Renal complications of sickle cell disease

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Abstract
The nephropathy and renal complications of sickle cell disease are associated with various events such as hypoxic or ischemic conditions and reperfusion injury. Erythrocyte sickling occurs following these events and renal medullary acidosis.
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Introduction

The incidence rate of sickle cell disease (SCD) is estimated at 300 000 births per year. In SCD patients, at the sixth amino acid position of the β-globin gene, valine is substituted for glutamine. The β-globin gene is located on the short arm of chromosome 11. Additionally, the sickle cell trait is caused by inheriting a copy of the mutation (1). Hemoglobin SS (HbSS) disease is the most common type of SCD and approximately one-third of SCD patients are heterozygous for hemoglobin SD (HbSD) (2). SCD is an inherited disorder that leads to defective hemoglobin production that creates erythrocytes with damaged membranes. This process occurs following cellular dehydration, chronic hemolytic disease, and episodes of vascular occlusion (3).

Search strategy

For this mini-review, we searched Directory of Open Access Journals (DOAJ), PubMed/Medline, Web of Science, Scopus, Embase and Google Scholar, using keywords including; sickle cell disease, renal failure, nephropathy, erythrocyte and hemoglobin SS

Nephropathy in sickle cell disease patients

The pathophysiology of renal failure and nephropathy in SCD patients is not yet fully understood. However, it has been associated with hypoxic or ischemic conditions, reperfusion injury, and changes in vascular reactivity. Hypoxia and renal medullary acidosis cause erythrocyte sickling which leads to glomerular micro-infarction and hyper-filtration. Subsequently, progressive glomerulosclerosis and chronic kidney disease (CKD) occur (4). In addition, it has been reported that the TGFβ/BMP pathway is involved in the development of kidney diseases in SCD patients (5).

A study reported that 4.2% and 2.4% of HbSS and HbSC patients develop renal failure, respectively. Additionally, kidney failure is a progressive disorder and common in SS and SB phenotypes of SCD (5). Severe early anemia and hemoglobin levels less than 8 g/dL are the most important symptoms in SCD patients with HbSS and HbSβ[0] subtypes that develop microalbuminuria (6). On the other hand, EPO (erythropoietin) synthesis is impaired in cases with renal dysfunction and reduced glomerular filtration rate (GFR) (5).

Renal complications in sickle cell disease

SCD patients are at risk for renal complications and in most cases, SCD-induced nephropathy occurs gradually. Renal complications vary from glomerular hypo-filtration to microalbuminuria or occasionally macro-albuminuria, and finally leads to CKD (5). However, fewer pain attacks and stable hemoglobin levels are less likely to lead to proteinuria and kidney failure (7). Renal manifestations include low-medullary blood flow rate during the first decade of life, hyposthenuria, renal papillary necrosis, proteinuria, hematuria, focal segmental glomerulosclerosis (FSGS), and finally, renal medullary carcinoma. Furthermore, hyper-filtration is the first sign of renal dysfunction with an increased risk of progression to end-stage renal disease (ESRD) (3). In addition, chronic hemolysis causes iron deposition in

the kidney leading to mesenchymal cell proliferation and glomerular fibrosis (8). On the other hand, recurrent pain attacks cause ischemic renal injury and lead to the loss of kidney function and decrease the levels of prostaglandin and GFR (7).

The role of cardiac output in renal diseases
Cardiac output increases in SCD patients due to various reasons. These patients experience endothelial nitric oxide synthase (eNOS) deficiency due to chronic hemolysis. Therefore, the arteries do not have a proper hemodynamic response and there is an increased risk of developing acute kidney injury (AKI) (8).

The role of micro-infarction in developing hematuria and renal diseases
Hematuria in SCD patients is due to micro-infarction in the renal papilla, which is often self-limiting but may lead to renal necrosis and clot formation (1, 5). Hematuria often occurs at an older age and there is no difference in the incidence of both genders (7). Papillary necrosis secondary to vascular occlusion episodes leads to macroscopic hematuria (8). Hematuria may develop due to medullary carcinoma which may occur even at the age of 2 years (5).

Urine concentrating inability
The inability to increase urinary concentration to 450 mmol/kg is a common finding in SCD patients (5). Urine concentrating ability in SCD patients is associated with the deletion of the α-globin gene; deletion of two genes reduces urine concentration (1).

