing increased blood pressure in the vein, thereby increasing relative anoxia in the renal medulla and promoting sickling (the nutcracker phenomenon)[12].

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Sickling occurring in the vasa rectae of the inner medulla alters the countercurrent exchange mechanisms, impairs reabsorption of free water and diminishes the ability of urine concentration causing polyuria and nocturia, an early clinical finding in both SCD and SCT. Increasing ischemia and hypoxia leads to renal infarction and papillary necrosis, which can be associated to fever, vomiting, abdominal pain, hypertension and painless gross hematuria[13].

Abnormal proximal tubular function with renal tubular acidosis, manifested by hyperkalemia, hyperphosphatemia, elevated creatinine clearance and increased secretion of uric acid, may also occur in SC nephropathy[14].

Acute kidney injury occurs in 5% to 10% of patients as a consequence of intravascular volume depletion (prerenal), drug nephrotoxicity, sepsis, rhabdomyolysis, renal vein thrombosis, hepatorenal syndrome (renal), papillary necrosis and urinary tract obstruction secondary to blood clots (postrenal)[15].

In summary, SC nephropathy begins early in life, occurs in all forms of SCD and is associated with the severity of the disease. The early detection of patients with or at risk for SC nephropathy may permit an approach that aims to delay the progression of kidney disease. Patients with ESRD due to SCD can be treated with any of the modalities of renal replacement therapy.

In this edition of the *Revista Brasileira de Hematologia e Hemoterapia*, Paula et al. compare the GFR of SCA and SCT patients[16].

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