The role of blood pressure level in developing kidney disease
Blood pressure (BP) is usually low in SCD patients due to the hemodynamic response to the extensive systemic vasodilation induced by nitric oxide (NO) and prostacyclin production (2). The mean BP is lower than normal compared to healthy individuals of the same age and race. In the cases that have hypertension, the diastolic pressure increases which is associated with increased creatinine and pulmonary hypertension (5). High BP and elevated heart rate are both important in increasing the risk of morbidity caused by kidney disease in SCD patients (2).

Microalbuminuria and proteinuria
Microalbuminuria occurs at an early age and progresses to proteinuria and, eventually, kidney failure with increased age and anemia severity (4). Microalbuminuria is associated with decreased plasma hemoglobin and increased reticulocyte counts (4). The prevalence of microalbuminuria and increased β2 microglobulin levels are higher in SS patients compared to AS patients (9). In addition, albuminuria is more common in SS patients than AS patients (2).

The prevalence of proteinuria in SS patients has been reported to be 17 to 33% (8). Proteinuria may occur alone or in combination with renal vein thrombosis, foot ulcer, hematuria, and acute or chronic glomerulonephritis (7). Proteinuria and progression to kidney failure increase in the severe phenotype of SCD that is associated with multiple episodes of acute coronary syndrome and stroke (4).

Renal glomerular diseases
Nephromegaly due to glomerular hypertrophy is detected on ultrasound in infants aged 7 to 18 months. Under light microscope, the most common finding is FSGS (8).

Renal tubular disorders and acute renal injury
SCD is associated with distal and proximal renal tubular disorders. Most patients experience hyperphosphatemia and, commonly, have elevated uric acid and creatinine. Distal renal tubular disorder presents with incomplete type IV RTA (renal tubular acidosis) symptoms and occurs in critically ill patients with hyperkalemia and acidosis (5).

AKI may occur due to episodes of vascular occlusion following a decrease in hemoglobin level and ketorolac consumption (8).

Other manifestations of kidney diseases
Nocturia is also prevalent in SS patients. The incidence of enuresis is severe in SS, moderate in hemoglobulin SA (HbSA), and less in SB (10). Concurrent α-thalassemia delays microalbuminuria. Low levels of hemoglobin F (HbF) predispose a person to kidney disease; therefore, an HbF level of >20% indicates a reduced risk of kidney failure (5). The pain attacks that lead to anemia and require blood transfusions are associated with low GFR levels (7).

Screening
Screening for glomerular injury with dipstick test should start at the age of 10 years (4). In addition, monitoring should be performed for patients with persistent microscopic hematuria, GFR <60 mL/min/1.73 m², and proteinuria with a Pr/Cr (protein/creatinine) ratio of 50 mg/mmol (5). These patients should be followed up with annual urinalysis (4).

Prevention
Prevention of anemia (caused by pain attacks) through

prophylactic blood transfusion could reduce glomerular hyperfiltration and slow the progression to kidney failure (7). The lowest acceptable hemoglobin level in ESRD patients is 8-9 g/dL (8). Hyposthenuria can be reversed at a young age by blood transfusions (5).

Biomarkers

The diagnosis of nephropathy in asymptomatic SCD patients is of particular importance (7).

Increased nephrin levels in SCD patients with persistent hyperfiltration indicate glomerular injury. Age as well as systolic and diastolic BPs are important factors in determining the GFR levels of the patients (3). The ratio of cystatin-C to creatinine is another key marker for assessing renal function in children and adults (5).

Treatment

In addition to treatment with hydroxyurea, stimulants of erythropoiesis can be administered to prevent anemia in these patients. Grade 3-4 of patients with chronic renal disease require high doses of erythropoiesis stimulants. However, chronic transfusion therapy does not affect the prevention of proteinuria (5). In children aged between 9 to 18 months, hydroxyurea helps increase urine concentration and reduce hyper-filtration. Angiotensin-converting enzyme inhibitors can be prescribed to reduce proteinuria in SCD adults that have normotension and microalbuminuria (11). Renal replacement therapy is required in cases when the GFR declines to less than 40 ml/min/1.73 m^2 (5).

Conclusion

The nephropathy and renal complications of SCD are associated with various events such as hypoxic or ischemic conditions and reperfusion injury. Erythrocyte sickling occurs following these events and renal medullary acidosis. Subsequently, renal complications and CKD may occur. Therefore, early diagnosis, regular screening and monitoring, preventive measurements, and immediate treatment may slow the progression to renal failure.

Authors' contribution
Primary draft by MB, MRMS and SB. Scientific edit by BK. English edit by SH and MB. All authors read and signed and approved the final paper.

Conflicts of interest
The authors declare that they have no competing interests.

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